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NDA 19835

1 OF 11

MDA 19835

Zyrtec

N 19835

AP

Pharm

LBL

Chem

EA

MOR

Stat

Bio Pharm

BIO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-835

DEC 8 1995

Pfizer Inc.
235 East 42nd Street
New York, New York 10017-5755

Attention: Rita A. Wittich
Director, Regulatory Affairs

Dear Ms. Wittich:

Please refer to your June 30, 1988 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyrtec (cetirizine hydrochloride) 5 mg and 10 mg tablets.

Reference is made to the November 13, 14, 21, and December 7, 1995 telephone conversations between your office and Mr. Koung Lee of this Division.

We acknowledge receipt of your amendments dated April 4, 25, May 12, 16, June 7, 14, 20, 29, July 17, August 11, 18, October 4, November 10, 14, 16, and 20, 1995.

We have completed the review of this application including the submitted draft labeling (carton, bottles, and blister labeling dated April 4, 1995; package insert dated October 4, 1995) and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for the relief of symptoms associated with seasonal allergic rhinitis, perennial allergic rhinitis, and chronic urticaria with revisions to the package insert. Accordingly, the application is approved effective on the date of this letter. As discussed by telephone in the referenced conversations between your office and Mr. Koung Lee of the Division of Pulmonary Drug Products, the package insert will be revised as indicated in the enclosed revised labeling.

These revisions are terms of the NDA approval. Marketing the product before making the revisions in the product's final printed labeling (FPL) may render the product misbranded and an unapproved new drug.

We remind you of your Phase 4 commitment specified in your submission dated November 16, 1995. Your commitment is listed below.

The first three commercial lots will be evaluated to determine whether specifications for the individual and total of all degradation products should be tightened. In addition, analytical development work will be undertaken to enhance the quantitative characteristics of the method.

All submissions relating to your Phase 4 commitment should be submitted to the NDA as correspondence and clearly designated as "Phase 4 Commitment" for administrative purposes.

Please submit fifteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FPL for approved NDA 19-835". Approval of this submission by FDA is not required before it is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of the labeling may be required.

Please submit one market package of the drug when it is available.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

NDA 19-835

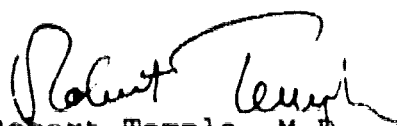
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We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Koung Lee
Project Manager
(301) 827-1051

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Robert Temple".

Robert Temple, M.D.

Director

Office of Drug Evaluation I

Center for Drug Evaluation and Research

ENCLOSURE

REVISED LABELING

The Redline and Strikeout functions on WordPerfect 6.0 were used to identify the labeling revisions. The Redline function highlights (e.g., ZYRTEC) insertions and the Strikeout function identifies the parts of the labeling that should be deleted (e.g., ~~ZYRTEC~~).

ANNOTATED PACKAGE INSERT

ZYRTEC

cetirizine hydrochloride

Tablets

For Oral Use

DESCRIPTION

Cetirizine hydrochloride, the active component of ZYRTEC tablets, is an orally active and selective H₁-receptor antagonist. The chemical name is (±)-[2-[4-(p-chloro-α-phenylbenzyl)-1-piperazinyl]ethoxy] acetic acid, dihydrochloride. Cetirizine hydrochloride is a racemic compound with an empirical formula of C₂₁H₂₆ClN₃O₂·2HCl. The molecular weight is 461.82 and the chemical structure is shown below:

Cetirizine hydrochloride is a white, crystalline powder and is water soluble. ZYRTEC is formulated as a white (dye-free), film-coated, rounded-off rectangular shaped tablet for oral administration and is available in 5 and 10 mg strengths. Inert ingredients are: lactose; magnesium stearate; povidone; titanium dioxide; hydroxypropyl methylcellulose; polyethylene glycol; and corn starch.

CLINICAL PHARMACOLOGY

Mechanism of Actions: Cetirizine, a human metabolite of hydroxyzine, is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H₁ receptors. The antihistaminic activity of cetirizine has been clearly documented in a variety of animal and human models. In vivo and ex vivo animal models have shown negligible anticholinergic and antiserotonergic activity. In clinical studies, however, dry mouth was more common with cetirizine than with placebo. In vitro receptor binding studies have shown no measurable affinity for other than H₁ receptors. Autoradiographic studies with radiolabeled cetirizine in the rat have shown negligible penetration into ~~of~~ the brain. Ex vivo experiments in the mouse have shown that systemically administered cetirizine does not significantly occupy cerebral H₁ receptors.

Pharmacokinetics: Cetirizine is rapidly absorbed after oral administration of a tablet, which had bioavailability similar to an oral solution. Food had no effect on the extent of cetirizine absorption, but T_{max} was delayed by 1.7 hours and C_{max} was decreased by 23% in the presence of food. A mass balance study in 6 healthy male volunteers indicated that 70% of the administered radioactive dose was recovered in the urine and 10% in the feces, for a combined total recovery of about 80%. Approximately 50% of the administered radioactive dose was excreted in urine as unchanged drug.

Most of the rapid increase in peak plasma radioactivity is associated with parent drug indicating low first pass metabolism. Cetirizine is metabolized to a very limited extent by oxidative o-dealkylation to a metabolite with negligible antihistaminic activity.

Cetirizine exhibits linear kinetics over the dosage range of 5 to 60 mg. In pharmacokinetic studies in 146 healthy volunteers, the mean $\pm$ SD terminal half-life was 8.3 ± 1.8 hours, oral clearance was 54 ± 13 mL/min, and the apparent volume of distribution was 0.50 ± 0.08 L/kg. No accumulation was observed for cetirizine following daily doses of 10 mg for 10 days. The steady-state maximum plasma concentration was 311 ± 40 ng/mL and was achieved within 1.0 ± 0.5 hour. Individual histograms of cetirizine C_{max} and AUC showed unimodal distributions with a two- to four-fold variability in healthy subjects. Plasma protein binding of cetirizine is 93 ± 0.3 % and is ~~was~~ independent of concentration in the range of 0.025 to 1.0 mcg/mL; this concentration range covers the therapeutic plasma levels.

Formal pharmacokinetic interaction studies were conducted with cetirizine and pseudoephedrine, antipyrine, ketoconazole, erythromycin, and azithromycin. No pharmacokinetic interactions were observed. In a multiple dose study of theophylline (400 mg once daily) and cetirizine, there was a small (16%) decrease in clearance of cetirizine.

SPECIAL POPULATIONS

Effect of Age: Following a single 10 mg oral dose, half-life increased by about 50% and clearance decreased by 40% in 16 elderly subjects as compared to the 14 normal subjects. The decrease in cetirizine clearance in these elderly volunteers appeared to be related to their decreased renal function.

Effect of Gender: The effect of gender on cetirizine pharmacokinetics has not been

adequately studied.

Effect of Race: No race-related differences were observed in the kinetics of cetirizine between 86 white adult males and 11 black adult males.

Renally Impaired Patients: The kinetics of cetirizine were studied following multiple oral daily doses of 10 mg for 7 days in 7 normal volunteers (creatinine clearance 89-128 mL/min), 8 patients with mild renal function impairment (creatinine clearance 42-77 mL/min) and 7 patients with moderate renal function impairment (creatinine clearance 11-31 mL/min). The pharmacokinetics of the drug were similar in patients with mild impairment and normal volunteers. Moderately renally impaired patients had a 3-fold increase in half-life and 70% decrease in clearance compared to normal volunteers.

Patients (N=5) on hemodialysis (creatinine clearance less than 7 mL/min) given a single oral 10 mg dose of cetirizine had a 3 fold increase in half-life and a 70% decrease in clearance compared to normals. Cetirizine was not completely cleared by hemodialysis as less than 10% of the administered dose was removed during the dialysis session.

Dosing adjustment is necessary in patients with moderate or severe renal impairment and patients on dialysis. (See also DOSAGE AND ADMINISTRATION).

Hepatically Impaired Patients: Sixteen patients with chronic liver diseases (hepatocellular, cholestatic, and biliary cirrhosis), given 10 or 20 mg of cetirizine as a single oral dose had a 50% increase in half-life along with a 40% decrease in clearance compared to 16 healthy subjects.

Dosing adjustment may be necessary in hepatically impaired patients. (See also DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

~~Formal pharmacokinetic interaction studies were conducted with cetirizine and pseudoephedrine, antipyrine, ketoconazole, erythromycin, and azithromycin. No pharmacokinetic interactions were observed. In a multiple dose study of theophylline (400 mg once daily) and cetirizine, there was a small (16%) decrease in clearance of cetirizine.~~

Pharmacodynamics: Studies in normal volunteers show that ZYRTEC at doses of 5 and 10 mg strongly inhibits the skin wheal and flare caused by the intradermal injection of histamine. The onset of this activity after a single 10 mg dose occurs within 20 minutes in 50% of subjects and within one hour in 95% of subjects ~~within one hour;~~ and this activity persists for at least 24 hours. In a 35 day study in children ages 5 to 12, no tolerance to the antihistaminic (suppression of wheal and flare response) effects of ZYRTEC was found. The effects of intradermal injection of various other mediators or histamine releasers are also inhibited by cetirizine, as is response to a cold challenge in patients with cold-induced urticaria. In mildly asthmatic subjects, ZYRTEC at 5 to 20 mg blocked bronchoconstriction due to nebulized histamine, with virtually total blockade after a 20 mg dose. In studies conducted for up to 12 hours following cutaneous antigen challenge, the late phase recruitment of eosinophils, neutrophils and basophils, components of the allergic inflammatory response, was ~~is~~ inhibited by ZYRTEC at a dose of 20 mg.

In four clinical studies in healthy adult males, no clinically significant mean increases in QTc were observed in ZYRTEC treated subjects. In the first study, a placebo-controlled crossover trial, ZYRTEC was given at doses up to 60 mg per day, 6 times the maximum clinical dose, for 1 week, and no significant mean QTc prolongation occurred. In the second study, a crossover trial, ZYRTEC 20 mg and erythromycin (500 mg every 8 hours) were given alone and in combination. There was no significant effect on QTc with the combination or with ZYRTEC alone. In the third trial, also a crossover study, ZYRTEC 20 mg and ketoconazole (400 mg per day) were given alone and/or in combination. ZYRTEC caused a mean increase in QTc of 9.1 msec from baseline of ~~9.1 msec~~ after 10 days of therapy. Ketoconazole also increased QTc by 8.3 msec. The combination caused an increase of 17.4 msec, ~~about~~ equal to the sum of the individual effects. Thus, there was no significant drug interaction ~~effect~~ on QTc with the combination of ZYRTEC and ketoconazole. In the fourth study, a placebo-controlled parallel trial, ZYRTEC 20 mg was given alone or in combination with azithromycin (500 mg as a single dose on the first day followed by 250 mg once daily). There was no significant increase in QTc with ZYRTEC 20 mg alone or in combination with azithromycin.

In a six-week, placebo-controlled study of 186 patients with allergic rhinitis and mild to moderate asthma, ZYRTEC 10 mg once daily ~~QD~~ improved rhinitis symptoms and did not alter pulmonary function. This study supports the safety of administering ZYRTEC to allergic rhinitis patients with mild to moderate asthma.

Clinical Studies: Nine multicenter, randomized, double-blind, clinical trials comparing cetirizine 5 to 20 mg to placebo in patients with seasonal or perennial allergic rhinitis were conducted in the United States. Five of these showed significant reductions in symptoms of allergic rhinitis, 3 in seasonal allergic rhinitis (1 to 4 weeks in duration) and 2 in perennial allergic rhinitis for up to 8 weeks in duration. Two 4-week multicenter, randomized, double-blind, clinical trials comparing cetirizine 5 to 20 mg to placebo in patients with chronic idiopathic urticaria were also conducted

and showed significant improvement in symptoms of chronic idiopathic urticaria. In general, the 10 mg dose was more effective than the 5 mg dose and the 20 mg dose gave no added effect. Some of these trials included pediatric patients age 12 to 16 years.

INDICATIONS AND USAGE

Seasonal Allergic Rhinitis: ZYRTEC is indicated for the relief of symptoms associated with seasonal allergic rhinitis due to allergens such as ragweed, grass and tree pollens in adults and children 12 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, nasal pruritus, ocular pruritus, tearing and redness of the eyes.

Perennial Allergic Rhinitis: ZYRTEC is indicated for the relief of symptoms associated with perennial allergic rhinitis due to allergens such as dust mites, animal dander and molds in adults and children 12 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, post-nasal discharge, nasal pruritus, ocular pruritus and tearing.

Chronic Urticaria: ZYRTEC is indicated for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 12 years of age and older. It significantly reduces the occurrence, severity and duration of hives and significantly reduces pruritus.

CONTRAINDICATIONS

ZYRTEC is contraindicated in those patients with a known hypersensitivity to it or any of its ingredients or hydroxyzine.

PRECAUTIONS

Activities Requiring Mental Alertness: In clinical trials, the occurrence of somnolence has been reported in some patients taking ZYRTEC; due caution should therefore be exercised when driving a car or operating potentially dangerous machinery. Concurrent use of ZYRTEC with alcohol or other CNS depressants should be avoided because additional reductions in alertness and additional impairment of CNS performance may occur.

Drug-drug Interactions: No clinically significant drug interactions have been found with theophylline at a low dose, azithromycin, pseudoephedrine, ketoconazole, or erythromycin. There was a small decrease in the clearance of cetirizine caused by a 400 mg dose of theophylline; it is possible that larger theophylline doses could have a ~~greater-larger~~ effect.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No evidence of carcinogenicity was observed in a 2-year carcinogenicity study in rats at dietary doses up to 20 mg/kg/day (15 times the maximum recommended human dose on a mg/m²/day basis). An increased incidence of benign liver tumors was found in a 2-year carcinogenicity study in male mice at a dietary dose of 16 mg/kg/day (6 times the maximum recommended human dose on a mg/m²/day basis). The clinical significance of these findings during long-term use of ZYRTEC is not known. Cetirizine was not mutagenic in the Ames test, and not clastogenic in the human lymphocyte assay, the mouse lymphoma assay, and the *in vivo* micronucleus test in rats. No impairment of fertility was found in a fertility and general reproductive performance study in mice at a dose of 64 mg/kg/day (26 times the maximum recommended human dose on a mg/m²/day basis).

Pregnancy Category B: Cetirizine was not teratogenic in mice, rats and rabbits at doses up to 96, 225, and 135 mg/kg/day (~~or~~ 40, 180, and 216 times the maximum recommended human dose on a mg/m²/day basis), respectively. There are no adequate and well-controlled studies in

pregnant women. Because animal studies are not always predictive of human response, ZYRTEC should be used in pregnancy only if clearly needed.

Nursing Mothers: Retarded pup weight gain was found in mice during lactation when dams were given cetirizine at 96 mg/kg/day (40 times the maximum recommended human dose on a mg/m²/day basis). Studies in beagle dogs indicate that approximately 3% of the dose is excreted in breast milk. Cetirizine has been reported to be excreted in human breast milk; use of ZYRTEC in nursing mothers is not recommended.

Geriatric Use: ~~The safety and efficacy of ZYRTEC has been demonstrated in patients 65 years and older. (See CLINICAL PHARMACOLOGY section)~~ In placebo controlled trials, 186 patients age 65 to 94 years received doses of 5 to 20 mg of ZYRTEC per day. Adverse events were similar in this group to patients under age 65. Subset analysis of efficacy in this group was not done.

Pediatric Use: Safety and effectiveness in children under 12 years of age ~~the pediatric population~~ has not been established.

ADVERSE REACTIONS

Controlled and uncontrolled clinical trials conducted in the United States and Canada included more than 6000 patients, with more than 3900 receiving ZYRTEC at doses of 5 to 20 mg per day. The duration of treatment ranged from 1 week to 6 months, with a mean ~~of~~ exposure of 30 days.

Most adverse reactions reported during therapy with ZYRTEC were mild or moderate. In placebo-controlled trials, the incidence of discontinuations due to adverse reactions in patients receiving ZYRTEC 5 mg or 10 mg was not significantly different from placebo (2.9% vs 2.4%, respectively).

The most common adverse reaction that occurred more frequently on cetirizine than placebo was somnolence. The incidence of somnolence associated with ZYRTEC was dose related, 6% in placebo, 11% at 5 mg and 14% at 10 mg. Discontinuations due to somnolence for ZYRTEC were uncommon (1.0% on Zyrtec vs 0.6% on placebo). Fatigue and dry mouth also appeared to be treatment-related adverse reactions. There were ~~was~~ no differences by age, race, gender or by body weight with regard to the incidence of adverse reactions.

Table 1 lists adverse experiences which were reported for ZYRTEC 5 and 10 mg in controlled clinical trials in the United States and that were more common with ZYRTEC than placebo.

Table 1. Adverse Experiences Reported in Placebo-Controlled United States ZYRTEC Trials (Maximum Dose of 10 mg) at Rates of 2% or Greater
(Percent Incidence)

Adverse Experience	ZYRTEC (N=2034)	Placebo (N=1612)
Somnolence	13.7	6.3
Fatigue	5.9	2.6
Dry Mouth	5.0	2.3
Pharyngitis	2.0	1.9
Dizziness	2.0	1.2

In addition, headache and nausea occurred in more than 2% of the patients, but were more common in placebo patients.

The following events were observed infrequently (less than 2%), in 3982 patients who received ZYRTEC in U.S. trials, including an open study of six months duration; a causal relationship with ZYRTEC administration has not been established.

Autonomic Nervous System: anorexia, urinary retention, flushing, increased salivation

Cardiovascular: palpitation, tachycardia, hypertension, cardiac failure

Central and Peripheral Nervous Systems: insomnia, paresthesia, confusion, hyperkinesia, hypertonia, migraine, tremor, vertigo, leg cramps legs, ataxia, dysphonia, abnormal coordination, hyperesthesia, hypoesthesia, myelitis, paralysis, ptosis, twitching, visual field defect

Gastrointestinal: increased appetite, dyspepsia, abdominal pain, diarrhea, flatulence, constipation, vomiting, ulcerative stomatitis, aggravated tooth caries, stomatitis, tongue discoloration, tongue edema, gastritis, rectal ~~rectum~~-hemorrhage, hemorrhoids, melena, abnormal hepatic function

Genitourinary: polyuria, urinary tract infection, cystitis, dysuria, hematuria

Hearing and vestibular: earache, tinnitus, deafness, ototoxicity

Metabolic/Nutritional: thirst, dehydration, diabetes mellitus

Musculoskeletal: myalgia, arthralgia, arthrosis, arthritis, muscle weakness

Psychiatric: insomnia, nervousness, depression, emotional lability, impaired concentration, anxiety, depersonalization, paroniria, abnormal thinking, agitation, amnesia, decreased libido, euphoria

Respiratory System: epistaxis, rhinitis, coughing, bronchospasm, dyspnea, upper respiratory tract infection, hyperventilation, sinusitis, increased sputum, bronchitis, pneumonia

Reproductive: dysmenorrhea, female breast pain, intermenstrual bleeding, leukorrhea, menorrhagia, vaginitis

Reticuloendothelial: lymphadenopathy

Skin: pruritus, rash, dry skin, urticaria, acne, dermatitis, ~~rash~~ erythematous rash, increased sweating, alopecia, angioedema, furunculosis, bullous eruption, eczema, hyperkeratosis, hypertrichosis, photosensitivity reaction, photosensitivity toxic reaction, maculo-papular rash, seborrhea, purpura

Special Senses: taste perversion, taste loss, parosmia

Vision: blindness, loss of accommodation, eye pain, conjunctivitis, xerophthalmia, glaucoma, ocular hemorrhage

Body as a Whole: increase weight, back pain, malaise, fever, asthenia, generalized edema, periorbital edema, peripheral edema, rigors, leg ~~sw~~ edema, face edema, hot flashes ~~flushes~~, enlarged abdomen, nasal polyp

Occasional instances of transient, reversible hepatic transaminase elevations have occurred during cetirizine therapy. ~~There was a~~ A single case report of possible drug-induced hepatitis with significant transaminase elevation (500 to 1000 IU/L) and elevated bilirubin has been reported.

In foreign marketing experience the following additional rare, but potential severe adverse events have been reported: hemolytic anemia, thrombocytopenia, orofacial dyskinesia, severe hypotension, anaphylaxis, hepatitis, glomerulonephritis, stillbirth, and cholestasis.

DRUG ABUSE AND DEPENDENCE

There is no information to indicate that abuse or dependency occurs with ZYRTEC.

OVERDOSAGE

Overdosage has been reported with ZYRTEC. In one patient who took 150 mg of ZYRTEC, the patient was somnolent but did not display any other clinical signs or abnormal blood chemistry or hematology results. Should overdose occur, treatment should be symptomatic or supportive, taking into account any concomitantly ingested medications. There is no known specific antidote to ZYRTEC. ZYRTEC is not effectively removed by dialysis, and dialysis will be ineffective unless a dialyzable agent has been concomitantly ingested. The minimal lethal oral dose in rodents is approximately 100 times the maximum recommended clinical dose on a mg/m² basis and the liver is ~~was~~ the target organ of toxicity.

DOSAGE AND ADMINISTRATION

The recommended initial dose of ZYRTEC is 5 or 10 mg per day in adults and children 12 years and older, depending on symptom severity. Most patients in clinical trials started at 10 mg. ZYRTEC is given as a single daily dose, with or without food. The time of administration may be varied to suit individual patient needs.

In patients with decreased renal function (creatinine clearance 11-31 mL/min), patients on hemodialysis (creatinine clearance less than 7 mL/min), and in hepatically impaired patients, a dose of 5 mg once daily ~~QD~~ is recommended.

HOW SUPPLIED:

ZYRTEC tablets are white (dye free), film coated, rounded-off rectangular shaped containing 5 mg or 10 mg cetirizine hydrochloride.

5 mg tablets are engraved with "PFIZER" on one side and with "550" on the other.

Bottles of 100: (NDC 0069-5500-66)

10 mg tablets are engraved with "PFIZER" on one side and with "551" on the other.

Bottles of 100: (NDC 0069-5510-66)

Cetirizine is licensed from UCB, Pharma Inc.

STORAGE: Store at room temperature 59° to 86°F (15° - 30°C).

FEB 21 1995

NDA 19-835

Pfizer Inc.
235 East 42nd Street
New York, New York 10017-5755

Attention: Rita A. Wittich
Director, Regulatory Affairs

Dear Ms. Wittich.

Reference is made to your new drug application dated June 30, 1988, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for cetirizine hydrochloride tablets, 5 mg and 10 mg.

We also refer to your Pre-NDA submission of May 31, 1988 and to your amendments dated January 31, March 20, April 13, May 17, 22 and 24, August 7, October 3 and 6, November 2 and 29, 1989, January 12, February 16 (2) and 28, August 23, September 25, December 5, 12 and 28, 1990, January 29 (2), February 19, June 4, July 10, September 16, October 31, December 18 and 20, 1991, January 30, February 4, March 26, October 9, December 2, 1992, March 12, 19 (2) and 22, April 1 and 15, June 15, July 7 (2), 8 (2), 9, 15 and 22, August 11, 19 and 25, September 16, 28 and 30 (2), October 8, 12, 15, 26 and 29, November 17 and 19, 1993, January 20 and 28, February 1, 2, 16, 17 and 24, March 3, 1994, our December 19, 1994 telephone facsimile of the draft approvable letter, the December 21, 1994 meeting, the January 4 and 9 telephone conferences, and your January 26, 1995 amendment.

We have completed the review of this application as submitted with draft labeling and it is approvable. Before the application may be approved, however, it will be necessary for you to submit the following information. Please note that the comments in our December 19, 1994 facsimile were draft and have been modified. The division is considering labeling changes for the Pharmacokinetics section based on the January 9, 1995 teleconference. At this time, no change has been made to the Pharmacokinetics section since additional time is required to analyze the data obtained from the teleconference.

1. As discussed at the meeting of December 21, 1994, all controlled trial and the azithromycin interaction trial in which there is a 10% or greater prolongation in QT_c from baseline should be evaluated by a cardiologist for changes in T-U wave morphology. The change in QT_c on the trials should be evaluated for age, gender, race, dose, dose adjusted for weight, duration of treatment related effects and concurrent therapy, if any. Because of possible diurnal effects on QT_c , the analysis should incorporate a description of how the ECG's included in the analysis compare with regard to the time they were collected. If serum drug concentrations are available, an analysis of change in QT_c by drug level should be performed. Please compute the QT_c according to the Bazett formula. For the data and the azithromycin study, in addition to mean changes an analysis should also be performed comparing active treatment to placebo with regard to subjects with <10% increase in QT_c from baseline, 10-15%, 15-20% and >20% increase over baseline.
2. Please analyze the ECG data from the study as requested above, using the Bazett's formula for patients who received post ECGs within 24 hours of the last cetirizine dose. The QT_c analysis of this data should include a comparison by dose adjusted for weight, by gender and race. This should be done for both change from baseline as well as by percentage increase or decrease from baseline. As above, all ECG's with a 10% or greater prolongation of QT_c from baseline should be evaluated by a cardiologist for changes in T-U wave morphology.
3. Using the Bazett formula, please list the QT_c prolongations that are more than 10% over baseline, for the three studies: 90CK16-0497, 92CK16-0603 and 92CK16-0604, by patient, indicating study phase, day, and hour
4. Please explain the discrepancies between the results for the requested ECG analysis regarding the number of patients with more than 10% increase in QT_c in studies provided to us in the March 12, 1993 submission and the data submitted on March 3, 1994 in the safety update. An explanation of why the overall numbers of subjects in the treatment groups differ between the two submissions should also be given.

5. In reference to Table 1, Appendix 2 of the July 15, 1993 submission, please list the terms that were included under "psychiatric disorders" and update the corresponding frequencies per term. Please report these results by dose and duration of treatment.
6. Please provide an integrated safety update. As discussed, the cutoff date of February 1994 can be used. Intercurrent illnesses must be included in the adverse event database for the new patients. Any reports of serious adverse reactions after February 1994 should also be submitted; please include manufacturer number of the reports.

The following issues should be addressed in the integrated safety update. If the new database is small and will not be integrated into your previous database, these issues should be addressed for the March 3, 1994 integrated safety update.

- a. Please analyze and submit duration of exposure by dose, gender and race.
- b. Please analyze and submit adverse event rates by use of oral contraceptives. U.S. and foreign studies should be analyzed separately.
- c. Lab data (change from baseline, percent of subjects with abnormal labs), should be analyzed by treatment, dose, age, gender and race. Please submit the list of patients whose pre-treatment lab values were within normal limits and who had any of the following lab values post initiation of treatment with cetirizine: SGOT > 65 U/L, SGPT > 60 U/L, BUN > 25 mg/dl, or serum creatinine > 1.5mg/dl. Please provide a brief summary of the above outliers: age, gender, race, dose, duration of treatment prior to the event, concomitant medication used, reported adverse events and dates of reports.
- d. The integrated safety summary should also address weight gain, by duration of treatment, age and gender. Submit a scatter plot of the pre- versus post-study weight of subjects enrolled in clinical trials. The scatter plot should be based on the trials for which mean weight data are reported in the updated integrated safety summary.

- e. Please submit any available clinical data regarding the enantiomers of cetirizine.
 - f. As discussed at the meeting of December 21, 1994, please submit a listing of intercurrent illnesses by treatment reported by patients in your trials. Also please note which illnesses resulted in premature withdrawal from the study.
7. Please submit the complete medical records for the adverse event report with Mnf. number 9300233.
 8. Please address the increased frequency of Category 9 adverse events (liver enzymes) in the erythromycin-cetirizine study for 4 out of 16 patients receiving the combination.
 9. As previously advised, your proposed name "Reactine" connotes usefulness in acute situations and implies lack of drowsiness. Your alternate proposed names "Ultreon" implies maximum strength or effectiveness as compared to related products and "Alacrin" appears to be derived from "alacrity" which denotes quickness and alertness. These three tradenames are not acceptable. Your alternate proposed name, "Zyrtec", is acceptable.
 10. Your proposed annotated package insert has been revised. Please refer to the attachment and note that our recommended additions to the labeling are underlined and in bold typeface and our comments are in brackets, caps, and bold typeface.
 11. Please submit complete reports of the 4 week and 13 week oral toxicity studies in rats and dogs, that have not yet been submitted, conducted with the enantiomers of cetirizine. Please provide an explanation of the findings of the renal toxicity in rats by both enantiomers but not by the racemic mixture.
 12. The regulatory specification for dissolution must be revised to read:

Q of not less than in 30 minutes using USP

13. With regard to reworked material, a detailed description of each type of product failure and the corresponding rework procedure must be provided, as well as information on additional in-process and final product tests which will be used as controls. A dissolution profile with appropriate specifications should be included. A separate batch or lot numbering system should be used for reworked cores and tablets.

Additionally, accelerated and long term studies on all reworked tablets should be undertaken under an approved stability protocol which includes complete information on tests and specifications applicable to the reworked product.

14. The following comments and requests for information pertain to the environmental assessment (EA).
 - a. Please provide a description of the requested approval to manufacture, package and market the drug product by the proprietary and established names.
 - b. Please provide the full site addresses for the manufacturing sites to allow for facility location and inspection.
 - c. Please describe the environment adjacent to the drug substance manufacturing site at _____ and provide a material safety data sheet for the drug substance.
 - d. Please list all components, including proprietary components, intermediate and side products, used to manufacture the drug substance.
 - e. Please list all components expected to be emitted to the environment from the manufacture of the drug substance.
 - f. For emissions, the control procedures and devices should be identified (a flow chart of the control steps and tests may be provided).
 - g. The applicable permits must be identified for each route of emission. The permit information should include the permit number, issuing agency, and expiration date.

- h. It is recommended that for the method of manufacture of the drug product, a flow chart be provided which identifies the discrete steps in the manufacture and the process waste stream. Please note the differences in the method of manufacture between the sites.
- i. For substances expected to be emitted from both drug product manufacturing sites, please identify the waste streams. List all components, including proprietary components, intermediate and side products which are used to manufacture the drug product cetirizine hydrochloride. List all components emitted into the waste streams from manufacturing the drug substance.
- j. Please state the permit number, issuing agency, expiration date, and permit limits under which the incinerator operator is licensed.
- k. For controls exercised for emissions at the drug product sites,
the pre-treatment steps performed on the aqueous waste stream prior to emissions to the public waste water treatment plant should be stated. A flow chart of the pretreatment steps, the tests performed and the action limits is recommended.
- l. For compliance with current emission requirement at both drug product manufacturing sites, please provide the permit numbers, expiration date(s) and limits for aqueous waste stream disposal to publicly owned waste water treatment plants.
- m. Please provide an estimate of the vapor pressure or Henry's constant to determine cetirizine's potential to volatilize from water to air or provide justification for why vapor pressure should not be determined on the cetirizine (free base) in the estimation of the ecosystem fate.
- n. Please provide the aerobic biodegradation studies modeled after FDA's Technical Assistance Document (TAD) 3.11 which you have identified as on-going in your submission.
- o. Please provide the full sorption/desorption study in accord with TAD 3.08 since your screening results showed more than 25% cetirizine absorption.

- p. Please clarify your correlation of K_0 to percent removed by sludge. The equation in Appendix 13, page 3-654 appears inconsistent with the definition

- q. _____ should be listed as preparers for the fate and effects studies.

- r. Please provide an updated freedom of information copy purged of all confidential information after the EA has been amended to address the above deficiencies.

In addition, we have the following comments and requests for information.

- 15. Please provide a summary of the population variability of cetirizine kinetics. This should include presentations of histograms by dose of cetirizine, C_{max} and AUC after single and multiple (steady-state) dosing.

- 16. Which enantiomer form of cetirizine is formed when hydroxyzine is given to humans?

- 17. Does each one of the cetirizine enantiomers bind to the same plasma protein?

- 18. What is known about the pharmacokinetics of the enantiomers in humans? Does interconversion occur?

- 19. Has _____ receptors ever been tested? If so, what are the results?

- 20. What is the CNS and cardiac activity of cetirizine's metabolite? We note that in mice, the metabolite influences its general behavior at 2-4 times lower doses than cetirizine.

- 21. For future adverse events where the etiologic factor could be attributed to an immunologic or to an allergic reaction to cetirizine, please document the presence or absence of a positive history of an allergic or immunologic reaction to other piperazine related structures in these patients.

22. Because of the high degree of protein binding of cetirizine, please indicate and submit any in vivo or in vitro data that were generated by examining the displacement by highly protein bound drugs such as phenytoin, carbamazepine, or warfarin of cetirizine.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Also attached for your information is our medical review of this NDA completed on October 22, 1993.

Should you have any questions, please contact:

Mr. Koung Lee
Consumer Safety Officer
Telephone: (301) 594-5712

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ATTACHMENTS (2)

ATTACHMENT

Please note that our labeling additions are underlined and in bold typeface and our comments are in brackets, caps, and bold typeface. All references should be removed.

ANNOTATED PACKAGE INSERT

Zyrtec
cetirizine hydrochloride
Tablets
For Oral Use

DESCRIPTION:

Cetirizine hydrochloride, the active component of Zyrtec tablets, is an orally active and selective H₁-receptor antagonist. The chemical name is (-)-[2-[4-(p-Chloro- α -phenylbenzyl)-1-piperazinyl]ethoxy]acetic acid, dihydrochloride. Cetirizine is a racemic compound with an empirical formula of C₂₁H₂₅ClN₂O₃•2HCl. The molecular weight is 461.8 and the chemical structure is shown below:

Cetirizine hydrochloride is a white, crystalline powder and is water soluble. Zyrtec is formulated in white (dye-free), film-coated, oval tablets for oral administration and is available in 5 and 10 mg strengths. Inert ingredients are: lactose; magnesium stearate; povidone; titanium dioxide, hydroxypropyl methylcellulose, polyethylene glycol; and corn starch.

CLINICAL PHARMACOLOGY

Mechanism Of Action: Cetirizine, a human metabolite of hydroxyzine, is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H₁ receptors. The antihistaminic activity of cetirizine has been documented in a variety of animal and human models. In vivo animal models have shown negligible anticholinergic and antiserotonergic activity. In clinical studies, however, dry mouth was more common with cetirizine than with placebo. In vitro receptor binding studies have shown no measurable affinity for other than H₁ receptors. Autoradiographic studies with radiolabeled cetirizine in the rat have shown negligible penetration of the brain. Ex vivo experiments in

the mouse have shown that systemically administered cetirizine does not significantly occupy cerebral H₁ receptors.

Pharmacokinetics: Cetirizine is rapidly absorbed after oral administration of a tablet, which had bioavailability similar to an oral solution. Food had no effect on the extent of cetirizine absorption, but T_{max} was delayed by 1.7 hours and C_{max} was decreased by 23% in the presence of food. A mass balance study in 6 healthy male volunteers indicated that about 70% of the administered radioactive dose was recovered in the urine and 10% in the feces, for a combined total recovery of about 80%. Approximately 50% of the administered radioactive dose was excreted in the urine as unchanged drug. Cetirizine is metabolized to a very limited extent by oxidative O-dealkylation to a metabolite with negligible antihistaminic activity.

Cetirizine exhibits linear kinetics over the range of 5 to 60 mg. The mean $\pm$ SD terminal half-life is 8.5 $\pm$ 1.2 hours, oral clearance is 54 $\pm$ 13 mL/min, and the apparent volume of distribution is 2.62 $\pm$ 0.13 L/kg. No accumulation was observed for cetirizine following daily doses of 10 mg, for 10 days. The steady-state maximum plasma concentration was 311 $\pm$ 40 ng/mL and was achieved within 1.0 $\pm$ 0.5 hour.

Plasma protein binding of cetirizine is 93 $\pm$ 0.3% and was independent of concentration in the range of 0.025 to 1.0 μ g/mL; this concentration range covers the therapeutic plasma levels.

SPECIAL POPULATIONS

Effect of Age: Following a single 10 mg oral dose, half-life increased by about 50% and clearance decreased by about 40% in elderly subjects (n=16) compared to normal subjects (n=14).

Effect of Gender: No gender-related differences were observed in the kinetics of cetirizine between white adult males (n=86) and white adult females (n=3).

Effect of Race: No race-related differences were observed in the kinetics of cetirizine between white adult males (n=86) and black adult males (n=11).

Renally Impaired Patients: The kinetics of cetirizine were studied following multiple oral daily doses of 10 mg for 7 days in normals (CL_{cr}=89-128 mL/min, n=7), mild (CL_{cr}=42-77 mL/min, n=8) and moderately (CL_{cr}=11-31 mL/min, n=7) renally impaired patients. The pharmacokinetics of the drug were similar in the mild group and normals. Moderately renally impaired patients had a 3-fold increase in half-life and a 70% decrease in clearance compared to normals. Accumulation of cetirizine was also more pronounced in this group.

Following a single oral 10 mg dose of cetirizine, patients on hemodialysis (CL_{cr} < 7 mL/min, n=5) had a 3 fold increase in half-life accompanied by a 70% decrease in clearance. Cetirizine was not completely cleared by

hemodialysis as less than 10% of the administered dose was removed during the dialysis session.

Dosing adjustment is necessary in moderately renally impaired patients (CLcr=11-31 mL/min) and patients on dialysis (CLcr < 7 mL/min). (See also DOSAGE AND ADMINISTRATION)

Hepatically Impaired Patients: Following single oral doses of 10 mg (n=6) and 20 mg (n=10) cetirizine, patients with chronic liver diseases (hepatocellular cholestatic, and biliary cirrhosis) had a 50% increase in half-life along with a 40% decrease in clearance compared to healthy subjects (n=16).

Dosing adjustment may be necessary in hepatically impaired patients. (See also DOSAGE AND ADMINISTRATION)

Drug Interactions

Theophylline: Cetirizine (20 mg QD for 3 days has no effect on theophylline (400 mg QD for 3 days) kinetics, but theophylline increased the half-life of cetirizine by about 50% and decreased its clearance by about 27%. (See also PRECAUTIONS)

Pseudoephedrine: A multiple dose study showed no significant differences in any pharmacokinetic parameters for either cetirizine or pseudoephedrine when they were concomitantly administered to 24 healthy male subjects for 6 days.

Antipyrine: When cetirizine was co-administered with antipyrine to 10 healthy male volunteers for 9 days, no changes were observed in plasma clearance or elimination half-life of antipyrine. Therefore, cetirizine does not alter the oxidative metabolizing enzyme activity in the liver.

Ketoconazole: In a multiple dose study involving 16 healthy male volunteers, the pharmacokinetics of cetirizine (20 mg QD) and ketoconazole (400 mg QD) were not altered when they were given in combination.

Erythromycin: In a multiple dose study involving 16 healthy male volunteers, the pharmacokinetics of cetirizine (20 mg QD) and erythromycin (500 mg Q8h) were not altered when they were given in combination.

Pharmacodynamics: Studies in normal volunteers show that Zyrtec at doses of 5 to 20 mg strongly inhibits the skin wheal and flare caused by the intradermal injection of histamine. The onset of activity occurs within 20 minutes in 50% of subjects and in 95% of subjects within one hour, and this activity persists for at least 24 hours after a single dose [IS THERE AN ADULT STUDY?]. In a 35 day study in children ages _____ to _____, no tolerance to the antihistaminic effects of Zyrtec was found. The effects of intradermal injection of various other mediators or histamine releasers are also inhibited by cetirizine, as is cold-induced

urticaria. In mildly asthmatic subjects, Zyrtec at 5 to 20 mg blocked bronchoconstriction due to nebulized histamine, with virtually total blockade after a 20 mg dose. In addition, the late phase recruitment of eosinophils, neutrophils and basophils, components of the allergic inflammatory response, are inhibited by Zyrtec following cutaneous antigen challenge.

In an electrocardiographic (ECG) study in healthy volunteers, Zyrtec at doses up to 60 mg per day, three times the maximum clinical dose, for 1 week did not prolong QTc intervals. In two clinical trials which included ECG evaluations, there was no clinically significant prolongation of QTc in Zyrtec treated patients. [Data from interaction studies with Zyrtec and ketoconazole and Zyrtec and erythromycin are forthcoming] [PLEASE UPDATE AND MORE FULLY DESCRIBE THE OUTCOME OF THE THREE ECG STUDIES].

Clinical Studies: Eleven multi-center, randomized, double-blind, placebo controlled clinical trials were conducted in the United States; 7 of these support effectiveness, 3 in seasonal allergic rhinitis (1 to 4 weeks in duration), 2 in perennial allergic rhinitis for up to 8 weeks in duration, and 2 in chronic idiopathic urticaria of 4 weeks in duration. Doses of 5-20 mg per day were studied. In general, 20 mg did not give added effectiveness, 10 mg was slightly better than 5 mg in one perennial rhinitis study, but the two were indistinguishable in other studies.

INDICATIONS AND USAGE

Seasonal Allergic Rhinitis: Zyrtec is indicated for the relief of symptoms associated with seasonal allergic rhinitis due to allergens such as ragweed, grass and tree pollens. Symptoms treated effectively include sneezing, rhinorrhea, nasal pruritus, ocular pruritus, tearing and redness of the eyes.

Perennial Allergic Rhinitis: Zyrtec is indicated for the relief of symptoms associated with perennial allergic rhinitis due to allergens such as dust mites, animal dander and molds. Symptoms treated effectively include sneezing, rhinorrhea, post-nasal discharge, nasal pruritus, ocular pruritus and tearing.

Chronic Urticaria: Zyrtec is indicated for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria. It significantly reduces the occurrence, severity and duration of hives and significantly reduces pruritus.

CONTRAINDICATIONS

Zyrtec is contraindicated in patients with a known hypersensitivity to it or any of its ingredients, or to its parent compound, hydroxyzine.

PRECAUTIONS

General: Activities requiring mental alertness in

clinical trials, the occurrence of somnolence has been reported in some patients taking Zyrtec; due caution should therefore be exercised when driving a car or operating potentially dangerous machinery. Concurrent use of Zyrtec with alcohol or other CNS depressants should be avoided because additional reductions in alertness and additional impairment of CNS performance may occur.

Drug-drug interaction: No clinically significant drug interactions have been found with theophylline, pseudoephedrine, or cimetidine. [Data from interaction studies with Zyrtec and erythromycin are forthcoming.] Theophylline is known to exhibit non-linear kinetics. It is possible that if the usual daily doses of theophylline are administered with cetirizine, the influence of theophylline on the kinetics of cetirizine may be more pronounced possibly leading to greater sedation. In clinical trials, Zyrtec has been safely administered with beta-agonists, non-steroidal anti-inflammatory drugs, oral contraceptives, narcotic analgesics, corticosteroids, H₂-antagonists, cephalosporins, penicillins, thyroid hormones and thiazide diuretics [SUBMIT SUPPORT FOR THESE CLAIMS WITH NUMBERS OF CONCOMITANT EXPOSURE TO EACH DRUG AND DURATION OF EXPOSURE].

Carcinogenesis, mutagenesis and impairment of fertility: No evidence of carcinogenicity was observed in 2-year carcinogenicity study in rats at dietary doses up to 20 mg/kg/day (15 times the recommended human dose on a mg/m²/day basis). An increased incidence of benign liver tumors was found in a 2-year carcinogenicity study in male mice at a dietary dose of 16 mg/kg/day (6 times the recommended human dose on a mg/m²/day basis). The clinical significance of these findings during long-term use of Zyrtec Tablets is not known. Cetirizine was not mutagenic in Ames test, and not clastogenic in human lymphocyte assay, mouse lymphoma assay, and in vivo micronucleus test in rats. No impairment of fertility was found in a fertility and general reproductive performance study in mice at a dose of 64 mg/kg/day (26 times the recommended human dose on a mg/m²/day basis).

Pregnancy Category B: Cetirizine has not been shown to be teratogenic in mice, rats and rabbits at doses up to 96, 225, and 135 mg/kg/day (or 40, 180, and 216 times the recommended human dose on a mg/m²/day basis), respectively. There are no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, Zyrtec should be used in pregnancy only if clearly needed.

Nursing Mothers: Retarded pup weight gain was found in mice during lactation when dams were given cetirizine at 96 mg/kg/day (40 times the recommended human dose on a mg/m²/day basis). Studies in beagle dogs indicated that approximately 3% of the dose is excreted in milk. Because many drugs are excreted in human milk, use of Zyrtec in nursing mothers is

not recommended.

Geriatric Use: The safety and efficacy of Zyrtec has been demonstrated in patients 65 years and older. As with the general population, clearance of Zyrtec is reduced in proportion to creatinine clearance.

ADVERSE REACTIONS

Controlled and uncontrolled clinical trials included more than 6000 patients, with more than 3800 receiving Zyrtec at doses of 5 to 20 mg per day; the duration of treatment ranged from 1 week to 6 months. In addition, there were more than 1400 Zyrtec treated patients in foreign clinical trials.

Most adverse reactions reported during therapy with Zyrtec were mild or moderate. In placebo-controlled trials, the incidence of discontinuations due to adverse reactions in patients receiving Zyrtec was not significantly different from placebo (2.9% vs 2.4%, respectively). There was no difference by gender or by body weight with regard to the incidence of adverse reactions. [PLEASE REASSESS THE LAST SENTENCE IN TERMS OF THE INTEGRATED SAFETY SUMMARY UPDATE AND INCLUDE ANALYSIS IN TERMS OF RACE.]

The most common adverse reactions were headache and somnolence. The incidence of headache associated with Zyrtec was not different from placebo. The incidence of somnolence associated with Zyrtec was dose related and, predominantly, mild to moderate. The incidence of somnolence in fixed dose studies was 6% in placebo, 11% at 5 mg, 14% at 10 mg, and 20% at 20 mg. Discontinuations due to somnolence for Zyrtec were not significantly different from placebo (1.1% vs 0.5%, respectively).

Table 1 lists adverse experiences which were reported for Zyrtec in controlled clinical trials in the United States.

Table 1. Adverse Reactions Reported in Placebo-Controlled United States Zyrtec Trials at Rates of 1% or Greater and More Frequently than in the Placebo Group.
(Percent Incidence)

<u>Adverse Experience</u>	<u>Zyrtec</u> <u>(N=2513)</u>	<u>Placebo</u> <u>(N=1501)</u>
<u>Somnolence</u>		
Fatigue	5.6	2.7
Dry Mouth	5.3	2.4

[TABLE 1 SHOULD INCLUDE ALL ADRs, WHETHER OR NOT CONSIDERED DRUG-RELATED.]

In addition to the events in Table 1, headache, nausea, , and were seen at rates above 1% but were more frequent in the placebo group.

The following events were observed infrequently (equal to or less than 1%), but more than once, in 3810 patients who received Zyrtec in all U.S. trials, including an open study of six months duration; a causal relationship with Zyrtec administration has not been established. [PLEASE REVISE THE LIST AS TABLE 1 IS REVISED]

Autonomic Nervous System: anorexia, flushing, increased appetite, increased sweating
Cardiovascular: palpitations, tachycardia
Central and Peripheral Nervous Systems: hyperkinesia, hypertonia, migraine, paresthesia, tremor
EENT: abnormal vision, altered sense of taste, conjunctivitis, epistaxis, eye abnormality, eye pain, periorbital edema, pharyngitis, tinnitus, tongue disorder
Gastrointestinal: constipation, dyspepsia, flatulence
Genitourinary: polyuria, urinary retention, urinary tract infection
Musculoskeletal: arthralgia, back pain, bone disorder (fracture), leg cramps, myalgia
Psychiatric: agitation, anxiety, confusion, depression, emotional lability, insomnia, impaired concentration, nervousness, paranoia
Respiratory System: bronchospasm, coughing, dyspnea, upper respiratory tract infection
Skin: furunculosis, dry skin, rash, skin disorder
Body as a Whole: asthenia, chest pain, decreased libido, dizziness, dysmenorrhea, edema, fever, pain, rigors, thirst, weight increase

Occasional instances of transient, reversible hepatic transaminase elevations have occurred during cetirizine therapy, without evidence of jaundice, hepatitis or other clinical findings.

In foreign marketing experience the following additional rare, but potential severe adverse events have been reported: hemolytic anemia, thrombocytopenia, orofacial dyskinesia, severe hypotension, anaphylaxis, hepatitis, and glomerulonephritis. [PLEASE ALSO INCLUDE ANY OTHER SERIOUS ADVERSE EVENT(S) THAT HAS (HAVE) BEEN THE SUBJECT OF THE LETTERS TO INVESTIGATORS USING CETIRIZINE UNDER THE INDs, WHERE CETIRIZINE'S ROLE CANNOT BE EXCLUDED.]

DRUG ABUSE AND DEPENDENCE

There is no information to indicate that abuse or dependency occurs with Zyrtec.

OVERDOSAGE

Overdose has been reported with cetirizine in one patient who took 150 mg of cetirizine. The patient was somnolent but did not display any other signs or abnormal blood chemistry or

hematology results. Should it occur, treatment should be symptomatic or supportive, taking into account any concomitantly ingested medications. There is no known specific antidote to cetirizine. Cetirizine is not effectively removed by dialysis and dialysis will be ineffective unless a dialyzable agent has been concomitantly ingested. The minimal lethal dose in rodents is approximately 100 times the maximum recommended clinical dose on a mg/m² basis and the liver was the target organ of toxicity.

DOSAGE AND ADMINISTRATION

The recommended initial dose of Zyrtec is 5 or 10 mg, depending on symptom severity, given as a single daily dose, with or without food. Most patients in clinical trials started at 10 mg. The time of administration may be varied to suit individual patient needs.

In patients with decreased renal function (CLcr=11-31 mL/min), patients on hemodialysis (CLcr < 7 mL/min), and hepatically impaired patients, a dose of 5 mg QD is recommended.

HOW SUPPLIED:

Zyrtec tablets are white (dye free), film coated, oval-tablets containing 5 mg or 10 mg cetirizine hydrochloride.

5 mg tablets are engraved with "PFIZER" on one side and with "550" on the other.

Bottles of 100: (NDC 0069-5500-66)

10 mg tablets are engraved with "Zyrtec" on one side and with "10 MG" on the other.

Bottles of 100: (NDC 0069-5510-66)

STORAGE: Store at room temperature 59⁰ to 86⁰ F (15⁰ - 30⁰ C).

SECTION 14

PATENT CERTIFICATION

Pfizer certifies that cetirizine which is the subject of this application (NDA #19-835) and the tablet formulation of cetirizine claimed by the patent provided in Section 13 of this NDA is the subject of the approval being sought under Section 505 of the Federal Food, Drug and Cosmetic Act.

SECTION 13

PATENT INFORMATION

<u>U.S. Patent No.</u>	<u>Expiration Date</u>	<u>Description</u>
4,525,358	June 25, 2002	Cetirizine and Pharmaceutical compositions

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 19-855 Trade (generic) names Zytec (Cytarabine HCl 5mg + 10mg)

Check any of the following that apply and explain, as necessary, on the next page:

1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.
2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.
- a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.
- b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)
3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).
- a. The applicant has committed to doing such studies as will be required.
- (1) Studies are ongoing.
- (2) Protocols have been submitted and approved.
- (3) Protocols have been submitted and are under review.
- (4) If no protocol has been submitted, on the next page explain the status of discussions.
- b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

Page 2 -- Drug Studies in Pediatric Patients

b. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

[Lined area for handwritten explanation]

Thomas Lee
Signature of Preparer

11-27-95
Date

cc: Orig NUA
MFU- /Div File
NUA Action Package

EXCLUSIVITY SUMMARY FOR NDA # 19-835 SUPPL# _____

Trade Name Zyrtec Tablet Generic Name cetirizine 5 mg and 10 mg

Applicant Name Pfizer HFD# 570

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA? YES / / NO / /

b) Is it an effectiveness supplement? YES / / NO / /

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.") YES / / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / / NO / ✓ /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength and route of administration, previously been approved by FDA for the same use?

YES / / NO / ✓ /

If yes, NDA # _____

Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / ✓ /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / / NO / ✓ /

If "yes" identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA _____

NDA _____

NDA _____

2. Combination product

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / _ / NO / _ /

I "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA _____

NDA _____

NDA _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer to "yes", then skip to question 3(a). If the answer to 3(a) is "yes" for any investigations referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCK ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / NO / /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion?

YES / / NO / /

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / / NO / /

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES / / NO / /

Investigation #2 YES / / NO / /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES / / NO / /

Investigation #2 YES / / NO / /

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by "the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the for FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	!	
IND #_____ YES /___/	!	NO /___/ Explain: _____
	!	_____
Investigation #2	!	
IND #_____ YES /___/	!	No /___/ Explain: _____
	!	_____

(b) For each investigation not carried out under an IND or which the applicant was not identified as the sponsor, did applicant certify that it or the applicant's predecessor interest provided substantial support for the study?

Investigation #1	!	
YES / / Explain: _____	!	NO / / Explain: _____
_____	!	_____
_____	!	_____
Investigation #2	!	
YES / / Explain: _____	!	NO / / Explain: _____
_____	!	_____
_____	!	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

 Young Lee

Signature

Title: Consumer Safety Officer

 11-17-95

Date

 [Signature]

Signature of Office/
Division Director

 11/22/95

Date

cc: Original NDA 19-835

Division File HFD-570

HFD-84 Mary Ann Holovac

Medical Officer Review

NDA 19835

Drug : Cetirizine tablets

Correspondence: 1) N(BL)10/4/95

Sponsor's response to the Agency's telephone facsimile dated September 29, 1995 regarding the revised labeling for this product.

2) CSO Preliminary Labeling Review dated October 20, 1995

Date: October 24, 1995

Medical Officer Reviewer: Ana M. Saavedra-Delgado, M.D.

The Sponsor's labeling dated 10/4/95 was reviewed against the Agency's labeling dated September 29, 1995. *10/24/95*

The changes made by the Sponsor to the Agency's revised labeling dated September 29, 1995 have been captured in the CSO preliminary review dated October 20, 1995. *Noted. See comments on package insert in my memo m. Saavedra 11/9/95*

Changes were also made to the labeling by the Sponsor in response to the Agency's request to provide QTC measurements in the labeling using the Bazett correction. These changes were checked by the medical reviewer and they appear to be correct.

1. The numerical figures for the estimated ketoconazole and cetirizine effect using the Bazett correction in this labeling revision (10/04/95) correspond to those listed in Table E.1.2, September 30, 1993 (attached).

2. The numerical figure for the estimated effect of the combination using the Hodges correction is not given in Table E.1.2. In the 9/30/93 submission, the section Statistical Methods for Change from Baseline pages 15 and 16 and the section in Results-Mean QT Interval pages 18 and 19, describe how the effect of the combination was estimated using the Hodges correction. A copy of Table E.1.1. from the 9/30/93 submission using the Hodges correction, as well as copies of pages 15, 16, 18, and 19 are provided for the comparison. The same method would be used to estimate the effect of the combination using the Bazett correction.

Reference is made to the comments and recommendations made in the Medical Officer Review (10/17/95) of the sponsor's response to the approvable letter of 2/21/95 and to the proposed labeling. No further changes to the labeling are recommended at this time.

PROTOCOL 92CK16-0603: A MULTIPLE DOSE STUDY TO DETERMINE THE INTERACTION OF CETIRIZINE WITH KETOCONAZOLE IN YOUNG HEALTHY MALES

TABLE E.1.2
STATISTICAL ANALYSIS OF CHANGE FROM BASELINE BAZETT QTC (AVERAGED OVER HOUR OF DAY)

OBSERVED MEAN ± STD DEVIATION BY TREATMENT AND ESTIMATED DRUG EFFECTS

TREATMENT PERIOD	PLACEBO/ CETIRIZINE ¹ ³	KETOCONAZOLE/ COMBINATION ² ³	ESTIMATED KETOCONAZOLE EFFECTS	ESTIMATED OVERALL KETO EFFECTS
BASELINE	390.36± 13.52	388.09± 18.16		
CHANGE				
DAY 6 W/O CETIRIZINE	1.07± 6.69	7.22± 10.10	6.14	
DAY 16 WITH CETIRIZINE	7.98± 10.35	18.43± 15.07	10.46	8.30 (P=.031)
ESTIMATED CETIRIZINE EFFECTS BY REGIMEN	6.90	11.22		
ESTIMATED OVERALL CETIRIZINE EFFECT		9.06 (P=.001)		

ANALYSIS OF VARIANCE(SAS TYPE III MS)

EFFECT	DF	MEAN SQUARE	F-RATIO ⁴	P-VALUE	P-VALUES FOR DIRECT PAIRWISE COMPARISONS OF COMPONENTS AND COMBINATION			
					CETIRIZINE	KETOCONAZOLE	COMBINATION	
SUBJECT	14	186.29	2.62	.041				
KETOCONAZOLE	1	1833.70	5.78	.031				
SUBJ#KETO	14	178.89	2.51	.048				
CETIRIZINE	1	1230.96	27.63	.001	PLACEBO	.042	.066	.080
SUBJ#CETIR	14	44.55	0.63	.004	CETIRIZINE		.809	.004
KETO#CETIR	1	69.84	0.98	.339	KETOCONAZOLE			.003
SUBJ#KETO#CETIR	14	71.16						

¹SUBJECTS RECEIVED PLACEBO FOR THE FIRST FIVE DAYS AND THEN RECEIVED CETIRIZINE FOR AN ADDITIONAL TEN DAYS

²SUBJECTS RECEIVED KETOCONAZOLE FOR THE FIRST FIVE DAYS AND THEN RECEIVED COMBINATION FOR AN ADDITIONAL TEN DAYS

³SUBJECTS RECEIVED BOTH REGIMENS WITH INTERVENING WASHOUT IN CROSSOVER FASHION

⁴EFFECTS ARE TESTED AGAINST CORRESPONDING MS FOR INTERACTION WITH SUBJECT.

PROTOCOL 92CK16-0603: A MULTIPLE DOSE STUDY TO DETERMINE THE INTERACTION OF CETIRIZINE WITH KETOCONAZOLE IN YOUNG HEALTHY MALES

TABLE E.1.1
STATISTICAL ANALYSIS OF CHANGE FROM BASELINE HODGES QTC (AVERAGED OVER HOUR OF DAY)

OBSERVED MEAN ± STD DEVIATION BY TREATMENT AND ESTIMATED DRUG EFFECTS

TREATMENT PERIOD	PLACEBO/ CETIRIZINE ¹ ³	KETOCONAZOLE/ COMBINATION ² ³	ESTIMATED KETOCONAZOLE EFFECTS	ESTIMATED OVERALL KETO EFFECTS
BASELINE	386.16± 14.73	385.13± 15.69		
CHANGE				
DAY 6 W/O CETIRIZINE	-2.32± 5.21	4.91± 9.69	7.23	
DAY 16 WITH CETIRIZINE	4.75± 9.73	14.15± 12.17	9.41	8.32 (P=.028)
ESTIMATED CETIRIZINE EFFECTS BY REGIMEN				
	7.07	9.24		
ESTIMATED OVERALL CETIRIZINE EFFECT				
		8.15 (P=.001)		

ANALYSIS OF VARIANCE(SAS TYPE III MS)

EFFECT	DF	MEAN SQUARE	F-RATIO ⁴	P-VALUE	P-VALUES FOR DIRECT PAIRWISE COMPARISONS OF COMPONENTS AND COMBINATION		
					CETIRIZINE	KETOCONAZOLE	COMBINATION
SUBJECT	14	115.14	2.48	.051			
KETOCONAZOLE	1	1037.90	5.98	.028			
SUBJ#KETO	14	173.58	3.73	.010			
CETIRIZINE	1	997.31	34.92	.001	PLACEBO	.013	.000
SUBJ#CETIR	14	28.56	0.61	.814	CETIRIZINE	.948	.002
KETO#CETIR	1	17.77	0.38	.546	KETOCONAZOLE		.002
SUBJ#KETO#CETIR	14	46.51					

¹SUBJECTS RECEIVED PLACEBO FOR THE FIRST FIVE DAYS AND THEN RECEIVED CETIRIZINE FOR AN ADDITIONAL TEN DAYS

²SUBJECTS RECEIVED KETOCONAZOLE FOR THE FIRST FIVE DAYS AND THEN RECEIVED COMBINATION FOR AN ADDITIONAL TEN DAYS

³SUBJECTS RECEIVED BOTH REGIMENS WITH INTERVENING WASHOUT IN CROSSOVER FASHION

⁴EFFECTS ARE TESTED AGAINST CORRESPONDING MS FOR INTERACTION WITH SUBJECT.

6. Also the hour 30, 36 and 48 post-dose recordings associated with treatment day 16 were redefined as hour 6, 12 and 24 of day 17. Note that day 17 was not a dosing day.

3. Statistical Methods for Change From Baseline

Changes in Hodges QTc, as well as changes in Bazett QTc, uncorrected QT and RR interval, were analyzed comparatively among treatments using analysis of variance procedures appropriate to a mixed random and fixed effects model. The analysis focused on the changes from day 1 to treatment day 6 and 16 since ECG recordings were made at every hour corresponding to baseline day (day 1). Day 6 is the last day of dosing with either placebo or ketoconazole alone, and day 16 is the last day of dosing after cetirizine was added to the treatment regimen for 10 days. For completeness, plots of mean Hodges QTc for each hour separately are provided in Appendix E.4, showing mean QTc for all days on which ECGs were recorded at the particular hour. The study design allowed for the parameterization of the statistical model as a factorial model consisting of an overall effect of ketoconazole, an overall effect of cetirizine, and the drug interaction effect of cetirizine and ketoconazole. These terms are defined as follows (refer to Table 3 for a diagrammatic representation).

As described in Section IV.A, each subject received both 15-day treatment regimens: placebo on treatment phase day 2 through 6 followed immediately by cetirizine alone on days 7 through 16; and ketoconazole alone on day 2 through 6 followed by combination treatment on days 7 through 16. The overall ketoconazole effect is the mean of the following two effect estimates: (K1) the mean difference between ketoconazole alone and placebo at day 6 when no cetirizine is present, and (K2) the mean difference between the combination and cetirizine alone at day 16. Similarly, the overall cetirizine effect is the mean of the following two effect estimates: (C1) the mean difference between cetirizine alone at day 16 and placebo at day 6 within the treatment regimen that does not include ketoconazole, and (C2) the mean difference between the combination at day 16 and ketoconazole alone at day 6 within the regimen including ketoconazole throughout. When the effects of K1 and K2 are identical then the overall effect estimate measures the ketoconazole effect independent of cetirizine. Likewise, when the effects of C1 and C2 are identical then the overall effect estimate measures the cetirizine effect independent of ketoconazole. Otherwise, the effect of component drug alone can only be estimated from K1 and C1.

The drug interaction term measures the amount by which the ketoconazole effect when cetirizine is present differs from the effect without concurrent cetirizine, and is estimated by $K2 - K1$. Identically, the drug interaction is the amount by which the cetirizine effect when ketoconazole is administered concurrently differs from the effect without ketoconazole present, and is identically estimated by $C2 - C1$. When the drug interaction term is equal to zero, the total effect of combination treatment on change in QTc is equal to the sum of the overall component effects.

It is important to note that the cetirizine effect cannot be separated from a serial measurement effect, i.e., a time effect from day 6 to day 16. Likewise, the drug interaction effect cannot be separated from a cumulative effect of fifteen days of ketoconazole treatment.

An initial statistical model was examined to ascertain whether effects were consistent over the eight recording hours. With respect to Hodges QTc change from baseline no significant variation across hours and no drug by hour interactions were statistically significant indicating that effects could be averaged over hours. Details of this analysis are provided in Appendix E.3.

Because of this consistency the change from baseline was averaged over hours and the average changes were analyzed (see Appendix F.1 for a listing of these averages on day 6 and day 16) in order to simplify the model. Therefore the primary model included the random effect of subject, the overall effect of ketoconazole, the overall effect of cetirizine, and the drug interaction along with the interactions of each fixed effect with subject. The error term for testing the significance of any effect in the model is the mean square for the corresponding interaction with subject. The ketoconazole effect, the cetirizine effect and the interaction effect were declared statistically significant if the associated F-statistic was greater than or equal to the 5% critical value of the F-distribution. The sums of squares in each analysis were computed using SAS PROC GLM.

4. QTc Prolongations of 10% Over Baseline

The number of subjects experiencing prolongations of 10% over baseline Hodges QTc was computed and summarized for each of the component treatments and the combination. Each subject was counted only once for each treatment regardless of the number of occurrences of 10% prolongation. However, the likelihood of observing at least one event is not constant among the treatments since only 10 ECG recordings were scheduled during the first 5 days of each treatment regimen when subjects were on placebo or ketoconazole only treatment, but 16 or 24 were scheduled during the next 10 days, during study phase I and study phase II respectively, when subjects received cetirizine or combination treatment. All 16 subjects who received study medication were included in this account, including subject 13 who discontinued early.

B. Adverse Experiences

All reported adverse experiences were coded according to the WHO dictionary preferred term and entered into the clinical database, along with the onset and resolution date, severity and probable cause. A summary table presenting the incidence of adverse experiences by study drug administered was prepared, and is discussed in Section VIII.C. In this table, adverse experiences are assigned to the treatment the subject was taking on the study date when the adverse experience occurred. If an adverse experience had a duration over several study dates on which the subject received different treatments, the adverse experience was counted once for each treatment. Multiple episodes of an adverse experience are counted once per

study phase I.

For the statistical analysis, the cetirizine and ketoconazole pharmacokinetic parameters were analyzed independently. Cetirizine parameters for cetirizine administered alone (day 16) were compared to those estimated on combination dosing (day 16), following ketoconazole pretreatment. Ketoconazole parameters were compared between ketoconazole alone (day 6) and with cetirizine added (day 16). For each parameter, only subjects with values for both treatments were used in the statistical analyses. The analysis of variance was performed on the logarithms of the pharmacokinetic parameters. The results of the ANOVA were used to compute 90% confidence intervals for the ratios of C_{max} and AUC(24) means between administration of each of the drugs alone and in combination.

A detailed description of the pharmacokinetic analysis and statistical analysis methodology are presented in Appendix L.

VI. Subject Disposition

Sixteen normal volunteers were randomized to treatment sequence groups. One subject (#13) was discontinued on the second day of study phase II because his baseline drug screen was positive (Table 1). All of the remaining 15 subjects completed the study.

VII. Subject Demographic and Baseline Characteristics

The study population consisted of 12 Hispanic males, 2 white males and 2 black males, between 22 and 40 years old with a mean age of 30.0 years. The average weight was 156.5 lbs, ranging from 142 to 182 lbs. At the screening visit all the subjects had normal blood pressures, between 98 and 130 mmHg systolic, and 66 and 84 mmHg diastolic; and normal heart rate, between 60 and 86 beats per minute. Table 2 shows demographic characteristics and screening vital signs for the subjects in the study.

VIII. Results

A. ECG Measurements

1. Mean QT Interval

Table 3 shows a synopsis of the results of the analysis of change from baseline Hodges QTc. Mean changes are shown for placebo, cetirizine alone, ketoconazole alone and combination treatment. The estimates of the ketoconazole effects (K1 and K2) and the cetirizine effects (C1 and C2) are shown along with the estimates of the overall effect of each drug and the estimate of the interaction effect. Details of the analysis are shown in Appendix E.1. Figure 1 shows a plot of mean Hodges QTc (not changes from baseline) for each treatment on day 6 and 16 and also for baseline placebo day 1 of each regimen.

There was no statistically significant drug interaction effect on the change from baseline Hodges QTc. The mean difference (C1) between treatment with cetirizine alone and placebo treatment was 7.07 msec as compared to the mean difference (C2) between combination treatment and treatment with ketoconazole alone of 9.24 msec. The estimated drug interaction effect is $9.24 \text{ msec} - 7.07 \text{ msec} = 2.17 \text{ msec}$. Similarly, the mean difference (K1) between ketoconazole alone and placebo was 7.23 msec compared to a mean difference (K2) of 9.40 msec between the combination and cetirizine alone, which alternatively estimate the interaction of 2.17 msec. The estimated drug interaction effect of 2.17 msec is not statistically significantly different from zero. This indicates that the overall component drug effects, 8.16 msec for cetirizine and 8.32 msec for ketoconazole estimate the effect of each component drug alone (respectively) independent of the presence of the other. Each overall effect estimate is significantly different from zero. Additionally, the total effect of combination treatment is characterized as an additive effect of the individual drugs, but having no enhanced effect over the sum, and is estimated by $8.16 \text{ msec} + 8.32 \text{ msec} = 16.48 \text{ msec}$.

2. Incidence of Prolongations of 10% Over Baseline Hodges QTc

Table 4 summarizes the subject incidence of at least one occurrence of a prolongation of 10% over baseline Hodges QTc. No subject experienced a 10% prolongation during the 5 day placebo treatment. Seven subjects experienced at least 1 prolongation. Two subjects (13.3%) experienced an event during the 10 day cetirizine treatment, 1 subject (6.3%) during the 5 day ketoconazole treatment and 5 subjects (31.3%) had an occurrence during combination treatment (2 in study phase I and 3 in study phase II). A list of specific subjects is provided in Table 5.

3. Clinical Significance

As reported, this analysis is based on Hodges correction. The literature on this subject has primarily reported QT changes corrected according to Bazett's formula. The following discussion of clinical relevance of study results will be based on QT corrected according to Bazett's formula, in order to facilitate literature comparison (*ref*: Appendix E.1 for statistical analysis and Appendix F.2 for data listing). Review of the literature shows that a normal human subject may have changes in QTc duration varying by 15 to 70 msec (*Am J Cardiol* 1991; 67:774). The maximum in Bazett QTc change for all subjects in this study was 57 msec (Subject #14, Phase 2, Day 16, Hour 0: QTc = 422 msec). This result is well within the normal range. Thus, neither cetirizine alone nor in combination with ketoconazole was associated with a clinically significant change in Bazett QTc.

The listing of ECG measurements and changes from baseline are shown in Appendix F2. Using the criterion of QTc > 440 msec (*Am J Cardiol* 1991; 67:774) to identify abnormal QTc results, three subjects met this criterion, as shown below. The QTc changes were not sustained and occurred during

Addendum #1 to Medical Officer Review dated 10/17/95

NDA 19835

Drug: Cetirizine tablets (Zyrtec)

Sponsor: Pfizer

Date: November 3, 1995

Subject: Revisions to Medical Officer Review dated 10/17/95
incorporating Dr. Marty Himmel's recommendations.

Review of the sponsor's response via telephone
facsimile dated November 2, 1995 to our request for
further information of a patient with elevated liver
transaminases (annual report for IND dated
9/25/95).

Medical Officer Reviewer: Ana M. Saavedra-Delgado, M.D.

Section 1 of this addendum contains the revisions to the original *4/3/95*
Medical Officer Review to the NDA dated 10/17/95. The original
pages are followed by the revised pages. The changes made are
bolded and underlined.

Section 2 describes the case with elevated transaminases and
includes the review of the annual report to the IND as
Appendix 1 and the sponsor's telephone facsimile response as
Appendix 2.

*See supervisor's
memo.
on 11/9/95*

CC:

Original NDA 14-835-

HFD-570/D.v. Files

HFD-570/M.H.m.c.1

HFD-570/A. Saavedra-Delgado

HFD-570/K. Lee

Section 1

Outline and Table of Contents of this review:

Section 1.

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Outline and Table of Contents of this review:

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Section 3

- I. Revised package insert faxed to the sponsor September 29, 1995.

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- II. Reviewer's general comments and regulatory recommendations.

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No MO reviewer's comments were made to the sponsor's response to questions 4, 6b, 6d, and 6e, 9, 19 and 21 of the approvable letter; they were found to be acceptable. The sponsor's response or salient points of the response were included in these sections. Comments to the sponsor's response to questions 15, 17, 19 and 20 are part of the reviews from the pertinent disciplines (Pharmacology or Biopharm).

Study 90CK16-0497

Multiple dose, placebo controlled crossover study, third party blinded and a wash-out of 5 days. Subjects (24, males, 24 white, 1 black) received placebo for 2 days before receiving either 20 or 60 mg of cetirizine for 7 days.

Placebo Pt.# (# events, max. %prolongation, * = > 440 msec)	Cet 20 mg Pt.#(# events, max. % prolongation, * = > 440 msec)	Cet 60 mg Pt.# (# events, max. %prolongation, * = > 440 msec)
5 (1, 15.6)		
10 (1, 11.7*)	10 (1, 11.0)	10 (1, 11.4)
		11 (1, 11.2*)
12 (1, 12.9)	12 (1, 12.0*)	
16 (1, 11.3)		16 (5, 15.4,(1/5*)
		18 (1, 13.5)
19 (3, 13.4,(1/3*)		19 (2,12.0)
20 (1,13.3)	20 (2, 11.5)	
		21 (1, 11.6)
	22 (4, 19.0,(1/4*-481msec)	
Totals: 6 patients, 8 events 15.6%- max prolongation	Totals: 4 patients, 8 events 19.0%- max prolongation	Totals: 6 patients, 11 events 15.4%- max prolongation

NEW**Study 90CK16-0497**

Multiple dose, placebo controlled crossover study, third party blinded and a wash-out of 5 days. Subjects (24, males, 24 white, 1 black) received placebo for 2 days before receiving either placebo, 20 or 60 mg of cetirizine for 7 days.

Placebo Pt.# (# events, max. %prolongation, * = >440 msec)	Cet 20 mg Pt.#(# events, max. % prolongation, * = >440 msec)	Cet 60 mg Pt.# (# events, max. %prolongation, * = >440 msec)
5 (1, 15.6)		
10 (1, 11.7*)	10 (1, 11.0)	10 (1, 11.4)
		11 (1, 11.2*)
12 (1, 12.9)	12 (1, 12.0*)	
16 (1, 11.3)		16 (5, 15.4,(1/5*)
		18 (1, 13.5)
19 (3, 13.4,(1/3*)		19 (2,12.0)
20 (1,13.3)	20 (2, 11.5)	
		21 (1, 11.6)
	22 (4, 19.0,(1/4*-481msec)	
Totals: 6 patients, 8 events 15.6%- max prolongation	Totals: 4 patients, 8 events 19.0%- max prolongation	Totals: 6 patients, 11 events 15.4%- max prolongation

Incidence of psychiatric disorders adverse experiences in placebo controlled studies by duration of treatment.

Adverse experience	cet up to 2 wks No. Pts (%)	cet 3-4 wks	cet 5-12 wks	placebo up to 2 wks	placebo 3-4 wks	placebo 5-12 wks
Total No. of Pts	2676	1835	957	1671	1147	586
N. of Pts with any Psychiatric Disorders	425 (15.9%)	160 (8.7%)	82 (8.6%)	133 (8.0%)	45 (3.9%)	22 (3.8%)
Somnolence	374 (14.0%)	135 (7.4%)	71 (7.4%)	96 (5.8%)	32 (2.8%)	17 (3.0%)
Concentration impaired	5 (0.2%)	0 (0%)	1 (0.1%)	1 (0.1%)	0 (0%)	0 (0%)
Emotional liability	3 (0.1%)	2 (0.1%)	3 (0.3%)	0 (0%)	0 (0%)	0 (0%)
Depression	4 (0.2%)	2 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.2%)
Thinking abnormal	4 (0.2%)	3 (0.2%)	2 (0.2%)	0 (0%)	0 (0%)	0 (0.0%)

* A patient can have an adverse experience reported for more than one interval of cetirizine therapy.

Agree with the sponsor's conclusion that somnolence accounts with the majority of the incidence of the reports in this category. The above series of tables also demonstrate that at doses of 5 and 10 mg it is approximately double the reported incidence in placebo treated patients (Table F8. B2-B3) and that this incidence persists at the different time intervals: up to 2 weeks, 3-4 weeks and 5-12 weeks of treatment (Table F8. B-4).

The reported incidence rates of other adverse events such as: concentration impaired, emotional liability and thinking abnormal are less than 1% but they are reported more frequently and for a longer duration than in placebo treated patients.

NEW

Incidence of psychiatric disorders adverse experiences in placebo controlled studies by duration of treatment.

Adverse experience	cet up to 2 wks No. Pts (%)	cet 3-4 wks	cet 5-12 wks	placebo up to 2 wks	placebo 3-4 wks	placebo 5-12 wks
Total No. of Pts	2676	1835	957	1671	1147	586
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Concentration Impaired	5 (0.2%)	0 (0%)	1 (0.1%)	1 (0.1%)	0 (0%)	0 (0%)
Emotional liability	3 (0.1%)	2 (0.1%)	3 (0.3%)	0 (0%)	0 (0%)	0 (0%)
Depression	4 (0.2%)	2 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.2%)
Thinking abnormal	4 (0.2%)	3 (0.2%)	2 (0.2%)	0 (0%)	0 (0%)	0 (0.0%)

* A patient can have an adverse experience reported for more than one interval of cetirizine therapy.

Agree with the sponsor's conclusion that somnolence accounts for the majority of the incidence of the reports in this category. The above series of tables also demonstrate that at doses of 5 and 10 mg it is approximately double the reported incidence in placebo treated patients (Table F8. B2-B3) and that this incidence persists at the different time intervals: up to 2 weeks, 3-4 weeks and 5-12 weeks of treatment (Table F8. B-4).

The reported incidence rates of other adverse events such as: concentration impaired, emotional liability and thinking abnormal are less than 1% but they are reported more frequently and for a longer duration than in placebo treated patients.

Even though the % of patients reporting increase in appetite is greater for those treated with 5 mg, the % of patients reporting a weight increase is greater for those patients that had been treated with the 10 mg tablet.

Adverse experience	Cet 5 mg up to 2 wks	Cet 5 mg 3-4 wks	Cet 5 mg 5-12 wks	Cet 5 mg 15wks to 6 mo
Total No. of pts	539	397	273	34
Total No. of pts with adverse experiences	214 (36.3%)	98 (24.7%)	75 (27.5%)	11 (32.4%)
fatigue	18 (3.1%)	9 (2.3%)	8 (2.9%)	0 (0%)
weight increase	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)
Adverse experience	Cet 10 mg up to 2 wks	Cet 10 mg 3-4 wks	Cet 10 mg 5-12 wks	Cet 10 mg 15wks to 6 mo
Total No. pts.	1961	1225	529	69
Total No. of pts with adverse experiences	758 (38.7%)	312 (25.5%)	139 (26.3%)	13 (18.9%)
fatigue	102 (5.2%)	48 (3.9%)	14 (2.7%)	1 (1.5%)
weight increase	9 (0.5%)	11 (0.9%)	10 (1.9%)	3 (4.4%)

The reports of weight increase during longer duration of treatment are more apparent in the higher dose group.

In these listings, the following are noted, in parenthesis, duration of exposure:

Diabetes Mellitus: 5mg dose at the 5-12 week interval (1)
 Polyuria: 10 mg (up to 2 wks) (4), 3-4 wks) (1)
 Purpura: 5 mg dose at the 3-4 week interval (1) and 5-12 wk interval (1)
 Purpura: 10 mg (up to 2 weeks) (1)
 Hematuria: 10 mg (3-4 weeks) (1)
 Ocular hemorrhage: 10 mg (up to 2 weeks) (1)
 visual field defect: 10 mg (up to 2 weeks) (1)
 vision abnormal: 5 mg (up to 2 wks) (2), (3-4 weeks) (1)
 vision abnormal: 10 mg (up to 2 wks) (2), (3-4 weeks) (1)
 Ptosis: 10 mg (up to 2 weeks) (1) and (3-4 weeks) (1)
 Tinnitus: 5 mg (up to 2 weeks) (1)
 Tinnitus: 10 mg (up to 2 weeks) (1), (3-4 wk) (1), 5-12 wks) (1)

New Reviewer's comments: Even though the % of patients reporting increase in appetite is greater for those treated with 5 mg, the % of patients reporting a weight increase is greater for those patients that had been treated with the 10 mg tablet.

Adverse experience	Cet 5 mg up to 2 wks	Cet 5 mg 3-4 wks	Cet 5 mg 5-12 wks	Cet 5 mg 15wks to 6 mo
Total No. of pts	589	397	273	34
Total No. of pts with adverse experiences	214 (36.3%)	98 (24.7%)	75 (27.5%)	11 (32.4%)
fatigue	18 (3.1%)	9 (2.3%)	8 (2.9%)	0 (0%)
weight increase	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)
Adverse experience	Cet 10 mg up to 2 wks	Cet 10 mg 3-4 wks	Cet 10 mg 5-12 wks	Cet 10 mg 15wks to 6 mo
Total No. pts	1961	1225	529	69
Total No. of pts with adverse experiences	758 (38.7%)	312 (25.5%)	139 (26.3%)	13 (18.9%)
fatigue	102 (5.2%)	48 (3.9%)	14 (2.7%)	1 (1.5%)
weight increase	9 (0.5%)	11 (0.9%)	10 (1.9%)	3 (4.4%)

The reports of weight increase during longer duration of treatment are more apparent in the higher dose group.

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Diabetes Mellitus: 5mg dose at the 5-12 week interval (1)
 Polyuria: 10 mg (up to 2 wks) (4), 3-4 wks) (1)
 Purpura: 5 mg dose at the 3-4 week interval (1) and 5-12 wk interval (1)
 Purpura: 10 mg (up to 2 weeks) (1)
 Hematuria: 10 mg (3-4 weeks) (1)
 Ocular hemorrhage: 10 mg (up to 2 weeks) (1)
 visual field defect: 10 mg (up to 2 weeks) (1)
 vision abnormal: 5 mg (up to 2 wks) (2), (3-4 weeks) (1)
 vision abnormal: 10 mg (up to 2 wks) (2), (3-4 weeks) (1)
 Ptosis: 10 mg (up to 2 weeks) (1) and (3-4 weeks) (1)
 Tinnitus: 5 mg (up to 2 weeks) (1)
 Tinnitus: 10 mg (up to 2 weeks) (1), (3-4 wk) (1), 5-12 wks) (1)

Scatterplots of BUN, creatinine, SGOT and SGPT by age, gender, race and dose did not reveal a clear trend between cetirizine and placebo.

Further information was requested from the sponsor regarding specific outliers in these scatterplots. The sponsor's response dated August 11, 1995 was reviewed. A alternative explanation as to the possible cause of lab abnormality was not found after review of the CRF for the following patients. These patients were required to have a baseline value within the normal range and at least one abnormal value after the start of treatment:

N-0047 84N0060/49

54 y/o white, female patient in SAR study. In CFR no record of concomitant drugs or illness. Patient received 10 mg cetirizine treatment from 9/19/84 to 9/26/94. Patient completed the study.

Prior to treatment 9/18/84	SGOT=31
	SGPT=27
	LDH=246
	T. bili=0.2
End of treatment 9/26/84	SGOT=80
	SGPT=108
	LDH=272
	T. bili=0.3
10/3/84	SGOT=40
	SGPT=89
	LDH=235
	T. bili=not available in CFR
10/9/84	SGOT=17
	SGPT=26
	LDH=not available in CFR
	T. bili=not available in CFR

N-0050 85N0044/5

35 y/o hispanic female patient in a 4 week chronic idiopathic urticaria study. In the CFR there is no record of concomitant drugs or illness. Patient received 10 mg cetirizine treatment from 9/19/84 to 9/26/94. Patient had received Benadryl for 9 mo. prior to study.

Prior to treatment 6/9/86	SGOT=23
	SGPT=24
	LDH=188
	T. bili=0.5
First Day of treatment 6/11/86	
End of week two 6/25/86	
	SGOT=82
	SGPT=70

New

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		LDH=246
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End of treatment	9/26/84	SGOT=80
		SGPT=108
		LDH=272
		T. bili=0.3
	10/3/84	SGOT=40
		SGPT=89
		LDH=235
		T. bili=not available in CFR
	10/9/84	SGOT=17
		SGPT=26
		LDH=not available in CFR
		T. bili=not available in CFR

N-0050 85N0044/5

35 y/o hispanic female patient in a 4 week chronic idiopathic urticaria study. In the CFR there is no record of concomitant drugs or illness. Patient received 10 mg cetirizine treatment from 6/11/86 to 7/9/86. Patient had received Benadryl for 9 mo. prior to study.

Prior to treatment	6/9/86	SGOT=23
		SGPT=24
		LDH=188
		T. bili=0.5
First Day of treatment	6/11/86	
End of week two	6/25/86	SGOT=82
		SGPT=70

patients in both the NDA and cumulative database, the incidence for the term sinus infection are different:

For NDA database: cetirizine 1 (0.1%) placebo 0 (0.0%)

For Cumulative database: cetirizine 11 (0.4%) placebo 0 (0%)

The incidence of menstrual cramps also increased 0-0.7% from the NDA to the cumulative database presumably due to the increased number of women enrolled in the cumulative database.

The CRF and additional information was requested from the sponsor regarding three patients listed as having intercurrent illnesses. The reported events for these patients were: abnormal EKG, premature cardiac beats, and syncopal episode. The sponsor response (BM-7/17/95) was reviewed.

Patient 87-N-0017/36: 44 y/o asian male, in seasonal asthma study, symptomatic premature beats. These decreased after rinsing mouth after using a beta agonist inhaler. ECG reported normal by investigator.

Patient 91-S-0033/304: 18 y/o hispanic female in SAR and asthma study; syncopal episode 4 days post treatment initiation, patient continued treatment; no recurrent events reported by the investigator.

Patient 89-N-0103/74: 51 y/o caucasian female in PAR study, according to patient's primary physician, this patient had prior history of heart palpitations and shortness of breath not related to exercise, with 80% PFTs and was referred to the study investigator for asthma evaluation. The study investigator did not record any CV signs or symptoms in the initial screening hx and physical exam. During the course of treatment a routine ECG was done prior to a bunion operation which was abnormal: with T wave inversions and multiple PVCs. Echo revealed mitral prolapse and regurgitation as well as tricuspid regurgitation. The patient discontinued the study early.

Placebo controlled studies. "The overall incidence of intercurrent illnesses in the cumulative database in cetirizine treated patients (16.5%) and placebo treated patients (19.2%) were similar."

From Table F8.C, the number of patients with intercurrent

NEW

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The CRF and additional information was requested from the sponsor regarding three patients listed as having intercurrent illnesses. The reported events for these patients were: abnormal EKG, premature cardiac beats, and syncopal episode. The sponsor response (BM-7/17/95) was reviewed.

In the following case the adverse event appears to have been related to the use of beta agonist and not to an intercurrent illness.

Patient 87-N-0017/36: 44 y/o asian male. in seasonal asthma study, symptomatic premature beats. These decreased after rinsing mouth after using a beta agonist inhaler. ECG reported normal by investigator.

There was no characterization of the syncopal episode in the CFR for the following patient. Although cetirizine may not have been its cause, it should have been reported as an adverse event.

Patient 91-S-0033/304: 18 y/o hispanic female in SAR and asthma study; syncopal episode 4 days post treatment initiation, patient continued treatment; no recurrent events reported by the investigator.

For the following patient the mitral valve prolapse was the most likely cause for the reported palpitations. In this case the report of the adverse experience as an intercurrent illness was justified.

Patient 89-N-0103/74: 51y/o caucasian female in PAR study, according to patient's primary physician, this patient had prior history of heart palpitations and shortness of breath not related to exercise, with 80% PFTs and was referred to the study investigator for asthma evaluation. The study investigator did not record any CV signs or symptoms in the initial screening hx and physical exam. During the course of treatment a routine ECG was done prior to a bunion operation which was abnormal: with T wave inversions and multiple PVCs. Echo revealed mitral prolapse and regurgitation as well as tricuspid regurgitation. The patient discontinued the study early.

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52 msec?. The patient took the vistaril for inability to sleep. The dose: 1 capsule po q hs. The therapy dates: 12/25. Therapy duration 12/31. Event onset:12/31/92. Event duration: 1 day. Did event abate after stopping drug?: Yes. Did event reappear after reintroduction?:N/A. Date of report: 2/7/93.

The patient had tolerated the concomitant medication regimen which included procainamide, lanoxin, diuretics and potassium supplements without a history of adverse events. We do not know the status of the patient's electrolytes at the time of torsades. In view that no additional information will be available in this case, it cannot be ruled out that hydroxyzine at normal doses did not contribute to the QT prolongation and torsades in this patient.

8. Please address the increased frequency of Category 9 adverse events (liver enzymes) in the erythromycin-cetirizine study for 4 out of 16 patients receiving the combination.

"Results falling outside the normal range were reviewed by the investigator for clinical significance and relationship to study drug. The abnormal results were later computer categorized as Category 9 were those that were considered to be clinically significant and possibly related to study medication. These in turn were blindly reviewed by a Pfizer physician and were either left as Category 9 or recategorized to one of the following: 5=documented lab. error, 6=likely due to concurrent illness, 7=likely due to concomitant medication."

See attached photocopy. (SU 4/25/95, vol 35.2, p9 61)

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Refer to the sponsor's response in the following page-attach. photocopy. (SU 4/25/95, vol 35.2, p9 61).

Reviewer's comments:

In this study that incorporated sequential measurements of liver transaminases the incidence of elevated SGPT is higher (4/16, 25%), than the reported incidence in the placebo controlled clinical study population. It is not completely clear in this study whether the elevations in SGPT are due to cetirizine or erythromycin alone or to the combination. This study was a cross-over study; there were no concurrent placebo, erythromycin or cetirizine controls. The data in two of the four patients (from the sequence: cetirizine for 5 days then add erythromycin) suggests that the combination may contribute to further elevate the SGPTs than when the drug is given alone.

The four patients listed had a normal SGPT at baseline. In three patients (#5, 16, and 102) the values from Day 5 on

NEW cetirizine alone to day 6 (first day on the combination) go from being within normal limits to = or >2x. It is unlikely that the addition of one day of erythromycin would have caused this effect on the liver if it had not been started earlier by the drug (cetirizine for 5 days) alone. The same can be said for the patient that started on erythromycin (patient #1) that has a >2x increase in SGPT from Day 5 (erythromycin for 5 days) to Day 6 (first day on the combination).

The elevations in SGPT for patients (#6 and # 16) in the first sequence are of clinical concern. They continue to increase on Day 8 (three days on the combination) to levels up to 6x the levels recorded at Day 5 when cetirizine was given alone. However, there is a decrease in the SGPT levels after both drugs are discontinued. Patient #16 is discontinued from the study and the last value recorded for SGPT is greater than the upper limit of normal. For patient #6 the SGPT values normalized during the wash-out period and both drugs are given again in the opposite sequence. The values in SGPT double again on Day 6, however this elevation is less than that reported for this patient in the previous sequence. Following the wash out period the SGPT decreases.

Since patient #16 did not receive the opposite sequence (erythromycin followed by cetirizine) and the reported values of patient (#6) do not include a value for Day #8 of the second sequence (erythromycin followed by cetirizine) it can only be suggested that clinically in terms of SGPT elevations, patient (#6) would tolerate better the second combination sequence (erythromycin follow by cetirizine) than viceversa.

9. As previously advised, your proposed name "Reactine" connotes usefulness in acute situations and implies lack of drowsiness. Your alternate proposed names "Ultreon" implies maximum strength or effectiveness as compared to related products and "Alacrin" appears to be derived from "alacrity" which denotes quickness and alertness. These three tradenames are not acceptable. Your alternate proposed name, "Zyrtec", is acceptable.

The sponsor accepted the trade name Zyrtec. Refer to proposed package insert.

10. Your proposed annotated package insert has been revised. Please refer to the attachment and note that our recommended additions to the labeling are underlined and in bold typeface and our comments are in brackets, caps, and bold typeface.

The proposed package insert was included in this submission. Specific comments regarding the proposed labeling are included in Section 2 of this review.

SGPT (U/L) Values

//

Pt.	Base line	Cet Day 5	Comb Day 6	Comb Day 8	Comb Day 10	Wash Day 2	Wash Day 4	Wash Day 7	Wash Day 19	Eryth Day 5	Comb Day 6	Wash Day 2	Wash Day 7
6													
16													
102													

Pt.	Base line	Ery Day 5	Comb Day 6	Comb Day 8	Comb Day 10	Wash Day 2	Wash Day 4	Wash Day 7	Wash Day 19	Cet Day 5	Comb Day 6	Wash Day 2
1												

One of the subjects demonstrated a maximal elevation of SGPT $< 2x$ the upper limit of normal, another subject showed a maximal SGPT elevation between 2 and 4 times the upper limit of normal, and the other two subjects had maximum elevations $>4X$ the upper limit of normal. All subjects were asymptomatic, and no subject discontinued for abnormal liver function tests. Two subjects (nos. 6 and 102) experienced elevations of SGPT on the combination of drugs following single administration of both cetirizine and erythromycin; subject 102 experienced an elevated SGPT on erythromycin alone as well. One patient (no. 16) experienced an abnormal SGPT on the combination following cetirizine, but he discontinued from the study prior to the second regimen for personal reasons. Subject 1 had an abnormal SGPT on combination treatment following initial treatment with erythromycin, but not on cetirizine alone or on the combination following initial treatment with cetirizine. In general, the SGPT returned to normal when the combined drugs were stopped during the three week washout phase.

Both cetirizine and erythromycin are known to be associated with abnormal transaminases in a small percent of patients. It is difficult to attribute the abnormalities observed in the small number of volunteers in this study to either the combination, cetirizine alone or erythromycin alone because of the sequential nature of the design and lack of concurrent placebo, erythromycin, and cetirizine controls. In addition, the abnormalities resolved during the washout period when both drugs were withdrawn. Therefore, we cannot attribute these abnormalities to concomitant administration of cetirizine and erythromycin. ■

SGPT (U/L) Values

Pt.	Base line	Cet Day 5	Comb Day 6	Comb Day 8	Comb Day 10	Wash Day 2	Wash Day 4	Wash Day 7	Wash Day 19	Eryth Day 5	Comb Day 6	Wash Day 2	Wash Day 7
6													
16													
102													

Pt.	Base line	Ery Day 5	Comb Day 6	Comb Day 8	Comb Day 10	Wash Day 2	Wash Day 4	Wash Day 7	Wash Day 19	Cet Day 5	Comb Day 6	Wash Day 2
1												

One of the subjects demonstrated a maximal elevation of SGPT < 2x the upper limit of normal, another subject showed a maximal SGPT elevation between 2 and 4 times the upper limit of normal, and the other two subjects had maximum elevations >4X the upper limit of normal. All subjects were asymptomatic, and no subject discontinued for abnormal liver function tests. Two subjects (nos. 6 and 102) experienced elevations of SGPT on the combination of drugs following single administration of both cetirizine and erythromycin; subject 102 experienced an elevated SGPT on erythromycin alone as well. One patient (no. 16) experienced an abnormal SGPT on the combination following cetirizine, but he discontinued from the study prior to the second regimen for personal reasons. Subject 1 had an abnormal SGPT on combination treatment following initial treatment with erythromycin, but not on cetirizine alone or on the combination following initial treatment with cetirizine. In general, the SGPT returned to normal when the combined drugs were stopped during the three week washout phase

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found in the cetirizine group are small and similar to the placebo group. The mean changes by dose do not suggest a relationship between cetirizine dose and change in vital sign parameter." **Appendix 1**

- B. Hydroxyzine/Meclizine and cardiovascular events (update) in Appendix F volume 35.4 -January 1, 1994 to April 19, 1995. The review identified 14 new hydroxyzine cases, one updated hydroxyzine case, and two new meclizine cases. Of these 16 were spontaneously reported and one was a literature report.

"The updated review of the new cases supports the previous conclusion that there is no indication that serious arrhythmias occur in association with hydroxyzine or meclizine when used in normal therapeutic doses in patients who are otherwise healthy." **Appendix 2.**

- C. Response to a consult request to the Division of Epidemiology and Surveillance, HFD-730 on Ketoconazole and Hydroxyzine drug interaction dated June 23, 1995.

Line-listing corresponding to the Spontaneous Reporting System reports where ketoconazole and Hydroxyzine are listed as concomitant drugs. Between 1982 and the present there have been 20 such reports in the SRS.

Demographics:

Outcome: 2 deaths; 5 hospitalizations; 1 disability

Origin: 18 domestic; 2 foreign

Sex: 6 female; 14 male

Age: range 6-90

Most often reported COSTART terms (2 or more cases each):

Liver function abnorm	5
Bilirubinemia	3
Phosphatase alk inc	3
Pruritus	3
Intracran hyperten	2
Jaundice cholestat	2
Rash	2
Rash mac pap	2

The ketoconazole labeling addresses hepatic adverse events. An interaction with hydroxyzine is not mentioned. In reviewing the report its important to remember the limitations associated with data derived from the Spontaneous Reporting System. **Appendix 3.**

- D. Update on cetirizine literature review in Appendix E, vol 4, SU 4/25/95 with copy of article in correspondence dated 8/8/95.

The photocopy of a case report suggestive of drug induced hepatitis is enclosed in **Appendix 4**.

New

found in the cetirizine group are small and similar to the placebo group. The mean changes by dose do not suggest a relationship between cetirizine dose and change in vital sign parameter." Appendix 1

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"The updated review of the new cases supports the previous conclusion that there is no indication that serious arrhythmias occur in association with hydroxyzine or meclizine when used in normal therapeutic doses in patients who are otherwise healthy." Appendix 2.

Reference is made to the review (MOR-2/27/94) of a series of patients identified by the sponsor (submission dated 1/20/94) as having reported a cardiovascular event that could relate to a prolonged QT and that had received treatment with hydroxyzine or meclizine. Of the 4/12 hydroxyzine cases with identified torsades, one was an overdose, and in the other three hydroxyzine was a concomitant medication with another drug that could produce torsades. Of the 6 meclizine cases, one patient developed torsades and in this case the dose was higher than recommended and the patient had concomitant heart failure and liver disease.

None of the cases that follow has the complete information or provides a clear cut evidence that hydroxyzine or meclizine can on their own at recommended doses produce a direct cardiac effect and prolong the QT interval to the point of producing serious arrhythmias. However, these cases as a group suggest that for both hydroxyzine and meclizine this effect is possible; the mechanism is not clear. They have been identified as a concomitant medication in ventricular arrhythmias in apparently healthy individuals, in patients with underlying cardiovascular disease and in patients with drug overdose. For the parenteral formulations of hydroxyzine symptomatic hypotension and bradycardia are also reported.

The list provided by the sponsor in this submission does not identify any patient with torsades. Of the new 14 hydroxyzine patients identified, cardiac arrest is reported in 4 of them (9501282-25 y/o male, 1250 mg po, intentional overdose, recovered; 9408568-unknown age and gender, concomitant venlafaxine, recovered; 950193, 4y/o, as dental anesthesia 50 mg po, concomitant diazepam and lidocaine, arrested following apneic episode, died; 9503398, 30 y/o,

NEW

44a

prior to surgery 50 mg po x 3days, ventricular fibrillation following severe bronchospasm, arrested, died).

Symptomatic transient hypotension in a 36 y/o female (9400513) that received 100 mg IM along with meperidine for pain, was followed with ischemia in ECG leads and myocardial enzyme elevation; "cardiac catheterization and echo revealed a completely normal heart". Other cases that also reported hypotension were: 9503404, 32 y/o male, 150 mg IM and atropine 0.5 mg prior to surgery; and 9503403, 55 y/o female, 150mg IM along with atropine 0.5 mg prior to surgery.

Bradycardia was also reported by 9503404 and 9501282 as well as by 9503401, unknown age and gender and concomitant disease ("deficient heart state" an gastric cancer), hydroxyzine and amiodarone, bradycardia improved when hydroxyzine was discontinued; 9503397 and 9503400 patients of unknown age and gender, intravenous hydroxyzine, dose unknown.

One of the two reported meclizine patients 9401063, 42 y/o male, on unknown dose for vertigo for "a couple of weeks" had ventricular fibrillation, patient recovered, work up for cardiac disease was negative.

- C. Response to a consult request to the Division of Epidemiology and Surveillance, HFD-730 on Ketoconazole and Hydroxyzine drug interaction dated June 23, 1995. See Appendix 3.

The intent of the consult was to screen out if there were any other cases of cardiovascular events reported with the interaction. An additional case of torsades was produced by this search. However, the patient was hypocalcemic and was both on terfenadine (120mg po 15 days) and ketoconazole (400 mg po 14 days) in addition to hydroxyzine.

The findings of the consult point out to another effect, hepatic adverse events.

Ketoconazole has been associated with hepatic toxicity, including some fatalities, a warning box is included in the labeling. Hydroxyzine labeling does not mention the association with liver function abnormalities. The cases reported in this search had in addition to the ketoconazole hydroxyzine combination other concomitant medications. The duration of treatment that the patients received both drugs is not specified. Therefore, it is not clear what role hydroxyzine could have had in these cases.

New

- D. Copy of literature article reporting a case of hepatitis associated with the use of cetirizine. The article was mentioned in the update on cetirizine literature review in Appendix E, vol 4, SU 4/25/95 and the article was submitted in correspondence dated 8/8/95. Appendix 4.

the results using the combination are comparable with single dose administration data (azithromycin) from other studies.

Sponsor's conclusion:

The results indicate that cetirizine 20 mg QD administered for ten 10 does not affect the QT interval. There is no indication that concomitant administration of azithromycin and cetirizine produces any significant changes in QT interval. No pharmacokinetic interaction occurs when subjects who are taking cetirizine and have attained steady state levels of the drug are additionally administered the five-day recommended dosage regimen of azithromycin. Cetirizine alone and in combination with azithromycin was well tolerated in this study.

Reviewer's comments:

After reviewing the study the following questions were faxed to the Sponsor August 4, 1995. For clarity th'e questions are bolded and a summary of the response that was submitted and the amendment to the NDA dated, 8/11/95, follows.

1. **Please provide the corresponding ECG values in the format of Appendix F.2 in vol 14, for the following ECGs with QTc prolongations that are listed in Table 1.5, vol 1:**

Please explain why the corresponding ECG values for the above patients were not included in the Appendix F.2 listing and what was the reason for obtaining these ECGs out of the regular protocol schedule. Please submit the listings for any other ECGs obtained out of the regular protocol

New

Days	# of patients with QTc prolongation 10% or greater	# ECGs, QTc 10% or greater	# ECGs, QTc>440
1-5	4	4	1
6-9	3	3	0
10	7	12	5

Combination treatment:

Days	# of patients with QTc prolongation 10% or greater	# ECGs, QTc 10% or greater	# ECGs, QTc>440
5*	5	6	3
6-9	5	5	1
10	4	7	2

* Please note that from days 1-5 inclusive patients were receiving only cetirizine

In the attached Table E.2.2., there are no statistical significant differences at Day 6 among treatment groups including placebo. We would have expected the patients for both cetirizine and combination to have approximate equal Day 6 change, since the two groups were receiving the same drug for those 5 days of treatment. The cetirizine only group had a lower increase in QTc from baseline at Day 6 than the combination, however this change was not statistically significant.

When the treatment effect from Day 6 to Day 11 is calculated, (Day 11-Day 6), this difference for the cetirizine group is 13.41 msec, versus the -1.43 in the combination and 3.14 in the placebo treated group. There is a statistically significant difference between cetirizine and the combination, p=0.02, for the treatment effect from Day 6 to Day 11. However there is no difference between placebo and either cetirizine alone or the combination in treatment effect from Day 6 to Day 11.

Change from baseline for ECGs recorded within days 11-17 of first dose from Table 2.1:

Number of patients	Placebo 40	Cet 5 mg 35	Cet 10 mg 44	p-value
QTc (Bazett)				
Baseline	425.05 +/- 25.47	417.36 +/- 25.33	420.54 +/- 22.34	
Change	-0.79 +/- 24.25	-0.08 +/- 35.67	10.32 +/- 25.18	
(p-value within)	0.833	0.970	0.015	0.061
Adjusted change	1.77	-2.52	9.94	

Change from baseline for ECGs recorded last or maximum ECG recorded on treatment (11-17 Days ECGs), from Table 2.2:

Number of patients	Placebo 64	Cet 5 mg 64	Cet 10 mg 65	p-value
QTc (Bazett)				
Baseline	418.93 +/- 24.88	421.02 +/- 25.98	421.15 +/- 21.31	
Change	-5.89 +/- 27.21	-2.84 +/- 31.52	10.22 +/- 24.84	
(p-value within)	0.107	0.887	0.002	0.006
Adjusted change	4.92	-2.40	10.73	

Distribution of percent change from baseline for ECGs recorded within days 11-17 of first dose, from Table 2.4:

	under 5%	5 - <10%	10 - <20%
Placebo-# of pts.	32	6	2
Row %	80%	15%	5%
5 mg cet	27	4	4
Row %	77.14%	11.43%	11.43%
10 mg cet	31	7	6
Row %	70.45%	15.91%	13.64%

New

Change from baseline for ECGs recorded within days 11-17 of first dose from Table 2.1:

Number of patients	Placebo 40	Cet 5 mg 35	Cet 10 mg 44	p-value
QTc (Bazett)				
Baseline	425.05 +/- 25.47	417.36 +/- 25.33	420.54 +/- 22.34	
Change	-0.79 +/- 24.25	-0.08 +/- 35.67	10.32 +/- 25.18	
(p-value within)	0.833	0.970	0.015	0.061
Adjusted change	1.77	-2.52	9.94	

Change from baseline for **maximum** ECG recorded on treatment (11-17 Days ECGs), from Table 2.2:

Number of patients	Placebo 64	Cet 5 mg 64	Cet 10 mg 65	p-value
QTc (Bazett)				
Baseline	418.93 +/- 24.88	421.02 +/- 25.98	421.15 +/- 21.31	
Change	5.89 +/- 27.21	-2.84 +/- 31.52	10.22 +/- 24.84	
(p-value within)	0.107	0.887	0.002	0.006
Adjusted change	4.92	-2.40	10.73	

Distribution of percent change from baseline for ECGs recorded within days 11-17 of first dose, from Table 2.4:

	under 5%	5- <10%	10- <20%
Placebo-# of pts.	32	6	2
Row %	80%	15%	5%
5 mg cet	27	4	4
Row %	77.14%	11.43%	11.43%
10 mg cet	31	7	6
Row %	70.45%	15.91%	13.64%

Section 2

Reference is made to the MO review (10/30/95-in **Apperdix 1**) of the annual report to the IND dated 9/25/95.

Reference is also made to the sponsor's response in the telephone facsimile dated 11/2/95 in **Appendix 2**. The information requested refers to a case of a 26 y/o female patient that participated in study L-0270 for seasonal allergic rhinitis. In addition, this patient had history of allergy headaches. The patient completed the study. Treatment with cetirizine began on 5/18/94 and ended on 6/8/94. The patient experienced sinus headache on 5/29/94 and 5/30/94 that was treated with ibuprofen and nausea on 6/5/95 treated with Dramamine.

Laboratory results pretreatment on 5/18/94: SGOT=24 U/L
SGPT=38 U/L
T.Bili=1.1 mg/dl

At the end of treatment 6/8/94: SGOT=87 U/L
SGPT=210 U/L
T. Bili=1.2 mg/dl

Follow up repeat labs 6/23/94: SGOT=29 U/L
SGPT=34 U/L
T. Bili=1.2 mg/dl

Reviewer's comments:

Three days prior to the end of 3 weeks of treatment this patient felt nauseous for 1 day. Three days later, at the end of study evaluation the elevation of liver transaminases and an increase in total bilirubin (that was within the lab normal limits) was noted; no other symptoms were recorded in the CFR. Fifteen days after the drug had been stopped a lab retest was done and the liver enzymes had returned to normal values; a positive dechallenge. The CRF does not record a history of a concomitant illness, concomitant use of medications or other abnormal labs that would account for the abnormal enzyme elevations. It is very likely that the liver enzyme elevation in this patient was related to the use of cetirizine.

Appendix 1

Medical Officer Review

IND

Drug: Cetirizine tablets

Correspondence: N228YY-annual report 2/27/94-2/26/95

Document date: September 14, 1995

Date of review: October 30, 1995

Medical Officer Reviewer: Ana M. Saavedra-Delgado, M.D.

The following items that were not included in the 4/25/95 safety update are noted:

In Table 3, the incidence of adverse experiences in U.S. pharmaceutical studies during the reporting period is displayed for multiple dose, open-label/single blind/unblinded studies is displayed. For patients treated with cetirizine=474, loratadine=194 and placebo=197, the incidence of adverse experiences was 47%, 35% and 35% respectively.

In Table 4, the incidence of intercurrent illnesses in U.S. pharmaceutical studies during the reporting period is displayed for multiple dose, open-label/single blind/unblinded studies is displayed. For patients treated with cetirizine=381, loratadine=101 and placebo=104, the incidence of intercurrent illnesses was 19%, 17% and 13% respectively.

For future annual reports we would want to see the adverse events associated with intercurrent illnesses integrated in the adverse event database and presented to us as a single table.

The following items that were included in the 4/25/95 safety update are also noted:

In the listing providing serious spontaneous adverse events from non-clinical trial, four cases are reported with ventricular tachycardia and or fibrillation. A clear relation to the drug was not apparent in any of these cases, since either there were pre-existing conditions, electrolyte deficiencies or concomitant medications that could have been responsible for the event. The four cases resolved and cetirizine was permanently stopped. The summary of these four cases from the 4/25/95 safety update is attached.

More information is needed on the following patient(s):

In Table 5, the incidence of clinically significant

A. Saavedra-Delgado MD 10/30/95
medical officer should be sponsored to request information in request #2.
Tom Munnick 10/30/95
Request #2 was faxed on 10-31-95 to Mr. Saavedra Delgado of P.S. by 10-31-95 via telephone K.L. 10-31-95

laboratory abnormalities in U.S. pharmaceutical studies is displayed for protocol L-0270 (patients active during the reporting period). In this table, for cetirizine treated patients N=1 is listed for increase >3x ULN in SGPT and T. bili.

Study L-0270 was initiated after 2/26/95, and was included in the 4/25/95 safety update for serious adverse events discussion only. Under this definition the patient must have not needed hospitalization. However, more information is needed to assess the cause of the rise in liver enzymes.

The following information will be requested: patient ID, gender, age, treatment dose at onset of event, duration of treatment at onset of event, concomitant therapy or illnesses, follow up lab results, continuation of treatment, and resolution.

Recommendations to Sponsor: --

We have completed the review of your annual report for IND dated September 14, 1995. We have the following requests:

1. For future annual reports we would want to see the adverse events associated with intercurrent illnesses integrated in the adverse event database and presented as a single table.
2. In Table 5. the incidence of clinically significant laboratory abnormalities in U.S. pharmaceutical studies is displayed for protocol L-0270 (patients active during the reporting period). In this table, for cetirizine treated patients N=1 is listed for increase >3x ULN in SGPT and T. bili. Please provide patient ID, gender, age, treatment dose at onset of event, duration of treatment at onset of event, concomitant therapy or illnesses, follow up lab results, whether treatment was continued, and resolution of event.

cc: original IND

HFD-570/Div files

HFD-570/K.Lee/Saavedra-Delgado

TABLE 5. CETIRIZINE - INCIDENCE OF CLINICALLY SIGNIFICANT LABORATORY ABNORMALITIES
 PROTOCOL L-0270 (PATIENTS ACTIVE DURING THE REPORTING PERIOD 27FEB94 TO 26FEB95)

NUMBER OF SUBJECTS: EVALUABLE FOR LABORATORY ABNORMALITIES WITH CLINICALLY SIGNIFICANT LABORATORY ABNORMALITIES				CETIRIZINE			LORATADINE			PLACEBO		
				95			99			98		
				21			13			13		
GROUP	PARAMETER	UNITS	CRITERIA	SUBJECTS WITH ABNORMALITIES			SUBJECTS WITH ABNORMALITIES			SUBJECTS WITH ABNORMALITIES		
				N	n	%	N	n	%	N	n	%
HEMATOLOGY	HGB (F)	G/DL	> 20% DECREASE*	55	0	0.0	51	0	0.0	56	0	0.0
	HGB (M)	G/DL	> 20% DECREASE*	39	0	0.0	47	0	0.0	40	0	0.0
	HCT (F)	%	> 20% DECREASE*	55	0	0.0	51	0	0.0	56	0	0.0
	HCT (M)	%	> 20% DECREASE*	39	0	0.0	47	0	0.0	40	0	0.0
	WBC	THOU/MCL	< 2.5	94	0	0.0	98	0	0.0	96	0	0.0
			> 17.5	94	0	0.0	98	0	0.0	96	0	0.0
	NEUTROS EOS	THOU/CMN	< 1	94	1	1.1	98	0	0.0	96	0	0.0
	%	>= 10	94	10	10.6	99	7	7.1	96	5	5.2	
LIVER FUNCTION	SGOT	U/L	> 3 X ULN	94	0	0.0	99	0	0.0	96	0	0.0
	SGPT	U/L	> 3 X ULN	94	1	1.1	99	0	0.0	96	0	0.0
	T.BILI.	MG/DL	> 1.5 X ULN	94	1	1.1	99	0	0.0	96	0	0.0
RENAL FUNCTION	BUN	MG/DL	> 1.3 X ULN	94	0	0.0	99	0	0.0	96	0	0.0
	CREATININE	MG/DL	> 1.3 X ULN	94	0	0.0	99	0	0.0	96	0	0.0
URINALYSIS	BILIRUBIN		>= 1+	95	0	0.0	99	0	0.0	98	0	0.0
	GLUCOSE		>= 2+	95	0	0.0	99	0	0.0	98	1	1.0
	KETONE		>= 1+	95	0	0.0	99	0	0.0	98	1	1.0
	PH (REACTION)		< 0.9 X LLN	95	0	0.0	99	0	0.0	98	0	0.0
			> 1.1 X ULN	95	0	0.0	99	0	0.0	98	0	0.0
	PROTEIN		>= 2+	95	1	1.1	99	0	0.0	98	0	0.0
	RBC/WPF		>= 6	95	4	4.2	99	4	4.0	97	3	3.1
	SPEC.GRAV.		< 1	95	0	0.0	99	0	0.0	98	0	0.0
			> 1.035	95	0	0.0	99	0	0.0	98	0	0.0
WBC/WPF		>= 6	95	4	4.2	99	4	4.0	97	3	3.1	

NOTE: N = TOTAL NUMBER OF SUBJECTS WITH AT LEAST ONE OBSERVATION OF THE GIVEN LAB PARAMETER WHILE ON STUDY TREATMENT
 n = NUMBER OF SUBJECTS WITH A CLINICALLY SIGNIFICANT ABNORMALITY
 * = CHANGE FROM BASELINE

RUN DATE: 27JUL95

89. 9410358	A congenital anomaly of a spinal malformation was reported by the The registry felt that cetirizine could possibly be causal in this malformation. No further information is available.	
90. 9500834	A female infant was born prematurely at 33 weeks of gestation with multiple malformations (Pierre Robin Syndrome) with streptococcal septicemia, and died. The mother had taken cetirizine 5-10 mg daily during weeks 5-7 of pregnancy. The Regulatory Authority felt it unlikely that the malformations were attributable to cetirizine.	
91. 9500835	A 69 year old polymedicated woman with a known history of cardiac disease and a prior myocardial infarction developed ventricular tachycardia while taking 10 mg of cetirizine daily for urticaria. The cetirizine was permanently stopped although underlying cardiac disease was most likely the reason for the event. Concomitant medications included indomethacin, cinnarizine, clonazepam, amiloride, isosorbide, enalapril, and nitroglycerne. The events resolved.	✓
92. 9500836	A 67 year old woman, who had been taking 10 mg of cetirizine daily for rhinitis, developed sudden dizziness followed by shortness of breath and chest pain. She was hospitalized. An ECG showed rapid ventricular tachycardia, which was successfully treated with lignocaine infusion. However, occasional ectopic beats were still noted; it is not known if the ectopics ever completely disappeared. Echocardiogram showed an akinetic segment of the heart with blood clot, which was felt by her physician to be related to the arrhythmia. Additionally, the patient was taking brompheniramine, had been taking terfenadine until two weeks before the event, and used a terbutaline turbobhaler as necessary. Although the cetirizine was permanently discontinued, it was not felt to have been related to the arrhythmia	✓

96. 9501280	A 55 year old man with a prior history of ischemic heart disease, a coronary artery bypass graft, and poor left ventricular function developed ventricular tachycardia and ventricular fibrillation. He was hospitalized and treated with electric shocks. He was taking 10 mg of cetirizine intermittently for hay fever. Other medications included captopril, acetylsalicylic acid, furosemide, and another unspecified medication. Pfizer felt that the underlying heart disease seemed a more likely cause of the cardiac arrhythmia than cetirizine.	Unknown ✓
97. 9501420	A 48 year old polymedicated man developed ventricular fibrillation and ventricular ectopic beats successfully treated by defibrillation and lidocaine. On admission to the hospital he was severely hypokalemic and anemic. He was taking cetirizine 10 mg daily and paroxetine 20 mg daily. Both drugs were discontinued and suspected to have contributed to his arrhythmia, in addition to the hypokalemia and anemia.	✓ -
98. 9500909	An 80 year old man developed urinary retention after the ingestion of a single intake of 150 mg of cetirizine (accidental overdose). The patient was not hospitalized but the event necessitated catheterization.	

**Serious foreign clinical trial adverse experiences

† This case does not meet FDA criteria for serious, but was noteworthy.

Appendix 2

To: K. Lee, Consumer Safety Officer, Division of Pulmonary
Drug Products

Fax: 13018271271

From: Suzanne E. LoGalbo

Date: November 2, 1995

Pages: 35, including cover sheet. As requested, attached please
find information about patient no. 344 from study no. L-
0270.

fax

From the desk of...

Suzanne E. LoGalbo
Associate Director, Drug Regulatory Affairs
Pfizer Inc
235 East 42nd Street
NY NY 10017

212 573 2950
Fax: 212 573 1563

34 pages

PURGED

Medical Officer Review

NDA 19835

Drug: Cetirizine tablets (Zyrtec)

Sponsor: Pfizer

Date: October 17, 1995

Subject: Response to the NDA approvable letter dated February 21, 1995 and proposed physician package insert included in the SU dated 4/25/95

Medical Officer Reviewer: Ana M. Saavedra-Delgado, M.D.

Correspondence:

The medical officer has completed the review of material included in the following correspondence.

- A. Saavedra-Delgado MD*
10/17/95
see supervisor's memo
m. Herring
11/9/95
- SU 4/25/95 Final Safety Update, volumes 1-30
Includes response to questions 1-11 of the
cetirizine approvable letter of 2/21/95
 - BZ 5/12/95 Response to items 15-22 of the 2/21/95
approvable letter
 - C 5/25/95 Response to items 1 and 3 of FDA facsimile
dated 5/11/95
 - N(BM) 6/7/95 Response to item 2 of FDA facsimile
dated 5/11/95
 - N(BM) 6/14/95 Report of 2 deaths in a foreign
clinical study
 - N(BM) 6/20/95 Additional data in response to item 2
of FDA facsimile dated 5/11/95
 - N(BM) 6/29/95 Case report forms of patients
reported in correspondence dated 6/14/95
 - N(BM) 7/17/95 Response to information requested in
teleconference with FDA dated 7/6/95
 - C 8/8/95 Response to FDA facsimile dated
7/20/95
 - BZ 8/11/95 Response to information requested in
FDA facsimile dated 8/4/95
 - II BL, SU, BM 8/18/95 Draft physician package insert

labeling incorporating the pediatric data and Study Report of No. A 132 (RPCE92L2503)-Efficacy and safety in children and adolescents with asthma. The medical officer has completed the review of the draft physician package insert included in this correspondence as it refers to the tablet.

N (BM) 8/11/95 Case Report Forms and patient identifiers requested in FDA facsimile dated 8/1/95

Response to consult by Epidemiology on ketoconazole and hydroxyzine dated 6/23/95

C 9/12/95 Response to FDA facsimile dated 8/25/95.

CC: Orig. NOA 19-835
HFD-570/D.V. Files
HFD 570/A. Saavedra-Delgado
HFD-570/M. Himmel

Outline and Table of Contents of this review:

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Section 2

- I. Draft review of the proposed package insert included in the SU 4/25/95

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Section 3

- I. Revised package insert faxed to the sponsor September 29, 1995.

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- II. Reviewer's general comments and regulatory recommendations.

page 91

Section 1.

I. Response to our clinical requests on the February 21, 1995 NDA approvable letter.

In the following section the requests submitted to the sponsor in the approvable letter are presented in small font followed by a summary of their response in regular (10cpi Courier) font. Unless otherwise specified, these responses are found in the sponsor's submission dated April 20, 1995.

1. As discussed at the meeting of December 21, 1994, all ECG's in controlled trial and the azithromycin interaction trial in which there is a 10% or greater prolongation in QT_c from baseline should be evaluated by a cardiologist for changes in T-U wave morphology. The change in QT_c on the ECG's of t and trials should be evaluated for age, gender, race, dose, dose adjusted for weight, duration of treatment related effects and concurrent therapy, if any. Because of possible diurnal effects on QT_c, the analysis should incorporate a description of how the ECG's included in the analysis compare with regard to the time they were collected. If serum drug concentrations are available, an analysis of change in QT_c by drug level should be performed. Please compute the QT_c according to the Bazett formula. For the data and the azithromycin study, in addition to mean changes an analysis should also be performed comparing active treatment to placebo with regard to subjects with <10% increase in QT_c from baseline, 10-15%, 15-20% and >20% increase over baseline.

Response:

- a. "All ECGs from and azithromycin studies were evaluated by a cardiologist. The ECGs from and were evaluated and interpreted by (Medical Director), Cardiology for Clinical Trials. This interpretation was submitted in the March 3, 1994 safety update. The ECGs from the azithromycin interaction study were interpreted by and they form part of this response. The ECGs from the studies were evaluated by a physician trained in cardiology."

The specific occurrences of QT_c(Bazett's) prolongation of greater than or equal to 10% over baseline for the studies were included in Vol 1 pages 2-17. Since these studies were not specifically designed to study QT_c prolongations, only the data from individual patient results in terms of QT_c prolongation are included in this document.

The results from the cetirizine-azithromycin interaction study where QT_c evaluation was part of the study protocol are discussed separately as part of Section 2 on the

proposed labeling, in Appendix 1.

ECG cardiology evaluation of the
following ECGs- blinded

Clarification by the sponsor following telephone
conversation of 5/24/95:

There were two treatment arms in this study and the
following number of patients were considered to be
safety evaluable: 80 cetirizine and 80 terfenadine.
Reference was made to Table F1.B, vol. 3 of this
submission (4/25/95).

**Patients with a 10% or greater prolongation in QTc from
baseline. Table 1.1**

From a total of 160 patients in this study a total
of 12 patients had a prolongation in QTc 10% or
greater over baseline. These were 4 males and 8
females between the ages of 26 to 51 yrs of age.

cetirizine=8	terfenadine=4
females=5	3
males=3	1

Of the eight cetirizine treated patients with a 10% or
greater prolongation in QTc over baseline, five had a
QTc >440msec in the ECG. Table 1.2:

#90S0026-10	sinus rhythm 51 y/o w/female pt on estrogen progesterone and thyroxine
#90S0029-2	sinus rhythm 43 y/o w/female
#90S0030-11	sinus tachycardia/ early repolarization pattern 32 y/o w/male
#90S0030-14	sinus rhythm/ sinus arrhythmia 26 y/o w/female on triphasil (BCP)
#90S0030-19	sinus rhythm/T wave inversions/ abnormal ECG clinically significant 30 y/o female on Sudafed 30 mg and Trileven (BCP)

Of the four terfenadine patients with a 10% or greater
prolongation in QTc over baseline, two had a QTc
>440msec in the ECG. Table 1.2:

NDA 19835

2 OF 11



TABLE 1.1
 2480: ONE WEEK STUDY OF CETIRIZINE AND TERFENADINE IN SEASONAL ALLERGIC RHINITIS
 PROTOCOL 1-0149
 LISTING OF PROLONGATIONS OF 18Z OR GREATER THAN BASELINE QTC
 QTC COMPUTED USING BAZZETT'S FORMULA

SITE	PAT NO	AGE	SEX	WEIGHT	SMCE	TREATMENT GROUP	TREATMENT DURATION (DAYS)	QTC (BAZZETT) BASE	QTC (BAZZETT) POST 2 CHANGE CONCOMITANT MEDICATIONS

TABLE 1.2: CARDS FOR REVIEW OF EOS WITH QTC >= 15% INCREASE FROM BASELINE: SUB-8 (PROTOCOL L-5148)

SITE	SUBJECT	TREATMENT	RESPIRATORY	EOS	EOS	EOS	EOS
		GROUP	STATUS	2	2	2	2
			STOP	DATE	CHANGE	(BASELINE)	EOS
							INTERPRETATION

• CET • CETIZINE TBR • TEMPERATURE

#90S0028-19 sinus rhythm
37 y/o other/female

#90S0030-9 sinus rhythm, poor R wave
progression V1-V5/ borderline ECG
41 y/o w/female on Ibuprofen 600 mg and
Afrin nasal spray

SAR/LORA (C91-0001) cardiology evaluation blinded

Clarification by the sponsor following telephone
conversation of 5/24/95:

There were three treatment arms in this study and the
following number of patients were considered to be
safety evaluable: 82, loratadine, 81 cetirizine and 77
placebo. Reference is made to Table F1.B, vol. 3 of
this submission (4/25/95). —

**Patients with a 10% or greater prolongation in QTc from
baseline. Table 1.3**

From the total number of patients in this study 6
patients had a prolongation in QTc 10% or greater
over baseline. These were 5 males and 1 female
between the ages of 14 to 38 yrs of age.

cetirizine=4	placebo=2	loratadine=0
females=1	0	
males=3	2	

Of the four cetirizine treated patients with a 10% or
greater prolongation in QTc over baseline, two had a
QTc >440msec in the ECG. Table 1.3 and 1.4:

#91C0002-91 sinus bradycardia/ early
repolarization pattern
25 y/o w/male

#91C0005-190 sinus rhythm
14 y/o w/male

No placebo or loratadine patient had a 10% or greater
change in QTc over baseline and a QTc >440msec in the
ECG (Tables 1.3 and 1.4).

studies

Clarification by the sponsor following telephone

SAR/LORON: TWO WEEK STUDY OF CETIRIZINE AND LORATADINE IN SEASONAL ALLERGIC RHINITIS
 TABLE 1.3
 PHASE III, CTR-COM-91-001
 LISTING OF PROLONGATIONS OF 10% OR GREATER THAN BASELINE QTC
 QTC COMPUTED USING BAZETT'S FORMULA

SITE	PAT NUM	AGE	SEX	WEIGHT	RACE	TREATMENT GROUP	TREATMENT DURATION (DAYS)	QTC (BAZETT) BASE	QTC (BAZETT) POST 1 CHANGE CONCOMITANT MEDICATIONS

TABLE 1.4: CARDIOLOGIST REVIEW OF EGGS WITH QTC >= 10% INCREASE FROM BASELINE: SAR/LORA (PROTOCOL C-92-0001)

SITE	SUBJECT	TREATMENT GROUP	MEDICATION START	STOP	ECG Z DATE	QTC CHANGE (BAZETT)	ECG INTERPRETATION

* CET = CETILIZINE

conversation of 5/24/95:

There is an error in the original submission (4/25/95). The total number of patients from these 9 studies was 247. In these 9 trials, three types of protocol were conducted: pts. received cetirizine 10 mg for 1 yr (168), another group received cetirizine for 9 months and then were switch to cetirizine 20 mg and the third type of protocol consisted of patients that received 20 mg of cetirizine for 1 year. From the total number of patients evaluated 72 patients had ECGs done at baseline and on follow up. From these 72, 66 had received cetirizine for 12 months, 3 for 10 months, 2 for 9 months and 1 for 8 months. Of these 72 patients with pre and post ECGs, 49 were over 64 years of age.

The individual QT intervals for these 72 patients entered in Pfizer's database had their QTc recalculated using Basset's formula. Of these, 2 patients had QTc prolongations of $\geq 10\%$ over baseline. These were interpreted by Dr. Goodman.

From Table 1.6 the two patients with $>10\%$ prolongation in QTc that also had a QTc >440 msec were:

"compared to previous tracing, there are no changes except a slight lowering of the T wave an AVF but still within normal limits"

62 y/o ?m/f, 12 mo of treatment

"complete left bundle branch block since the previous tracing the non specific IVCD has progressed to LBBB"

88 y/o ?m/f, 12 mo of treatment, on Digitalis

- b. Cetirizine blood levels were not obtained for the SAR-8 and SAR/LORA studies. "The number of patients with a 10% prolongation or greater in QTc" was given by time interval post dose for these studies:

SAR-8, SARA/LORA

Within:

Of the above a total of 13/18 (72%) were noted within 6 hrs

post dose.

2. Please analyze the ECG data from the PED-4 study as requested above, using the Bazett's formula for patients who received post ECGs within 24 hours of the last cetirizine dose. The QT_c analysis of this data should include a comparison by dose adjusted for weight, by gender and race. This should be done for both change from baseline as well as by percentage increase or decrease from baseline. As above, all ECG's with a 10% or greater prolongation of QT_c from baseline should be evaluated by a cardiologist for changes in T-U wave morphology.
- a. A summary of the data from the PEDs-4 response that the reviewer considered to be relevant to the labeling was summarized in the Appendix 2 to the reviewer's comments to the proposed labeling in Section 2.

Analyses assessing the effect of weight, gender or race on change from baseline QT_c .

Statistical methods used:

"An ANOVA was performed on the change from baseline QT_c introducing weight class and weight by treatment interaction, as terms in the model, in addition to treatment and baseline QT_c . Similar analyses were performed for gender and race. For each factor an analysis was conducted for the three groups (1: QT_c recorded between 11-17 days, 2: all patients for endpoint change, 3: all patients for maximum change), Tables 2.9 to 2.11. In addition, Pearson correlation of change in QT_c and patient weight in KG was computed by treatment groups, Table 2.12.

The change in QT_c is not correlated for patient weight for either the placebo or the cetirizine groups. The analysis of variance shows that neither the overall effect of weight nor the interaction with treatment is significant in analysis grouping.

Similar results are seen for race.

With respect to gender effects (Table 2.10), overall differences between males and females were significant for the 11-17 day, endpoint change and maximum change analysis ($p < .047$ in each case), but the gender by treatment interaction was not significant."

No statistically significant positive correlations were observed for these three parameters for the ECGs obtained in this study.

It should be noted that these analyses were not part of the original protocol design. The study was a multicenter study and it can be assumed that there were differences in techniques and instruments used between centers.

The following data is noted although no statistical significant differences were demonstrated:

Weight:

CETIRIZINE-PEDIATRIC SEASONAL ALLERGIC RHINITIS IV (PROTOCOL #91CE16-0573)

TABLE 2.9 (ADDENDUM)

SUMMARY STATISTICS FOR CHANGE FROM BASELINE QTc BY WEIGHT CLASS

ANALYSIS GROUPING	OBSERVED MEAN ± STANDARD DEVIATION					
	< 25 kg Patients			≥ 25 kg Patients		
	PLACEBO	CETIR 5 MG	CETIR 10 MG	PLACEBO	CETIR 5 MG	CETIR 10 MG
11-17 DAYS (No. Pats)	(7)	(8)	(10)	(33)	(27)	(34)
Baseline QTc	430.2 ± 29.96	423.0 ± 18.65	421.8 ± 21.22	424.0 ± 24.81	415.7 ± 27.07	420.2 ± 22.95
Change	2.66 ± 18.69	-8.64 ± 27.52	3.87 ± 23.95	-1.52 ± 25.46	2.76 ± 37.72	12.21 ± 25.58
ENDPOINT (No. Pats)	(13)	(11)	(12)	(51)	(53)	(53)
Baseline QTc	423.0 ± 23.99	423.5 ± 17.58	418.5 ± 20.82	417.9 ± 25.23	420.5 ± 27.51	421.8 ± 21.57
Change	6.76 ± 26.80	-7.10 ± 18.73	6.70 ± 22.92	4.93 ± 27.74	-2.67 ± 32.61	9.64 ± 24.68
MAXIMUM (No. Pats)	(13)	(11)	(12)	(51)	(53)	(53)
Baseline QTc	423.0 ± 23.99	423.5 ± 17.58	418.5 ± 20.82	417.9 ± 25.23	420.5 ± 27.51	421.8 ± 21.57
Change	6.76 ± 26.80	-7.10 ± 18.73	7.21 ± 23.66	5.66 ± 27.57	-1.95 ± 33.64	10.90 ± 25.26

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CETIRIZINE-PEDIATRIC SEASONAL ALLERGIC RHINITIS IV (PROTOCOL #91CE16-0573)

TABLE 2.11 (ADDENDUM)

SUMMARY STATISTICS FOR CHANGE FROM BASELINE QTc BY RACE

ANALYSIS GROUPING	OBSERVED MEAN ± STANDARD DEVIATION					
	NON-WHITES			WHITES		
	PLACEBO	CETIR 5 MG	CETIR 10 MG	PLACEBO	CETIR 5 MG	CETIR 10 MG
11-17 DAYS (No. Pats)	(8)	(3)	(9)	(34)	(32)	(35)
Baseline QTc	421.3 ± 25.00	429.8 ± 36.65	426.1 ± 17.59	425.7 ± 25.87	416.2 ± 24.51	418.1 ± 23.41
Change	1.79 ± 34.76	-17.52 ± 47.72	14.19 ± 25.45	-1.24 ± 22.60	1.58 ± 34.87	8.32 ± 25.38
ENDPOINT (No. Pats)	(6)	(4)	(9)	(58)	(60)	(56)
Baseline QTc	421.3 ± 25.00	427.7 ± 30.21	426.1 ± 17.59	418.7 ± 25.08	420.6 ± 25.90	420.4 ± 21.88
Change	7.93 ± 44.15	-14.53 ± 39.42	14.19 ± 25.45	5.03 ± 25.59	-2.69 ± 30.20	8.28 ± 24.17
MAXIMUM (No. Pats)	(6)	(4)	(9)	(58)	(60)	(56)
Baseline QTc	421.3 ± 25.00	427.7 ± 30.21	426.1 ± 17.59	418.7 ± 25.08	420.6 ± 25.90	420.4 ± 21.88
Change	7.93 ± 44.15	-14.53 ± 39.42	14.19 ± 25.45	5.67 ± 25.43	-2.76 ± 31.17	9.58 ± 24.91

The sponsor provided us with the summary statistics for the above cited Table 2.9, on the telephone facsimile dated June 13, 1995.

In the Table 2.9 (addendum) for change from baseline QTc by weight class, no numerical differences are observed for the patients in the <25 kg group that had been treated with cetirizine when it is compared to placebo. However, the largest difference for the >25 kg group was a mean change in QTc of 12.21 msec from baseline in the 10 mg cetirizine group (N=34) compared to -1.52 msec in the placebo group (N=33) for those patients whose ECGs were obtained 11-17 days post treatment initiation.

At per our original request, a separate analysis was provided by the sponsor using mg/kg of body weight in the submission dated May 25, 1995. The dose adjusted for weight was computed as the patient's daily dose divided by the patient's weight in kg. The analyses were performed using the analysis groups defined above. There were no positive statistical significant correlations between change from baseline QTc and dose adjusted for weight. In Table 2 (2/25/95), the largest numerical difference in values for mean adjusted change in QTc from baseline between cetirizine and placebo was 6 msec observed at 0.221-0.294 mg/kg (N=14 patients) and 5.8 msec in the 0.294-0.368 mg/kg (N=17 patients) for the 11-17 day group analysis. At >0.368 mg/kg doses the mean adjusted change in QTc between cetirizine and placebo was 1.4 msec.

Gender:

The sponsor provided us with the summary statistics for the above cited Table 2.10 on the telephone facsimile dated June 13, 1995.

In the summary statistic Table 2.10 (addendum) for change from baseline QTc by gender, a numerical change in mean QTc is observed in females for ECGs obtained on days 11-17. **The change in QTc from baseline for the females** from this analysis group that included ECGs for 34 females and 85 males are as follows: placebo 4.38 msec prolongation (N=13), 5 mg cetirizine 12.96 msec prolongation (N=8) and 10 mg cetirizine 16.24 msec (N=13), in the other two groups that were considered for analysis, endpoint and maximum change, there was no appreciable change in QTc observed between cetirizine and placebo.

For male patients, a numerical difference in mean QTc from baseline was observed at each one of these analysis groups (11-17 days, endpoint and maximum change), with the largest difference observed for QTc measured 11-17 days post

CETIRIZINE-PEDIATRIC SEASONAL ALLERGIC RHINITIS IV (PROTOCOL #S1CE16-0573)

TABLE 2.10 (ADDENDUM)

SUMMARY STATISTICS FOR CHANGE FROM BASELINE QTc BY GENDER

ANALYSIS GROUPING	OBSERVED MEAN ± STANDARD DEVIATION					
	FEMALES			MALES		
	PLACEBO	CETIR 5 MG	CETIR 10 MG	PLACEBO	CETIR 5 MG	CETIR 10 MG
11-17 DAYS						
(No. Pats)	(13)	(8)	(13)	(27)	(27)	(31)
Baseline QTc	429.1 ± 28.86	413.3 ± 27.20	416.1 ± 18.79	423.1 ± 23.96	418.6 ± 25.17	422.4 ± 23.70
Change	4.38 ± 24.89	12.96 ± 39.17	16.24 ± 22.55	-3.28 ± 24.01	-3.84 ± 34.38	7.83 ± 26.15
ENDPOINT						
(No. Pats)	(26)	(21)	(17)	(38)	(43)	(48)
Baseline QTc	418.6 ± 27.73	424.2 ± 31.23	415.4 ± 19.60	419.2 ± 23.12	418.5 ± 23.24	423.2 ± 21.71
Change	12.33 ± 29.94	3.13 ± 31.07	12.57 ± 26.58	0.49 ± 24.59	-5.63 ± 30.21	7.87 ± 23.52
MAXIMUM						
(No. Pats)	(26)	(21)	(17)	(38)	(43)	(48)
Baseline QTc	418.6 ± 27.73	424.2 ± 31.23	415.4 ± 19.60	419.2 ± 23.12	418.5 ± 23.24	423.2 ± 21.71
Change	12.33 ± 29.94	3.13 ± 31.07	13.51 ± 25.55	1.48 ± 24.61	-5.75 ± 31.68	9.05 ± 24.75

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treatment initiation, 7.83 msec for 10 mg cetirizine (N=31) versus -3.26 msec for placebo treated patients (N=27).

In this table, the change in QTc in male patients was always negative or reduced for male patients treated with 5 mg of cetirizine and (positive or prolonged) for female patients.

Race:

The sponsor provided us with the summary statistics for the above Table 2.11 on the telephone facsimile dated June 13, 1995.

In the summary statistic Table 2.11 (addendum) for change from baseline QTc by race, there were a total of 18 non-white patients in the analysis compared to 101 white patients. In the white patients that had the ECG recorded 11-17 days post treatment initiation, the largest mean difference from baseline in mean QTc was a mean prolongation of 9.32 msec for the 10 mg cetirizine patients (N=35) versus a decrease of 1.24 msec in the placebo treated group (N=34). However, the largest numerical change from baseline in mean QTc by race was observed in the 11-17 days group analysis for the non-white patients. The mean prolongation in QTc for 9 patients treated with 10 mg cetirizine was 14.19 msec and 1.79msec for 6 placebo treated patients.

In terms of gender, even though the numerical differences are more prominent in females for the 11-17 days, a numerical difference between 10 mg cetirizine and placebo is seen for males, across the different groups used for the analyses: 11-17 days, endpoint and maximum. The range for this difference between 10 mg cetirizine versus placebo treated males in these three analysis groups is 7.38 to 11.11 msec.

There are larger or more noticeable numerical differences in mean QTc from baseline in the 11-17 day period analysis for the 10 mg cetirizine treated group versus placebo than in the other analysis groupings (maximum change and endpoint) for comparisons made by gender, race and for the over 25 kg in body weight.

Because the number of non-white and under 25 kg patients studied is small compared to their counterparts, very little can be said in terms of a particular effect on mean QTc prolongation.

To explain the larger numerical differences in QTc that are reported in Table 2.2 for change from baseline QTc in endpoint and maximum ECG (see following page, from vol. 35.1 page 23) between treatment groups using the Bazett correction as compared to the Hodges correction reported in the 9/3/93 submission to NDA 20346, the sponsor states that it is related to a higher heart rate observed in the 10 mg cetirizine treated group. However

CETIRIZINE - PEDIATRIC SEASONAL ALLERGIC RHINITIS IV (PROTOCOL 891CE16-0573)
TABLE 2.2 : SUMMARY OF ANALYSIS OF CHANGE FROM BASELINE IN HEART RATE AND QT INTERVAL
FOR LAST OR MAXIMUM ECG RECORDED ON TREATMENT
(EXCLUDING ANY ECG RECORDED MORE THAN 24 HOURS POST LAST DOSE)

	MEAN ± STANDARD DEVIATION			P-VALUE
	PLACEBO	5MG CETIRIZINE	10MG CETIRIZINE	
NUMBER OF PATIENTS	64	64	65	
HEART RATE				
BASELINE	79.03± 11.45	80.47± 15.09	78.40± 12.85	
CHANGE	0.89± 11.67	0.63± 12.81	4.00± 11.34	
(P-VALUE WITHIN)	0.677	0.135	3.826	
ADJUSTED CHANGE¹	0.79	1.09	3.72	0.241
QT (UNCORRECTED)				
BASELINE	367.14± 26.33	366.92± 26.89	371.15± 27.20	
CHANGE	2.83± 18.36	-5.16± 16.09	-0.78± 19.45	
(P-VALUE WITHIN)	0.226	0.011	0.398	
ADJUSTED CHANGE¹	2.58	-5.64 ^{##}	-0.09 ⁺	0.826
QTc (BAZETT)				
BASELINE	418.75± 24.88	421.82± 25.98	421.15± 21.31	
CHANGE	5.58± 27.35	-3.47± 38.60	5.18± 24.25	
(P-VALUE WITHIN)	0.192	0.735	0.008	
ADJUSTED CHANGE¹	4.39	-3.82 ^{##}	9.59 ⁺⁺	0.008
MAX QT (UNCORRECTED)				
BASELINE	367.14± 26.33	366.92± 26.89	371.15± 27.20	
CHANGE	3.13± 18.56	-5.00± 17.30	0.00± 19.49	
(P-VALUE WITHIN)	0.158	0.016	0.515	
ADJUSTED CHANGE¹	2.88	-5.38 ^{##}	0.77 ⁺⁺	0.021
MAX QTc (BAZETT)				
BASELINE	418.75± 24.88	421.82± 25.98	421.15± 21.31	
CHANGE	5.89± 27.21	-2.04± 31.62	10.22± 24.84	
(P-VALUE WITHIN)	0.107	0.087	0.002	
ADJUSTED CHANGE¹	4.92	-2.48 ^{##}	10.75 ⁺⁺	0.006

¹ ADJUSTED FOR BASELINE DIFFERENCES.

^{##} STATISTICALLY SIGNIFICANTLY DIFFERENT FROM PLACEBO (P<.10)

^{##} STATISTICALLY SIGNIFICANTLY DIFFERENT FROM PLACEBO (P<.05)

⁺ STATISTICALLY SIGNIFICANTLY DIFFERENT FROM 5MG CETIRIZINE (P<.10)

⁺⁺ STATISTICALLY SIGNIFICANTLY DIFFERENT FROM 5MG CETIRIZINE (P<.05)

according to the sponsor's Table 2.2, even though there is a numerical difference in heart rates observed between treatment groups in terms of change from baseline, no statistical differences are seen, $p=0.241$.

The following references were reviewed to ascertain to what extent the Bazett would over correct the QT at high heart rates:

In: Morganroth J. (ed). QTc interval prolongation: is it beneficial or harmful? The American Journal of Cardiology, vol 72, No. 6, 1993.

Funk-Brentano C and Jaillon P. Rate-Corrected QT interval: Techniques and limitations, p17B-p22B.

Rautaharju PM, Warren JW. Estimation of QT prolongation. A persistent, avoidable error in computer electrocardiography. Journal of Electrocardiography. 1990: 23(suppl):111-117.

Macfarlane PW, Coleman EN, Devine E et al. A new 12-lead pediatric ECG interpretation program. Journal of Electrocardiography. 1990: 23(suppl):76-81.

The authors in the review from the American Journal of Cardiology suggest reporting the QT at defined heart rates in preference to using one of the corrections; the article briefly discusses the future importance that using repolarization parameters may have in predicting arrhythmic events. However, the authors state that for studies where QTc is a major end-point they prefer the Fridericia correction. In this article differences between the Fridericia and Bazett are emphasized at RR intervals of 1000 msec and above. These would correspond to a heart rate of 60 beat/min and below.

Rautaharju's article points out that the traditional Bazett's fails at low heart rates and the Fridericia at high heart rates. According to the reported figures in this article, the cut off for the Bazett would be HR <60 b/min and for the Fidericia HR greater the 100 b/min. This article also points out that the fact that the QTc (Bazett) for normal women is longer than for normal men appears to be due to QT shortening in males after puberty and a gradual linear increase in adult males, with no significant age trends in females between puberty and menopause. For this purpose the authors propose a correction for QT prediction in males 15-50 years of age.

The Macfarlane article uses the Hodges correction in

the pediatric population, and 460 msec as the upper limit of normal. The authors report that for this correction there is a small but significant correlation between age and QTc, but that for the first 7 days of life, the QTc decreases. They point out that there is a need of a more satisfactory equation to improve sensitivity in detecting prolonged QTc in the pediatric population. The article also emphasizes the need to use ECG machines that take 500 samples/sec rather than 250 samples/sec, to achieve acceptable accuracy. From reading this article this reviewer considers that the authors concerns in terms of the sensitivity of QTc correction were related more to the neonatal period than to the rest of the pediatric age group.

In Table 8, Appendix 1 from Friedman's Diagnostic Electrocardiography and Vectocardiography, McGraw Hill, 1985, the following values, using the Bazett formula are given:

Age	# cases	Mean	Range
0-24 hr	32	0.42	0.37-0.53
0-2 years	16	0.40	0.37-0.42
2-4	16	0.40	0.38-0.42
8-10	16	0.41	0.39-0.42
11-14	15	0.41	0.40-0.42
Adults	48	0.38	0.35-0.44

Only two patients that had a 10% or greater prolongation in QTc from baseline and a QTc post treatment >440 also had a heart rate greater than 100 beats/min. These were placebo patient #186 and 10 mg cetirizine patient #275.

From reviewing the above references it does not appear that the need to use a QTc correction other than the Bazett would be justified in this study. In other studies where there are patients with a mean heart rate of < 60 b/sec other QTc corrections may be justified.

The following individual data from the PEDs-4 study is noted:

The following table looks at the individual data from patients that had the ECGs recorded on days 11-17 days of treatment that had an increase of 10% or greater over baseline QTc with a QTc that was > 440 msec:

Patients with a 10% or greater change from baseline in QTc (Bazett) and QTc > 440 msec for ECGs recorded on days 11 to 17 of treatment, in parenthesis, baseline QTc followed by prolonged QTc:

Placebo	5 mg cet	10 mg cet
92N0036-298 (408-452)	92N0038-264 (416-469)	92N0036-299 (425-472)
	92N0040-219 (377-450)	92N0037-275 (405-458)
	92N0038-282 (393-457)	92N0037-278 (402-458)

Patients with a 10% or greater change from baseline in QTc (Bazett) and QTc > 440 msec for ECGs recorded post day 17 of treatment in parenthesis, baseline QTc followed by prolonged QTc:

Placebo	5 mg cet	10 mg cet
92N0041-50 (380-454)	92N0043-179 (398-457)	92N0043-169 (395-442)
92N0042-57 (404-454)		92N0044-144 (403-445)
92N0042-186 (386-457)		

The following are the patients with a 10% or greater increase in QTc from baseline and a QTc greater than 440 msec when the patients with post treatment recorded ECGs at heart rates of 100 b/min or greater are excluded:

Patients with a 10% or greater change from baseline in QTc (Bazett) and QTc > 440 msec for ECGs recorded on days 11 to 17 of treatment:

Placebo	5 mg cet	10 mg cet

92N0036-298 (B,F)	92N0038-264 (W,M, 0.09 mg/kg) 92N0040-219 (W.M, 0.15 mg/kg) 92N0037-282 (W,F, 0.16 mg/kg)	92N0036-299 (W,F, 0.29 mg/kg) 92N0037-278 (B,F, 0.32 mg/kg)

The following additional patients have a change in QTc of 10% or greater (Bazett) and a post treatment QTc > 440 msec when ECGs were recorded beyond 17 days of treatment. When the patients with ECGs recorded beyond the above time frame of 11-17 days are included, :

Placebo	5 mg cet	10 mg cet
92N0042-50 (B,F) 92N0042-57 (W.M)	92N0040-179 (W,M, 0.17 mg/kg)	92N0043-169 (W,F, 0.36 mg/kg) 92N0044-144 (W.M, 0.32 mg/kg)

3. Using the Bazett formula, please list the QTc prolongations that are more than 10% over baseline, for the three studies: 90CK16-0497, 92CK16-0603 and 92CK16-0604, by patient, indicating study phase, day, and hour.

The listing requested for the QTc prolongations that are more than 10% over baseline for studies 90CK16-0497, 92CK16-0603 and 92CK16-0604 are provided in Tables 3.1, 3.2 and 3.3 respectively.

The following reviewer's tables depict the information provided in the submission grouping patients by treatment and listing the number of events with a QTc prolongation that is 10% or greater and the maximum % prolongation in QTc (>=or > 10%) for that patient, under that treatment.

Study 90CK16-0497

Multiple dose, placebo controlled crossover study, third party blinded and a wash-out of 5 days.

Subjects (24, males, 24 white, 1 black) received placebo for 2 days before receiving either 20 or 60 mg of cetirizine for 7 days.

Placebo Pt.# (# events, max. %prolongation, * = >440 msec)	Cet 20 mg Pt.#(# events, max. % prolongation, * = >440 msec)	Cet 60 mg Pt.# (# events, max. %prolongation, * = > 440 msec)
5 (1, 15.6)		
10 (1, 11.7*)	10 (1, 11.0)	10 (1, 11.4)
		11 (1, 11.2*)
12 (1, 12.9)	12 (1, 12.0*)	
16 (1, 11.3)		16 (5, 15.4,(1/5*)
		18 (1, 13.5)
19 (3, 13.4,(1/3*)		19 (2,12.0)
20 (1,13.3)	20 (2, 11.5)	
		21 (1, 11.6)
	22 (4, 19.0,(1/4*-481msec)	
Totals: 6 patients, 8 events 15.6%- max prolongation	Totals: 4 patients, 8 events 19.0%- max prolongation	Totals: 6 patients, 11 events 15.4%- max prolongation

Study 92CK16-0603

Multiple dose, randomized, open (cardiologist-blinded), two way crossover with a 20 day wash-out period. Subjects (16, male: 12 hispanics, 2 black, 2 white) received 1 day placebo followed by 400 mg ketoconazole or placebo for 5 days, and then for 10 days the combination of ketoconazole and cetirizine for those that had received ketoconazole or 20 mg cetirizine for those that had only received placebo.

Placebo Pt.# (# events, max. %prolongation, * = >440 msec)	Cet 20 mg Pt.# (# events, max. %prolongation, * = >440 msec)	Ketoconazole 400 mg Pt.# (# events, max. %prolongation, * = >440 msec)	Combination Pt.# (# events, max. %prolongation, * = >440 msec)
6 (1,10.9)	6 (2, 11.7,(1/2*)		6 (4, 14.5,(1/4*)
10 (1, 11.3)	10 (2, 12.6)		—
		2 (1, 10.7)	2 (5, 12.3)
	4 (2, 12.2)		
			5 (3, 12.7)
			7 (10, 15.7)
	8 (1, 10.6)		8 (1, 10.6)
	9 (1, 12.0)		
		11 (4, 14.2)	11 (4, 13.9)
			12 (5, 13.0)
	14 (3, 12.2,(2/3*)	14 (1, 10.1)	14 (7, 15.6)
			15 (1, 10.2)
	16 (1, 10.3)		
Totals: 2 patients, 2 events, 11.3 (max % prolongation)	Totals: 7 patients, 12 events, 12.6 (max % prolongation)	Totals: 3 patients, 6 events, 14.2 (max % prolongation)	Totals: 9 patients, 40 events, 15.7(max % prolongation)

Study 92CK16-0604

Multiple dose, randomized, open (cardiologist-blinded), two-way cross-over with a 20 day wash-out period. Subjects (16, male 9 hispanics, 7 white) received placebo for one day, followed by cetirizine (20 mg) or erythromycin (500 mg) alone for five days each before each group received the combination for 10 days.

Placebo Pt.# (#events, max. %prolongation, * > 440 msec)	Cet 20 mg Pt.# (#events, max. %prolongation, * > 440 msec)	Erythro 500mg Pt.# (#events, max. %prolongation, * > 440 msec)	Combination Pt.# (#events, max. %prolongation, * > 440 msec)	
			Cetirizine given first	erythro given first
			1 (2, 14.1)	
				3 (1, 18.4*)
				4 (1, 10.5)
		5 (1, 11.7)		
				6 (1, 13.2)
				8 (1, 20.6*)
	9 (1, 11.1)		9 (1, 10.3*)	
				10 (2, 19.1/2*)
		12 (1, 10.2)	12 (1, 10.8)	
		13 (1, 11.4)		13 (8, 20.1)
			15 (5, 20.1, (2/5*))	
			16 (1, 10.9)	
			102 (6, 18.9(1/6*))	102 (3, 12.5)
Totals: 0 patients, 0 events, 0, max % prolongation	Totals: 1 patient, 1 event, 11.1, max % prolongation	Totals: 3 patients, 3 events, 11.7, max %prolongation	Total: 6 patients 16 events 20.1, max % prolongation	Total: 7 patients, 17 events, 20.6, max % prolongation

In the ketoconazole-cetirizine interaction study 92CK16-

0603, there is an increased frequency of events of QTc prolongation (10% or greater) per subject receiving the combination than when these drugs are taken by themselves. This effect is more readily apparent here using the Bazett correction than with the Hodges correction that was used in the original study report. Using the Hodges correction there were: no event while on placebo, 2 subjects receiving 20 mg of cetirizine with 3 events (10% or greater prolongation in QTc from baseline), 1 ketoconazole with 2 events and 5 receiving the combination with 18 events (MOR date 2/27/94). With the Bazett correction the numbers are: 1 subject with 2 events while on placebo, 7 subjects receiving 20 mg of cetirizine with 12 events (10% or greater prolongation in QTc from baseline), 3 ketoconazole with 6 events and 9 receiving the combination with 40 events. Even though the QTc prolongations in this study were generally not in the 15-20% range the frequency of these particularly using the combination is of concern.

For study 92CK16-0604 the above individual data suggests an effect for the erythromycin-cetirizine combination and a clinical concern for the patients with prolongations around 18-20% over baseline.

The above discussed effects are not seen for study 90CK16-0497. The 19% prolongation in QTc (absolute=481 msec) for subject # 22 while on 20 mg of cetirizine (Day 1 hour 6) is of concern even though it is apparently a single event.

4. Please explain the discrepancies between the results for the requested ECG analysis regarding the number of patients with more than 10% increase in QTc in SAR/LORA and SAR-8 studies provided to us in the March 12, 1993 submission and the data submitted on March 3, 1994 in the safety update. An explanation of why the overall numbers of subjects in the treatment groups differ between the two submissions should also be given.

Response: The results of patients with prolonged QTc in the March 12, 1993 submission were based on the measurements provided by each participating investigator. The results submitted in the March 12, 1994 safety update represent the standardized QTc measurement done on all ECGs by Cardiology Clinical Trials. The total number of patients with ECGs differ in both submissions because in the first one all patients with ECGs were included and in the second submission (3/12/94) only those patients with baseline and posttreatment ECGs were included.

5. In reference to Table 1, Appendix 2 of the July 15, 1993 submission, please list the terms that were included under "psychiatric disorders" and update the corresponding frequencies per term. Please report these results by dose and duration of treatment.

Response: Section D.5.b.1.a.; Tables F8 B1-B4.

The cumulative database in placebo controlled studies included 2679 patients treated with cetirizine and 1671 placebo treated patients. The incidence of adverse experiences in cetirizine and placebo treated patients in the cumulative database are shown in Tables F8 A-B. These trials are in adult patients treated with the tablet and the capsule formulations and include 2 trials conducted in Canada. These are referred in the submission as U.S. sponsored trials. The cumulative safety data includes data in NDA 19835 filed on June 30, 1988 and the post NDA data through February 26, 1994.

The most common adverse experiences by body systems are Central and Peripheral Nervous system Disorders (which includes headache), Psychiatric Disorders (which includes somnolence) and Body as a Whole (which includes fatigue).

From Table F8.B1

Adverse experience	cetirizine No. Pts (%)	placebo No. PTS (%)
Total No. of Pts	2679	1671
N. of Pts with any AE	1158 (43.2%)	610 (36.5%)
Centr and Periph Nervous Syst Disorder	504 (18.8%)	324 (19.4%)
Psychiatric Disorders	464 (17.3%)	143 (8.6 %)
Body as a whole	225 (8.4%)	86 (5.1%)

As shown in Table F8.B2, somnolence accounts for the majority of the incidence of all terms which are included under psychiatric disorders.

The incidence of the specific terms are shown in Table F8.B2 from placebo controlled adult studies.

Adverse experience	cetirizine No. Pts (%)	placebo No. PTS (%)
Total No. of Pts	1679	1671
N. of Pts with Psychiatric Disorders	464 (17.3%)	143 (8.6%)

Somnolence	405 (15.1%)	105 (6.3%)
Nervousness	26 (1.0%)	14 (0.82%)
Concentration impaired	6 (0.2%)	1 (0.1%)
Emotional liability	5 (0.2%)	0 (0.0%)
Depression	4 (0.1%)	1 (0.1%)
Thinking abnormal	4 (0.1%)	0 (0.0%)

The incidence by dose of the Psychiatric Disorder are shown in Table F8.B3 for **placebo-controlled fixed dose studies**.

Adverse experience	Combined Cet No. Pts (%)	cet 5 mg	cet 10 mg	cet 20 mg	placebo No. PTS (%)
Total No. of Pts	2532	430	1489	554	1531
N. of Pts with Psychiatric Disorders	428 (16.9%)	58 (13.5%)	243 (16.3%)	119 (21.5%)	123 (8.1%)
Somnolence	373 (14.7%)	49 (11.4%)	205 (13.8%)	112 (20.2%)	90 (5.9%)
Nervousness	23 (0.9%)	2 (0.5%)	13 (0.9%)	8 (1.4%)	11 (0.7%)
Concentration impaired	6 (0.2%)	0 (0%)	6 (0.4%)	0 (0%)	1 (0.1%)
Emotional liability	5 (0.2%)	3 (0.7%)	1 (0.1%)	1 (0.2%)	0 (0.0%)
Depression	4 (0.2%)	1 (0.2%)	3 (0.2%)	0 (0%)	1 (0.1%)
Thinking abnormal	4 (0.2%)	1 (0.2%)	3 (0.2%)	0 (0%)	0 (0.0%)

Incidence of psychiatric disorders adverse experiences in placebo controlled studies by duration of treatment.

Adverse experience	cet up to 2 wks No. Pts (%)	cet 3-4 wks	cet 5-12 wks	placebo up to 2 wks	placebo 3-4 wks	placebo 5-12 wks
Total No. of Pts	2676	1835	957	1671	1147	586
N. of Pts with any Psychiatric Disorders	425 (15.9%)	160 (8.7%)	82 (8.6%)	133 (8.0%)	45 (3.9%)	22 (3.8%)
Somnolence	374 (14.0%)	135 (7.4%)	71 (7.4%)	96 (5.8%)	32 (2.8%)	17 (3.0%)
Concentration impaired	5 (0.2%)	0 (0%)	1 (0.1%)	1 (0.1%)	0 (0%)	0 (0%)
Emotional liability	3 (0.1%)	2 (0.1%)	3 (0.3%)	0 (0%)	0 (0%)	0 (0%)
Depression	4 (0.2%)	2 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.2%)
Thinking abnormal	4 (0.2%)	3 (0.2%)	2 (0.2%)	0 (0%)	0 (0%)	0 (0.0%)

* A patient can have an adverse experience reported for more than one interval of cetirizine therapy.

Agree with the sponsor's conclusion that somnolence accounts with the majority of the incidence of the reports in this category. The above series of tables also demonstrate that at doses of 5 and 10 mg it is approximately double the reported incidence in placebo treated patients (Table F8. B2-B3) and that this incidence persists at the different time intervals: up to 2 weeks, 3-4 weeks and 5-12 weeks of treatment (Table F8. B-4).

The reported incidence rates of other adverse events such as: concentration impaired, emotional liability and thinking abnormal are less than 1% but they are reported more frequently and for a longer duration than in placebo treated patients.

6. Please provide an integrated safety update. As discussed, the cutoff date of February 1994 can be used. Intercurrent illnesses must be included in the adverse event database for the new patients. Any reports of serious adverse reactions after February 1994 should also be submitted; please include manufacturer number of the reports.

The following issues should be addressed in the integrated safety update. If the new database is small and will not be integrated into your previous database, these issues should be addressed for the March 3, 1994 integrated safety update.

- a. Please analyze and submit duration of exposure by dose, gender and race.

Response: Section D.5.f.3. Tables F-16.A F16.N

Tables F16.A and C summarize the incidence of adverse experiences in patients treated with cetirizine maximum dose of 5 and 10 mg respectively by duration of treatment in the cumulative database. In these tables the total number of patients that discontinued due to adverse events was also included. Copy of these tables follow.

The percentage of patients reporting adverse events for the time periods selected are about the same for both doses, except for the 13 wk to 6 mo interval. Here the % of patients treated with the 5 mg dose reporting adverse events was greater, 11/34 (32.4%) than those on the 10 mg dose 13/69 (19.0%).

The majority of the patients treated with the 5 and 10 mg dose discontinued the study during the first two weeks of treatment. The percent of patients that discontinued due to adverse events for the two doses was about the same over the first four weeks of treatment. Five patients on the 10 mg dose discontinued the study during the 5-12 weeks of treatment whereas only 1 that was treated with the 5 mg did. The specific reasons for study discontinuations are not listed in these tables.

In **Tables F16.B and D** the detailed incidence of adverse events of patients (cumulative database) treated with cetirizine 5 and 10 mg respectively are shown. There are approximately 70 different adverse event terms reported for the 5 mg treated patients and 130 for the 10 mg treated patients in these tables.

Fatigue is reported at higher frequency in the 10 mg dose in the first 4 wks of treatment.

TABLE F16.A: SUMMARIZED INCIDENCE OF ADVERSE EXPERIENCES IN PATIENTS TREATED WITH CETIRIZINE MAXIMUM DOSE 5 MG BY DURATION OF TREATMENT (CUMULATIVE DATABASE)* BY MAXIMUM DOSE

TREATMENT: CETIRIZINE MAXIMUM DOSE 5 MG

ADVERSE EXPERIENCES ¹	CETIRIZINE			
	UP TO 2 WKS NO. PTS. (%)	3-4 WKS NO. PTS. (%)	5-12 WKS NO. PTS. (%)	13 WKS-6 MOS. NO. PTS. (%)
TOTAL NO. OF PATIENTS ²	589	397	273	34
TOTAL NO. OF PTS. WITH ADVERSE EXPERIENCES	214 (36.33%)	98 (24.69%)	75 (27.47%)	11 (32.35%)
TOTAL NO. OF PATIENTS DISCONTINUED DUE TO ADVERSE EXPERIENCES	12 (2.04%)	3 (0.76%)	1 (0.37%)	0 (0.00%)
TOTAL NO. OF ADVERSE EXPERIENCES	332	141	106	14

*CUMULATIVE DATABASE INCLUDES NDA, UPDATE AND NEW STUDIES

¹A PATIENT CAN HAVE AN ADVERSE EXPERIENCE REPORTED FOR MORE THAN ONE INTERVAL OF CETIRIZINE THERAPY.

THEREFORE, THE PATIENT INCIDENCE IS NOT NECESSARILY EQUAL TO THE SUM OF ENTRIES FOR ALL TIME INTERVAL COLUMNS.

²FOR 84 PATIENTS (04N0055 PATIENT 71,05N0051 PATIENT 8 AND 06N0199, PATIENT 8, PROTOCOL C-89001; 78 PATIENTS AND PROTOCOL L-0103; 3 PATIENTS) THE START DATE OF MEDICATION COULD NOT BE DETERMINED. THESE PATIENTS ARE EXCLUDED FROM THIS TABLE.

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TABLE F16.C: SUMMARIZED INCIDENCE OF ADVERSE EXPERIENCES IN PATIENTS TREATED WITH CETIRIZINE MAXIMUM DOSE 10 MG BY DURATION OF TREATMENT (CUMULATIVE DATABASE)* BY MAXIMUM DOSE

TREATMENT: CETIRIZINE MAXIMUM DOSE 10 MG

ADVERSE EXPERIENCES ¹	CETIRIZINE			
	UP TO 2 WKS NO. PTS. (%)	3-4 WKS NO. PTS. (%)	5-12 WKS NO. PTS. (%)	13 WKS-6 MOS. NO. PTS. (%)
TOTAL NO. OF PATIENTS ²	1961	1225	529	69
TOTAL NO. OF PTS. WITH ADVERSE EXPERIENCES	758 (38.65%)	312 (25.47%)	139 (26.28%)	13 (18.84%)
TOTAL NO. OF PATIENTS DISCONTINUED DUE TO ADVERSE EXPERIENCES	40 (2.04%)	7 (0.57%)	4 (0.76%)	1 (1.45%)
TOTAL NO. OF ADVERSE EXPERIENCES	1236	439	185	18

*CUMULATIVE DATABASE INCLUDES NDA, UPDATE AND NEW STUDIES

¹A PATIENT CAN HAVE AN ADVERSE EXPERIENCE REPORTED FOR MORE THAN ONE INTERVAL OF CETIRIZINE THERAPY.

THEREFORE, THE PATIENT INCIDENCE IS NOT NECESSARILY EQUAL TO THE SUM OF ENTRIES FOR ALL TIME INTERVAL COLUMNS.

²FOR 84 PATIENTS (84N0055 PATIENT 71, 05H0051 PATIENT 8 AND 86N0399, PATIENT 8, PROTOCOL C-89001: 78 PATIENTS AND PROTOCOL L-0103: 3 PATIENTS) THE START DATE OF MEDICATION COULD NOT BE DETERMINED. THESE PATIENTS ARE EXCLUDED FROM THIS TABLE.

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DATE: 04/12/95 9:15:14

Even though the % of patients reporting increase in appetite is greater for those treated with 5 mg, the % of patients reporting a weight increase is greater for those patients that had been treated with the 10 mg tablet.

Adverse experience	Cet 5 mg up to 2 wks	Cet 5 mg 3-4 wks	Cet 5 mg 5-12 wks	Cet 5 mg 15wks to 6 mo
Total No. of pts	589	397	273	34
Total No. of pts with adverse experiences	214 (36.3%)	98 (24.7%)	75 (27.5%)	11 (32.4%)
fatigue	18 (3.1%)	9 (2.3%)	8 (2.9%)	0 (0%)
weight increase	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)
Adverse experience	Cet 10 mg up to 2 wks	Cet 10 mg 3-4 wks	Cet 10 mg 5-12 wks	Cet 10 mg 15wks to 6 mo
Total No. pts.	1961	1225	529	69
Total No. of pts with adverse experiences	758 (38.7%)	312 (25.5%)	139 (26.3%)	13 (18.9%)
fatigue	102 (5.2%)	48 (3.9%)	14 (2.7%)	1 (1.5%)
weight increase	9 (0.5%)	11 (0.9%)	10 (1.9%)	3 (4.4%)

The reports of weight increase during longer duration of treatment are more apparent in the higher dose group.

In these listings, the following are noted, in parenthesis, duration of exposure:

Diabetes Mellitus: 5mg dose at the 5-12 week interval (1)
 Polyuria: 10 mg (up to 2 wks) (4), 3-4 wks) (1)
 Purpura: 5 mg dose at the 3-4 week interval (1) and 5-12 wk interval (1)
 Purpura: 10 mg (up to 2 weeks) (1)
 Hematuria: 10 mg (3-4 weeks) (1)
 Ocular hemorrhage: 10 mg (up to 2 weeks) (1)
 visual field defect: 10 mg (up to 2 weeks) (1)
 vision abnormal: 5 mg (up to 2 wks) (2), (3-4 weeks) (1)
 vision abnormal: 10 mg (up to 2 wks) (2), (3-4 weeks) (1)
 Ptosis: 10 mg (up to 2 weeks) (1) and (3-4 weeks) (1)
 Tinnitus: 5 mg (up to 2 weeks) (1)
 Tinnitus: 10 mg (up to 2 weeks) (1), (3-4 wk) (1), 5-12 wks) (1)

Deafness: 10 mg (up to 2 weeks) (1) and (3-4 weeks) (1)
 Ototoxicity: 10 mg (up to 2 weeks) (1)
 Ataxia: 10 mg, (up to 2 wks) (1), (3-4 wks) (1)
 Melena: 10 mg (up to 2 weeks) (1)
 Gastritis: 10 mg (up to 2 wks) (1), (3-4 weeks) (1)
 Cardiac failure: 10 mg (up to 2 weeks) (1)

Gender

Females. From Sponsor's Table F16.G

Adverse experience	cet up to 2 wks No. Pts (%)	cet 3-4 wks	cet 5-12 wks	cet 13 wks -6 mo
Total No. of Pts	2072	1211	640	139
N. of Pts with Adverse Experiences	873 (42.1%)	398 (32.9)	210 (32.8%)	59 (42.5%)
Pts. discontinued due to adverse experiences	54 (2.6%)	8(0.7%)	5 (0.8%)	2 (1.4%)
total number of adverse experiences	1427	569	309	81

Males. From Sponsor's Table F16.E

Adverse experience	cet up to 2 wks No. Pts (%)	cet 3-4 wks	cet 5-12 wks	cet 13 wks -6 mo
Total No. of Pts	1819	1147	577	98
N. of Pts with Adverse Experiences	629 (34.6%)	256 (22.3%)	130 (22.5%)	24 (24.5%)
Pts. discontinued due to adverse experiences	29 (1.6%)	6(0.5%)	1 (0.2%)	0 (0%)
total number of adverse experiences	965	359	170	34

"Table F13 summarizes the adverse experiences by race in placebo-controlled studies. The majority of the patients treated with cetirizine were white (88%-2358/2679), compared to 8% (223/2679) black patients, and 4% (98/2679) patients in the "other" category. The "other" group is composed of Hispanics and Oriental patients. Among the placebo group there were 86% (1440/1671) white patients, 9% (147/1671) black patients and 5% (84/1671) "other" patients.

The incidence of adverse experiences for white patients were: 44.4% cetirizine, 37.2% placebo; for black patients: 35.9% cetirizine, 32.7% placebo; for "other" patients 32.7% cetirizine and 32.1% placebo.

For the cetirizine treated patients, there were 2.9% discontinuations among white patients, 3.6% among black patients and 1% among "other" patients.

Regarding the most frequent adverse experiences reported by cetirizine treated patients, 9% of blacks reported headaches compared to 17.6% of whites and 17.3% of "other" patients. Somnolence was reported by 19.3% of black patients, 14.9% of white patients and 10.2% of "other" patients.

There were no statistically significant differences in relative incidence of discontinuation or incidence of overall adverse events. The relative incidence were also compared among races for the common adverse experiences of headache, somnolence, fatigue and dry mouth. Except for fatigue, race is not a significant factor in determining the risk of these events beyond the expected incidence in the general population. The observed incidence of fatigue is slightly higher for the "other" race category. However, in the absence of significant dependence on race on any other cetirizine-related adverse experience, this single finding is probably related to very low incidence in a small subgroup of patients, and therefore it is difficult to draw any meaningful conclusion."

- b. Please analyze and submit adverse event rates by use of oral contraceptives. U.S. and foreign studies should be analyzed separately.

Response: SU 4/25/95 vol. 2, D.5.b.1.c. and vol 3 Tables F8.E-F.

"A total of 185 cetirizine treated patients and 141 placebo treated patients received concomitant oral contraceptives. In comparison 1116 and 736 placebo treated patients did not receive concomitant oral contraceptives."

"There are no significant differences in the relative incidence of the most common adverse experiences, headaches, somnolence, fatigue and dry mouth in cetirizine patients treated concomitantly with oral contraceptives and cetirizine patients who did not receive concomitant oral contraceptives."

From Table F8.F, for patients on cetirizine that are not using oral contraceptives the reported incidence of

TABLE F8.E: SUMMARIZED INCIDENCE OF ADVERSE EXPERIENCES IN FEMALE PATIENTS TREATED WITH CETIRIZINE OR PLACEBO IN PLACEBO-CONTROLLED STUDIES

	INCIDENCE IN SAFETY EVALUABLE FEMALE PATIENTS			
	BIRTH CONTROL USER		NON-BIRTH CONTROL USER	
	CETIRIZINE NO. PTS. (%)	PLACEBO NO. PTS. (%)	CETIRIZINE NO. PTS. (%)	PLACEBO NO. PTS. (%)
TOTAL NO. OF PATIENTS	185	141	1116	736
TOTAL NO. OF PTS. WITH ADVERSE EXPERIENCES	84 (45.41%)	59 (41.84%)	526 (47.15%)	303 (41.17%)
TOTAL NO. OF PATIENTS DISCONTINUED DUE TO ADVERSE EXPERIENCES	5 (2.70%)	5 (3.55%)	41 (3.67%)	20 (2.72%)
TOTAL NO. OF ADVERSE EXPERIENCES	143	96	952	501

FILE: CSFK39
DATE: 04/11/95 14:31:37

TABLE F0.F: INCIDENCE OF ADVERSE EXPERIENCES IN FEMALE PATIENTS TREATED WITH CETIRIZINE OR PLACEBO
IN PLACEBO-CONTROLLED STUDIES

ADVERSE EXPERIENCES	INCIDENCE IN SAFETY EVALUABLE FEMALE PATIENTS			
	BIRTH CONTROL USER		NON-BIRTH CONTROL USER	
	CETIRIZINE NO. PTS. (%)	PLACEBO NO. PTS. (%)	CETIRIZINE NO. PTS. (%)	PLACEBO NO. PTS. (%)
TOTAL NO. OF PATIENTS	185	141	1116	736
NO. OF PTS. WITH ADVERSE EXPERIENCES	84 (45.41%)	59 (41.84%)	526 (47.13%)	303 (41.17%)
HEADACHE	31 (16.76%)	36 (25.53%)	216 (19.35%)	153 (20.79%)
SOMNOLENCE	26 (14.05%)	11 (7.80%)	181 (16.22%)	40 (5.43%)
FATIGUE	11 (5.95%)	1 (0.71%)	70 (6.27%)	19 (2.58%)
MOUTH DRY	5 (2.70%)	5 (3.55%)	71 (6.36%)	23 (3.13%)
NAUSEA	7 (3.78%)	6 (4.26%)	40 (3.58%)	27 (3.67%)
DIZZINESS	4 (2.16%)	2 (1.42%)	23 (2.06%)	14 (1.90%)
PHARYNGITIS	7 (3.78%)	4 (2.84%)	20 (1.79%)	16 (2.17%)
COUGHING	2 (1.08%)	0 (0.00%)	16 (1.43%)	7 (0.95%)
NERVOUSNESS	2 (1.08%)	1 (0.71%)	14 (1.25%)	8 (1.09%)
RESPIRATORY DISORDER	1 (0.54%)	1 (0.71%)	15 (1.34%)	10 (1.36%)
INSOMNIA	2 (1.08%)	0 (0.00%)	13 (1.16%)	13 (1.77%)
RHINITIS	4 (2.16%)	2 (1.42%)	10 (0.90%)	3 (0.41%)
BACK PAIN	2 (1.08%)	0 (0.00%)	11 (0.99%)	7 (0.95%)
EPISTAXIS	2 (1.08%)	1 (0.71%)	11 (0.99%)	2 (0.27%)
EARACHE	0 (0.00%)	0 (0.00%)	12 (1.08%)	4 (0.54%)
ABDOMINAL PAIN	0 (0.00%)	2 (1.42%)	11 (0.99%)	6 (0.82%)
DYSPEPSIA	3 (1.62%)	0 (0.00%)	8 (0.72%)	14 (1.90%)
WEIGHT INCREASE	3 (1.62%)	1 (0.71%)	8 (0.72%)	3 (0.41%)
DYSMENORRHEA	2 (1.08%)	3 (2.13%)	8 (0.72%)	3 (0.41%)
PARESTHESIA	3 (1.62%)	0 (0.00%)	6 (0.54%)	2 (0.27%)
APPETITE INCREASED	2 (1.08%)	1 (0.71%)	6 (0.54%)	2 (0.27%)
DIARRHEA	1 (0.54%)	1 (0.71%)	7 (0.63%)	6 (0.82%)
MALaise	1 (0.54%)	0 (0.00%)	7 (0.63%)	4 (0.54%)
PRURITUS	2 (1.08%)	3 (2.13%)	6 (0.54%)	13 (1.77%)
EYE ABNORMALITY	1 (0.54%)	1 (0.71%)	6 (0.54%)	1 (0.14%)
PALPITATION	1 (0.54%)	0 (0.00%)	6 (0.54%)	4 (0.54%)
VOMITING	1 (0.54%)	2 (1.42%)	6 (0.54%)	4 (0.54%)
CHEST PAIN	0 (0.00%)	0 (0.00%)	6 (0.54%)	3 (0.41%)

-- (CONTINUED) --

somnolence is 16.2% whereas in those that are is 14.1%. The incidence of patients reporting dry mouth not using oral contraceptives is 6.4% and for those that are not is 2.7%.

"There were no significant differences in discontinuation rates due to adverse experiences in cetirizine treated patients who were treated concomitantly with oral contraceptives and those who were not receiving oral contraceptives."

- C. Lab data (change from baseline, percent of subjects with abnormal labs), should be analyzed by treatment, dose, age, gender and race. Please submit the list of patients whose pre-treatment lab values were within normal limits and who had any of the following lab values post initiation of treatment with cetirizine: SGOT > 65 U/L, SGPT > 60 U/L, BUN > 25 mg/dl, or serum creatinine > 1.5mg/dl. Please provide a brief summary of the above outliers: age, gender, race, dose, duration of treatment prior to the event, concomitant medication used, reported adverse events and dates of reports.

Response: SU 4/25/95, vol.2:D.6.a., D.6.b. and D.6.c.; vol 3: Tables F21-F23F and F-Figures.

The incidence of abnormal hepatic transaminases in all cetirizine treated patients that were considered to be clinically significant and possibly related to study medication (Category 9), according to the sponsor was: SGOT (1%) 27/2979 and SGPT (2%) 52/2926 (SU 4/25/95, vol 35.2, page 9 58). For placebo treated patients these incidence were: SGOT (0%) 6/1525 and for SGPT (1%) 12/1480, (Table F 23.B in SU 4/25/95, vol 35.3, page 9 322).

The majority of the SGOT and SGPT abnormalities regardless of attributable causality were generally less than twice the upper limit of normal. For these, the incidence of abnormal SGOT of more than twice the upper limit of normal appears to be similar in cetirizine and placebo treated patients (0.4%), for SGPT the incidence is (0.3%) versus (0.1%)-SU 4/25/95, vol 35.2 page 9 60.

a. Scatter plots

Scatter plots of pre-therapy values versus end of therapy values were plotted for the hematology and serum chemistry tests. These included: Hct, Hgb, RBC, WBC, neutrophils, bands, lymphocytes, monocytes, basophils, eosinophils, platelets, BUN, creatinine, SGOT, SGPT, T. bilirubin, alkaline phosphatase, and LDH. There were no clear trends in the test results after treatment with cetirizine as compared to placebo.

Scatterplots of BUN, creatinine, SGOT and SGPT by age, gender, race and dose did not reveal a clear trend between cetirizine and placebo.

Further information was requested from the sponsor regarding specific outliers in these scatterplots. The sponsor's response dated August 11, 1995 was reviewed. A alternative explanation as to the possible cause of lab abnormality was not found after review of the CRF for the following patients. These patients were required to have a baseline value within the normal range and at least one abnormal value after the start of treatment:

N-0047 84N0060/49

54 y/o white, female patient in SAR study. In CFR no record of concomitant drugs or illness. Patient received 10 mg cetirizine treatment from 9/19/84 to 9/26/94. Patient completed the study.

Prior to treatment 9/18/84	SGOT=31
	SGPT=27
	LDH=246
	T. bili=0.2
End of treatment 9/26/84	SGOT=80
	SGPT=108
	LDH=272
	T. bili=0.3
10/3/84	SGOT=40
	SGPT=89
	LDH=235
	T. bili=not available in CFR
10/9/84	SGOT=17
	SGPT=26
	LDH=not available in CFR
	T. bili=not available in CFR

N-0050 85N0044/5

35 y/o hispanic female patient in a 4 week chronic idiopathic urticaria study. In the CFR there is no record of concomitant drugs or illness. Patient received 10 mg cetirizine treatment from 9/19/84 to 9/26/94. Patient had received Benadryl for 9 mo. prior to study.

Prior to treatment 6/9/86	SGOT=23
	SGPT=24
	LDH=188
	T. bili=0.5
First Day of treatment 6/11/86	
End of week two 6/25/86	SGOT=82
	SGPT=70

LDH=235
T. bili=0.6

End of Week 4, end of therapy, 7/9/86

SGOT=68
SGPT=168
LDH=211

T. bili=0.7

7/14/86

SGOT=49
SGPT=61

LDH=not available in CFR
T. bili=not available in CFR

N-0356 88-N0053/48

26 y/o white, female patient in an 8 week SAR study. In the CFR there is no record of concomitant drugs or illness. — Patient received 5mg cetirizine treatment from 7/29/88 to 9/23/88 and completed the study.

Prior to treatment 7/29/88 SGOT=17
SGPT=13
LDH=not available in CFR
T. bili=0.8

End of treatment 9/26/88 SGOT=311
SGPT=92
LDH=not available in CFR
T. bili=not available in CFR

10/11/88 SGOT=17
SGPT=17
LDH=not available in CFR
T. bili=not available in CFR

L-230 92-S0C13/100

23 y/o white, female patient in a 2 week SAR study. In the CFR there is a record of asthma as a concomitant illness and the use of Ventolin inhaler 2 puffs qd and of Ortho Novum qd. Patient received 10mg cetirizine treatment from 9/24/92 to 10/08/92 and completed the study.

Prior to treatment 9/10/92 SGOT=21
SGPT=17
LDH=not available in CFR
T. bili=0.4

End of treatment 9/26/88 SGOT=105
SGPT=170
LDH=not available in CFR
T. bili=0.3

10/12/92 SGOT=71
SGPT=129
LDH=not available in CFR

10/22/92 T. bili=not available in CFR
 SGOT=51
 SGPT=70
 LDH=not available in CFR
 T. bili=not available in CFR

b. Mean changes in laboratory results

"Mean changes in laboratory results for patients treated with cetirizine and placebo in placebo controlled studies were analyzed and are shown in **Table 22.A**. There were statistically significant differences between treatment groups for change from baseline in SGOT, SGPT, and creatinine. The mean change for SGOT was 0.84 U/L for the cetirizine group compared to -0.05 U/L for placebo (p<0.02). The mean change for the SGPT from baseline for the cetirizine treatment group was 1.35 U/L compared to -0.19 U/L for placebo (p<0.001). The creatinine mean change from baseline was 0 for creatinine treated patients and 0.13 mg/dl for placebo treated patients." According to the sponsor's **Table 22.A** (cumulative database), these mean changes from baseline represent the following mean percent changes from baseline:

N	Cetirizine	N	Placebo
2488	SGOT=11.64%	1511	SGOT=5.96%
2421	SGPT=15.6%	1451	SGPT=6.85%
2500	T.bili=6.9%	1527	T.bili=6.8%
2497	creatinine=1.84%	1523	creatinine=2.85%
2423	BUN=3.80%	1448	BUN=4.53%

Table 22.B summarizes the changes in laboratory results by dose as found in the NDA versus the cumulative database. When the cumulative database is compared to the NDA database, in the cumulative database the mean percent changes from baseline decreased for SGOT and SGPT for the 5 and 10 mg dose but not for the 20 mg dose where the mean percent change from baseline increased or stayed the same.

For **SGPT**, not considering the 15 mg treated group (N=58), the following are the mean percent changes from baseline in the cumulative database for cetirizine treated patients:

Dose	N	Mean % change
5 mg	559	15.86%
10 mg	1560	12.69%
20 mg	671	19.04%

TABLE F22.A: ANALYSIS OF CHANGES IN LABORATORY RESULTS IN PLACEBO-CONTROLLED STUDIES (CUMULATIVE)

LABORATORY TEST	CETIRIZINE				PLACEBO				P-VALUE OF MEAN BASELINES	P-VALUE OF MEAN CHANGES
	MEAN N BASELINE	CHANGE FROM BASE MEAN	S.D.	MEAN % CHANGE	MEAN N BASELINE	CHANGE FROM BASE MEAN	S.D.	MEAN % CHANGE		
HEMATOLOGY										
HCT(HEMATOCRIT)	2487 42.71	-.322	2.295	-.585	1514 42.4	-.305	2.314	-.558	0.020	0.824
HGB(HEMOGLOBIN)	1692 14.54	-.164	.7967	-.5332	1097 14.4	-.122	.7243	-.724	0.017	0.151
WBC (WHITE BLOOD COUNT)	1691 7.029	-.142	1.574	-.4493	1096 6.929	-0.06	1.569	1.652	0.171	0.179
RBC (RED BLOOD CELLS)	1675 4.837	-0.06	.2988	-1.05	1078 4.776	-.042	0.282	-.697	0.001	0.119
NEUTROPHILS	1605 57.86	-.399	9.479	-.8595	1011 57.76	-.114	9.56	1.437	0.808	0.456
LYMPHOCYTES	1599 31.93	0.369	8.402	5.891	1003 31.82	0.022	8.205	4.098	0.752	0.302
EOSINOPHILS	1591 3.516	0.145	2.555	27.08	1009 3.547	0.126	2.606	21.82	0.796	0.855
MONOCYTES	1582 5.381	-.107	2.689	18.74	1005 5.381	-.043	2.765	17.95	0.996	0.565
BASOPHILS	1567 .6952	0.038	.8041	12.94	989 .6613	0.025	.8364	18.43	0.245	0.707
PLATELETS	1600 273.9	-2.79	39.61	0.257	1048 273.7	-1.05	38.99	.7984	0.928	0.266
BANDS	806 1.114	0.003	2.788	11.86	592 1.252	-.124	2.887	1.427	0.280	0.409
SERUM CHEMISTRY										
SGOT UNITS	2488 22.24	0.84	11.64	9.939	1511 21.89	-.054	11.62	5.963	0.299	0.018
SGPT UNITS	2421 23.15	1.353	15.14	15.6	1451 22.5	-.189	11.41	6.849	0.240	0.001
ALK PHOSPHATASE	1458 84.19	-.636	14.12	.7219	865 85.2	-.663	16.37	.5505	0.657	0.966
BUN	2423 13.91	0.034	3.419	3.798	1468 13.95	-.144	3.914	4.525	0.824	0.138
T/BILIRUBIN	2500 0.549	-.007	.2145	6.924	1527 .5598	-.008	.2148	6.808	0.249	0.941
CREATININE	2497 .9981	0	.1526	1.84	1523 .9815	0.013	.1568	2.845	0.013	0.020
LDH	1330 167.3	1.607	37.56	3.76	772 168.8	0.696	36.74	2.493	0.552	0.589

CHANGE OF FINAL VISIT FROM BASELINE AND % CHANGE FROM BASELINE WERE CALCULATED FOR EACH PATIENT AND THE MEANS OF THESE CHANGES DETERMINED.

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TABLE F22.B: SUMMARY OF CHANGES IN LABORATORY RESULTS IN CETIRIZINE (NDA & CUMULATIVE) - BY DOSE AT FINAL DETERMINATION

LABORATORY TEST	CETIRIZINE-NDA				CETIRIZINE-CUMULATIVE			
	MEAN N BASELINE	CHANGE FROM BASE MEAN	S.D.	MEAN % CHANGE	MEAN N BASELINE	CHANGE FROM BASE MEAN	S.D.	MEAN % CHANGE
CETIRIZINE 5 MG								
SERUM CHEMISTRY								
SGOT UNITS	314 21.09	- .494	12.71	6.203	559 21.07	- .049	13.25	7.594
SGPT UNITS	314 23.74	- .100	21.05	10.01	559 23.10	0.19	21.11	15.06
BUN	310 13.7	0.195	3.31	4.975	555 13.7	- .055	4.706	3.774
CREATININE	313 1.024	2.014	.1696	3.271	558 1	0.012	.1497	2.69
CETIRIZINE 10 MG								
SERUM CHEMISTRY								
SGOT UNITS	704 21.74	0.500	9.219	11	1634 21.99	0.600	12.39	9.266
SGPT UNITS	690 23.43	0.95	14.79	14.34	1560 22.16	0.061	14.93	12.69
BUN	694 14.36	- .026	3.450	2.017	1563 13.93	0.071	3.453	3.092
CREATININE	701 1.023	0.002	.1574	2.765	1643 0.992	0.003	.1473	2.125
CETIRIZINE 15 MG								
SERUM CHEMISTRY								
SGOT UNITS	50 24.45	- .259	0.405	4.40	50 24.45	- .259	0.405	4.40
SGPT UNITS	50 25.1	3.034	11.21	25.61	50 25.1	3.034	11.21	25.61
BUN	50 14.64	- .724	3.797	.1402	50 14.64	- .724	3.797	.1402
CREATININE	57 1.023	- .020	.1424	- 2.11	57 1.023	- .020	.1424	- 2.11
CETIRIZINE 20 MG								
SERUM CHEMISTRY								
SGOT UNITS	410 23.21	0.239	12.37	0.901	672 23.23	0.94	11.46	10.50
SGPT UNITS	410 25.25	1.005	14.53	19.72	671 25.02	1.900	13.24	19.04
BUN	361 13.74	- .027	3.413	4.231	623 13.62	- .006	3.216	3.420
CREATININE	400 1.014	0.016	.1752	3.461	670 1.003	0.006	.1617	1.903

PATIENTS TO BE INCLUDED IN THIS TABLE REQUIRED A BASELINE AND AT LEAST ONE TREATMENT VALUE WITH A CORRESPONDING CET. DOSE CHANGE OF FINAL VISIT FROM BASELINE AND % CHANGE FROM BASELINE WERE CALCULATED FOR EACH PATIENT AND THE MEANS OF THESE CHANGES DETERMINED.

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For the NDA database the mean percent change in baseline for SGPT was:

Dose	N	Mean % change
5 mg	314	18.81%
10 mg	590	14.34%
20 mg	410	19.72%

For the cumulative database the mean percent change in SGOT from baseline, excluding the 15 mg dose data, was 7.59%, 9.27% and 10.58% for the 5, 10 and 20 mg dose respectively.

Table 22.C summarizes the changes in laboratory results by gender as found in the NDA versus the cumulative database; no apparent differences between genders were observed.

Table 22.D summarizes the changes in laboratory results by age (<65 and >65) as found in the NDA versus the cumulative database. The range of number of patients with lab results for the population >65 years of age is 119-120 patients for the NDA database and 141-144 patients for the cumulative database versus a range of 1307-1369 in the NDA database and 2686-2815 patients in the cumulative database for patients <65 years of age. When the results of the two age groups are compared, the patients >65 years of age have a lower mean percent change from baseline than those that are younger, including the serum creatinine.

Table 22.E summarizes the changes in laboratory results by race as found in the NDA versus the cumulative database. Although the numbers for non-white patients are small compared to the white patient population in the cumulative database, for SGPT, the mean percent change from baseline in the cumulative database is larger for blacks, 17% (N=228) and "others", 17.5% (N=109) versus 14.8% in the white population (N=2546). In addition, the mean percent change from baseline in SGPT in black patients increased from 12.7% to 17% from the NDA to the cumulative database, which was opposite to the decrease in the other two groups; twice the number of patients were studied in the cumulative database versus the NDA database.

C. Clinically significant and possibly drug related abnormalities.

Results falling outside the normal range were reviewed by the investigator for clinical significance and relationship to study drug. The abnormal results that were later computer categorized as Category 9 were those that were considered to be clinically significant and possibly related to study medication. These in turn were blindly reviewed by a Pfizer physician and were either left as Category 9 or

TABLE F22.C: SUMMARY OF CHANGES IN LABORATORY RESULTS IN CETIRIZINE (NDA & CUMULATIVE) - BY GENDER

LABORATORY TEST	CETIRIZINE-NDA				CETIRIZINE-CUMULATIVE					
	N	MEAN BASELINE	CHANGE FROM BASE MEAN	S.D. S.D.	MEAN % CHANGE	N	MEAN BASELINE	CHANGE FROM BASE MEAN	S.D. S.D.	MEAN % CHANGE
MALE										
SERUM CHEMISTRY										
SGOT UNITS	839	23.67	0.142	10.89	7.923	1480	24.38	0.609	14	9.541
SGPT UNITS	832	26.41	1.622	13.8	16.34	1441	26.62	1.724	14.95	15.12
BUN	811	14.76	0.983	3.462	3.492	1419	14.94	0.056	3.547	3.202
CREATININE	835	1.114	0.002	.1651	2.461	1481	1.1	0.003	.1537	1.953
FEMALE										
SERUM CHEMISTRY										
SGOT UNITS	650	20.47	0.338	10.95	10.75	1474	20.21	0.461	10.3	8.702
SGPT UNITS	643	21.83	0.337	10.72	18.29	1437	19.52	0.369	16.84	14.97
BUN	615	13.18	-.137	3.587	3.507	1411	12.71	-.031	3.86	4.114
CREATININE	647	0.9	0.013	.1645	3.499	1478	0.895	0.006	.1478	2.241

CHANGE OF FINAL VISIT FROM BASELINE AND % CHANGE FROM BASELINE WERE CALCULATED FOR EACH PATIENT AND THE MEANS OF THESE CHANGES DETERMINED.

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TABLE F22.D: SUMMARY OF CHANGES IN LABORATORY RESULTS IN CETIRIZINE (MDA & CUMULATIVE) - BY AGE

LABORATORY TEST	CETIRIZINE-MDA				CETIRIZINE-CUMULATIVE			
	MEAN N BASELINE	CHANGE FROM BASE MEAN	S.D.	MEAN % CHANGE	MEAN N BASELINE	CHANGE FROM BASE MEAN	S.D.	MEAN % CHANGE
< 65 YRS								
SERUM CHEMISTRY								
SGOT UNITS	1369 22.38	0.205	11.21	9.361	2809 22.34	0.544	12.52	9.288
SGPT UNITS	1358 24.35	1.23	16.47	18.11	2737 23.18	1.138	16.12	15.44
BUN	1307 13.76	0.019	3.37	3.694	2686 13.63	0.03	3.688	3.821
CREATININE	1363 1.015	0.009	.1655	3.165	2815 0.993	0.005	.1504	2.159
>= 65 YRS								
SERUM CHEMISTRY								
SGOT UNITS	120 21.88	0.483	6.675	6.832	145 21.53	0.379	6.441	5.921
SGPT UNITS	117 28.78	-.892	11.48	6.582	141 21.12	-.699	11.61	7.317
BUN	119 17.6	-.349	4.041	1.461	144 17.6	-.316	4.034	1.384
CREATININE	119 1.085	-.011	.1572	.0374	144 1.073	-.004	0.158	.8846

CHANGE OF FINAL VISIT FROM BASELINE AND % CHANGE FROM BASELINE WERE CALCULATED FOR EACH PATIENT AND THE MEANS OF THESE CHANGES DETERMINED.

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DATE: 04/13/95 9:26:09

TABLE F22.E: SUMMARY OF CHANGES IN LABORATORY RESULTS IN CETIRIZINE (MDA & CUMULATIVE) - BY RACE

LABORATORY TEST	CETIRIZINE-MDA				CETIRIZINE-CUMULATIVE					
	N	MEAN BASELINE	CHANGE MEAN	FROM BASE S.D.	MEAN % CHANGE	N	MEAN BASELINE	CHANGE MEAN	FROM BASE S.D.	MEAN % CHANGE
WHITE										

SERUM CHEMISTRY										
SGOT UNITS	1353	22.25	0.295	10.43	0.936	2613	22.32	0.556	12.28	9.67
SGPT UNITS	1348	24.17	1.116	16.41	17.36	2546	23.35	1.07	16.48	14.77
BUN	1297	14.16	0.02	3.412	3.739	2502	13.96	0.01	3.769	3.689
CREATININE	1347	1.019	0.006	.1629	2.794	2619	0.994	0.005	.1503	2.119
BLACK										

SERUM CHEMISTRY										
SGOT UNITS	110	22.42	-.773	16.12	10.51	232	22.15	0.418	14.44	10.06
SGPT UNITS	109	22.94	0.312	13.48	12.73	228	20.66	0.405	11.59	17
BUN	103	12.73	-.156	3.396	2.467	225	12.18	-.039	3.119	3.123
CREATININE	109	1.043	0.025	.1011	4.953	231	1.039	-.003	.1599	1.305
OTHER										

SERUM CHEMISTRY										
SGOT UNITS	26	22.54	0.923	7.975	14.99	109	22.14	0.303	6.15	6.668
SGPT UNITS	26	23.62	1.305	12.34	27.08	104	21.72	1.731	9.017	17.49
BUN	26	15.30	-1.04	4.377	-4.42	103	14.23	0.2	3.351	5.127
CREATININE	26	1.015	-.015	.1933	0.573	109	0.982	0.016	.1433	3.239

CHANGE OF FINAL VISIT FROM BASELINE AND % CHANGE FROM BASELINE WERE CALCULATED FOR EACH PATIENT AND THE MEANS OF THESE CHANGES DETERMINED.

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recategorized to one of the following: 5=documented lab error, 6=likely due to concurrent illness, 7=likely due to concomitant medication.

"Among the patients treated with maximum doses of 5, 10, 15 and 20 mg of cetirizine, there were no significant differences between placebo, 5 mg and 10 mg treated patients for SGOT and SGPT, but there were significantly more abnormalities in patients treated with doses higher than 10 mg." (SU 4/25/95, vol.35.2 9 58)

"For serum creatinine, the relative incidence of abnormalities was significantly more in elderly patients than in patients less than 65 years ($p < 0.033$). "(SU 4/25/95, vol.35.2 9 58)

"There is no apparent change from baseline in mean creatinine levels for either the elderly or the younger group of cetirizine treated patients. Therefore, the clinical significance of the different incidence of abnormal serum creatinine is questionable" (SU 4/25/95, vol.35.2 9 59)

Table 23.A In this table the number of patients and percent of total number of patients with abnormal laboratories are reported from the cumulative database, not limited to placebo controlled studies. Only the number of patients with category 9=may be related to drug, will be highlighted.

Cetirizine treated patients:

For SGPT: 52 out of 2932 (2%)

For SGOT: 27 out of 2926 (1%)

Table 23.B. The number of patients and percent of total number of patients with abnormal laboratories are reported from the cumulative database by **maximum dose** in placebo controlled studies. From these, only the number of patients with category 9=may be related to drug, will be highlighted:

SGOT	N	Cetirizine 5 mg	N	Placebo
	453	0 (0%)	1525	6 (0%)
		Cetirizine 10 mg		
	1445	13 (1%)		
		Cetirizine 20 mg		
	553	8 (1%)		
SGPT	N	Cetirizine 5 mg	N	Placebo
	453	6 (1%)	1480	12 (1%)
		Cetirizine 10 mg		

TABLE F25.B: SUMMARY OF LABORATORY TEST ABNORMALITIES BY CATEGORY FOR PBO-CONTROLLED STUDIES - BY MAXIMUM DOSE

LAB TEST	TOTAL NUMBER PATIENTS	NORMAL RESULTS (%)	NUMBER OF PATIENTS BY ABNORMAL CATEGORY									TOTAL
			1	2	3	4	5	6	7	8	9(%)	
CETIRIZINE												
CETIRIZINE MAXIMUM DOSE: 5 MG												
SERUM CHEMISTRY												
SGOT UNITS	453	436(96)	4	6					1	1	5	17
SGPT UNITS	453	411(91)	13	10				3	1	9	6(1)	42
BUN	453	427(94)	10	14						2		26
CREATININE	453	430(97)	5	9							1(0)	15
TOTAL			32	39				4	2	16	7	100
CETIRIZINE MAXIMUM DOSE: 10 MG												
SERUM CHEMISTRY												
SGOT UNITS	1445	1306(96)	15	15	1			2		13	13(1)	59
SGPT UNITS	1392	1260(91)	55	25	5			2	1	23	23(2)	132
BUN	1300	1290(94)	23	46	2			1	1	9		82
CREATININE	1459	1300(95)	30	37					1	3		79
TOTAL			131	121	8			5	3	48	36	352
CETIRIZINE MAXIMUM DOSE: 15 MG												
SERUM CHEMISTRY												
SGOT UNITS	50	52(98)	4	1						1		6
SGPT UNITS	50	39(67)	5	6				1		6	1(2)	19
BUN	50	54(93)	1	2						1		4
CREATININE	50	55(95)	1	2								3
TOTAL			11	11				1		8	1	32
CETIRIZINE MAXIMUM DOSE: 20 MG												
SERUM CHEMISTRY												
SGOT UNITS	553	514(93)	8	12	2		1		1	7	8(1)	39
SGPT UNITS	554	480(87)	27	16	4		1		1	16	9(2)	74
BUN	553	525(95)	12	13				1		2		28
CREATININE	553	526(95)	5	18				1		3		27
TOTAL			52	59	6		2	2	2	28	17	168
PLACEDO												
SERUM CHEMISTRY												
SGOT UNITS	1525	1470(96)	21	14	5			1	1	7	6(0)	55
SGPT UNITS	1480	1346(91)	61	20	4			2	1	34	12(1)	134
BUN	1463	1374(94)	33	43	2					11		89
CREATININE	1539	1451(94)	27	49				1		11		88
TOTAL			142	126	11			4	2	63	18	366

LABORATORY TEST CATEGORIES ARE -

1:BASELINE VALUE ABNORMAL	4:NORMAL WITH CONT. THERAPY	7:MAY BE DUE TO CONC. DRUGS
2:DEVIATION INSIGNIFICANT	5:DOCUMENTED LAB ERROR	8:INSIG, NOT DUE TO RX, BY PHYSICIAN
3:SINGLE ABNORMAL VALUE	6:EVIDENCE OF CONC. ILLNESS	9:MAY BE RELATED TO DRUG

* PERCENTAGE OF TOTAL PATIENTS WITH NORMAL TEST RESULTS
 ** PERCENTAGE OF TOTAL PATIENTS WITH CATEGORY 9 ABNORMALITY
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1392 23 (2%)
 Cetirizine 20 mg
 554 9 (2%)

D. Liver Function Tests Results

"Evaluation of the incidence of abnormal liver function tests in patients with normal baseline tests in placebo-controlled studies show that cetirizine is associated with elevations in SGOT and SGPT but not total bilirubin or alkaline phosphatase. Abnormalities are generally less than twice the upper limit of normal. The incidence of abnormal SGOT and SGPT more than twice the upper limit of normal appear to be similar in cetirizine and placebo-treated patients." (SU 4/25/95, vol 32, 9 60).

The sponsor's statement needs to be taken in the context of the mean duration of exposure (30.1 days-cumulative database) -- for these populations.

- d. The integrated safety summary should also address weight gain, by duration of treatment, age and gender. Submit a scatter plot of the pre- versus post-study weight of subjects enrolled in clinical trials. The scatter plot should be based on the trials for which mean weight data are reported in the updated integrated safety summary.

Response: SU 4/25/95, vol 2: D.7.b., vol 3 Tables F25.A-F25.B and F-Figures.

"It should be noted that no placebo controlled studies were of greater than 8 weeks duration."

"Based on the mean weight changes in the placebo controlled studies, cetirizine treatment up to eight weeks is associated with a statistically significant weight increase of 1.1 +/- 4.5 lbs. There are no statistically significant differences between age subgroups, between the sexes, or among races with respect to the amount of weight increase, indicating that these are not determining factors of risk for this effect. However, there is a significant relation of weight gain to duration of treatment, with mean weight changes indicating increased weight gain with longer duration of treatment."

- e. Please submit any available clinical data regarding the enantiomers of cetirizine.

Response: SU 4/25/95, vol 2: D.9.c vol 17 and 18: K.2.a.

The response regarding non-clinical data was reviewed by Pharmacology. The PK of study -101 was reviewed by Biopharm. The following comments pertain only to clinical

findings.

101: Double blind crossover comparison at random between cetirizine (5 mg, single oral intake), ucb 28556 (2.5 mg, single oral intake), and 28557 (2.5 mg, single oral intake) on the histamine induced wheal and flare skin reaction in normal healthy volunteers." "wash-out period 7 days between doses"

"A total of 19 healthy male volunteers entered this study. Histamine-induced wheal and flare were induced by the prick test using a high concentration of histamine (100 mg/ml). Responses were recorded pre-dose and at 4 and 8 hours after dosing. Eighteen subjects completed the study; one subject discontinued for personal reasons. Results show that cetirizine and 28556 produced comparable effects on inhibition of both the wheal and flare reaction induced by histamine, including onset of activity and extent of maximal inhibition with the exception of the 0-32 hour AUC for inhibition of the wheal reaction, where cetirizine was less active than 28556. There was no significant effect of ucb 28557 on either the wheal or flare reaction."

"No serious adverse reaction and no withdrawals due to adverse experiences occurred in the study. Of the 19 volunteers that received cetirizine, 4 volunteers reported the following mild adverse experiences: blocked sinuses and dry cough, headache, blocked nose, and raised rash over the lower back."

"Of the 18 volunteers who received 28556, only one volunteer reported one adverse experience: headache; assessed as mild."

"Of the 18 volunteers who received 28557, 2 volunteers reported a total of 3 adverse experiences: red, raised itchy, spot above the buttocks (mild), urticarial patches (moderate severity) and headache (mild)."

"In conclusion, cetirizine and 28556 were active in blocking histamine induced wheal and flare but ucb 28557 had no significant activity."

102: Double blind cross-over comparison at random between cetirizine (10 mg, single oral intake), 28556 (5 mg, single oral intake) 28557 (5mg, single oral intake) and placebo in a nasal provocation test with histamine in adult healthy volunteers." (wash-out period 7-14 days)

"A total of 28 healthy adult volunteers entered this study. A histamine nasal provocation test was performed 4 hours after treatment. A total of 24 volunteers completed the

study per the protocol."

"The results of this study show that 28556 and cetirizine significantly increased the median histamine nasal threshold concentration and this result was significantly different from 28557 and placebo. Nasal pressure was also significantly reduced by 28556 and cetirizine as compared with 28557 and placebo. Both 28556 and cetirizine reduced the number of histamine-induced sneezes compared with placebo and 28557."

"One adverse experience was observed. One volunteer experience bronchitis which started 8 days after treatment with 28556. This event was assessed as severe and the relationship to study drug was considered as unlikely."

- f. As discussed at the meeting of December 21, 1994, please submit a listing of intercurrent illnesses by treatment reported by patients in your trials. Also please note which illnesses resulted in premature withdrawal from the study.

Response: In 4/25/95 SU, vol 2. Sections D.5.a.2., D.5.b.1.b., D.5.h. In vol 3, F7A-B, F8.C-D and F 19.A.

"Intercurrent illnesses, defined as those which first appeared at the start of therapy, were recorded for all patients and are presented separately from the adverse event database. Illnesses which began prior to treatment were not included."

NDA versus cumulative database. " In general, the incidence of intercurrent illnesses for cetirizine treated patients was similar between the NDA and cumulative databases....In the cumulative database, respiratory illnesses were the most common illnesses reported (11.6%) followed by neurological (3.2%) and gastrointestinal (2.2%) which were similar to the NDA database (except neurological, which includes headache, was somewhat higher in cumulative vs NDA database."

From review of Table F7.B, the term headache is reported by 10/1568 (0.6%) for the NDA database and by 114/3982 (2.9%) for the cumulative database. In the same table headache (sinus) is reported by 1/1568 (0.1%) and in the cumulative database by 29/3982 (0.7%); sinus infection is (0.1%) for the NDA database and (0.7%) in the cumulative database.

In Table F8.D, the individual incidence listing, although the term chronic sinus infection is similar for placebo and cetirizine treated

patients in both the NDA and cumulative database, the incidence for the term sinus infection are different:

For NDA database:cetirizine 1 (0.1%) placebo 0 (0.0%)

For Cumulative database:cetirizine 11(0.4%) placebo 0 (0%)

The incidence of menstrual cramps also increased 0-0.7% from the NDA to the cumulative database, presumably due to the increased number of women enrolled in the cumulative database.

The CRF and additional information was requested from the sponsor regarding three patients listed as having intercurrent illnesses. The reported events for these patients were: abnormal EKG, premature cardiac beats, and syncopal episode. The sponsor response (BM-7/17/95) was reviewed.

Patient 87-N-0017/36: 44 y/o asian male, in seasonal asthma study, symptomatic premature beats. These decreased after rinsing mouth after using a beta agonist inhaler. ECG reported normal by investigator.

Patient 91-S-0033/304: 18 y/o hispanic female in SAR and asthma study; syncopal episode 4 days post treatment initiation, patient continued treatment; no recurrent events reported by the investigator.

Patient 89-N-0103/74: 51y/o caucasian female in PAR study, according to patient's primary physician, this patient had prior history of heart palpitations and shortness of breath not related to exercise, with 80% PFTs and was referred to the study investigator for asthma evaluation. The study investigator did not record any CV signs or symptoms in the initial screening hx and physical exam. During the course of treatment a routine ECG was done prior to a bunion operation which was abnormal: with T wave inversions and multiple PVCs. Echo revealed mitral prolapse and regurgitation as well as tricuspid regurgitation. The patient discontinued the study early.

Placebo controlled studies. "The overall incidence of intercurrent illnesses in the cumulative database in cetirizine treated patients (16.5%) and placebo treated patients (19.2%) were similar."

From Table F8.C, the number of patients with intercurrent

STUDY : COMBINED CETIRIZINE PROTOCOLS.
 TABLE F0C : INCIDENCE OF ILLNESS CATEGORIES EMERGENT DURING PLACEBO-CONTROLLED STUDIES.

ILLNESS CATEGORIES	NDA		CUMULATIVE	
	CETIRIZINE (N=1369)	PLACEBO (N=821)	CETIRIZINE (N=2679)	PLACEBO (N=1671)
NO. OF PTS WITH CONCURRENT ILLNESSES #	160 (11.7%)	142 (17.3%)	441 (16.5%)	320 (19.2%)
RESPIRATORY	95 (6.9%)	75 (9.1%)	236 (8.8%)	162 (9.7%)
NEUROLOGICAL	8 (0.6%)	18 (2.2%)	55 (2.1%)	50 (3.0%)
GASTROINTESTINAL	16 (1.2%)	16 (1.9%)	52 (1.9%)	36 (2.2%)
IMMUNOLOGICAL	11 (0.8%)	10 (1.2%)	41 (1.5%)	34 (2.0%)
MISCELLANEOUS	18 (1.3%)	14 (1.7%)	40 (1.5%)	29 (1.7%)
MUSCULO-SKELETAL	9 (0.7%)	15 (1.8%)	35 (1.3%)	34 (2.0%)
GENITO-URINARY	8 (0.6%)	10 (1.2%)	33 (1.2%)	28 (1.7%)
DERMATOLOGICAL	11 (0.8%)	8 (1.0%)	26 (1.0%)	21 (1.3%)
ODONTOLOGICAL	7 (0.5%)	5 (0.6%)	14 (0.5%)	12 (0.7%)
OTOLOGICAL	3 (0.2%)	2 (0.2%)	12 (0.4%)	8 (0.5%)
PROCEDURES	3 (0.2%)	2 (0.2%)	11 (0.4%)	5 (0.3%)
OPHTHALMOLOGICAL	5 (0.4%)	2 (0.2%)	11 (0.4%)	4 (0.2%)
CARDIOVASCULAR	3 (0.2%)	3 (0.4%)	8 (0.3%)	4 (0.2%)
ENDOCRINOLOGICAL	2 (0.1%)	0 (0.0%)	4 (0.1%)	1 (0.1%)
HEMATOLOGICAL	0 (0.0%)	2 (0.2%)	2 (0.1%)	4 (0.2%)

PATIENTS MAY BE INCLUDED IN MORE THAN ONE CATEGORY.

EACH PATIENT IS COUNTED ONLY ONCE ON THIS LINE.

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STUDY : COMBINED CETIRIZINE PROTOCOLS.
 TABLE F08 : INCIDENCE OF ILLNESSES EMERGENT DURING PLACEBO-CONTROLLED STUDIES.

ILLNESSES	NDA		CUMULATIVE	
	CETIRIZINE (N=1569)	PLACEBO (N=821)	CETIRIZINE (N=2679)	PLACEBO (N=1671)
NO. OF PTS WITH CONCURRENT ILLNESSES #	160 (11.7%)	142 (17.3%)	441 (16.5%)	320 (19.2%)
"COLD" WITH NASAL AND SINUS CONGESTION	59 (4.3%)	41 (5.0%)	133 (5.0%)	77 (4.6%)
SORE THROAT	21 (1.5%)	18 (2.2%)	49 (1.8%)	30 (1.8%)
HEADACHE	7 (0.5%)	13 (1.6%)	46 (1.7%)	40 (2.4%)
DIARRHEA (FLU)	9 (0.7%)	5 (0.6%)	23 (0.9%)	11 (0.7%)
ASTHMA	7 (0.5%)	4 (0.5%)	22 (0.8%)	17 (1.0%)
CHRONIC SINUSITIS	9 (0.7%)	6 (0.7%)	21 (0.8%)	13 (0.8%)
FLU SYMPTOMS	9 (0.7%)	6 (0.7%)	20 (0.7%)	20 (1.2%)
ELEVATED TEMPERATURE	7 (0.5%)	8 (1.0%)	17 (0.6%)	12 (0.7%)
VIRAL SYNDROME	1 (0.1%)	2 (0.2%)	17 (0.6%)	9 (0.5%)
COUGHING	7 (0.5%)	9 (1.1%)	16 (0.6%)	13 (0.8%)
CRAMPS (MENSTRUAL)	0 (0.0%)	1 (0.1%)	14 (0.5%)	16 (0.6%)
BRONCHITIS	8 (0.6%)	7 (0.9%)	12 (0.4%)	12 (0.7%)
NAUSEA	5 (0.4%)	9 (1.1%)	12 (0.4%)	12 (0.7%)
PROCEDURES (POOLED)	3 (0.2%)	2 (0.2%)	11 (0.4%)	5 (0.3%)
SINUS INFECTION	1 (0.1%)	0 (0.0%)	11 (0.4%)	0 (0.0%)
CRAMPS, ABDOMINAL	3 (0.2%)	0 (0.0%)	10 (0.4%)	3 (0.2%)
ACHES AND PAINS	4 (0.3%)	2 (0.2%)	9 (0.3%)	4 (0.2%)
BACK PAIN	2 (0.1%)	5 (0.6%)	8 (0.3%)	13 (0.8%)
HEADACHE (SINUS)	1 (0.1%)	0 (0.0%)	8 (0.3%)	11 (0.7%)
GI VIRUS	1 (0.1%)	1 (0.1%)	8 (0.3%)	7 (0.4%)
DENTAL PROBLEMS	3 (0.2%)	1 (0.1%)	8 (0.3%)	6 (0.4%)
UTI	5 (0.4%)	3 (0.4%)	7 (0.3%)	7 (0.4%)
GASTRITIS	1 (0.1%)	1 (0.1%)	7 (0.3%)	3 (0.2%)
JOINT PAIN	0 (0.0%)	0 (0.0%)	7 (0.3%)	2 (0.1%)
OTITIS MEDIA	1 (0.1%)	0 (0.0%)	7 (0.3%)	2 (0.1%)
MUSCLE SORENESS	3 (0.2%)	1 (0.1%)	6 (0.2%)	3 (0.2%)
CONJUNCTIVITIS	3 (0.2%)	1 (0.1%)	6 (0.2%)	2 (0.1%)
RESPIRATORY DISTRESS	2 (0.1%)	1 (0.1%)	5 (0.2%)	5 (0.3%)
STRESS	0 (0.0%)	1 (0.1%)	5 (0.2%)	3 (0.2%)
FATIGUE	2 (0.1%)	0 (0.0%)	5 (0.2%)	2 (0.1%)
MIGRAINE	1 (0.1%)	1 (0.1%)	5 (0.2%)	1 (0.1%)
PRURITUS AND REDNESS OF SKIN	3 (0.2%)	0 (0.0%)	5 (0.2%)	0 (0.0%)
HIVES	1 (0.1%)	2 (0.2%)	4 (0.1%)	6 (0.4%)
CONGESTION IN EAR	2 (0.1%)	2 (0.2%)	4 (0.1%)	5 (0.3%)

STUDY : COMBINED CETIRIZINE PROTOCOLS.
 TABLE F08 : INCIDENCE OF ILLNESSES EMERGENT DURING PLACEBO-CONTROLLED STUDIES.

ILLNESSES	NDA		CUMULATIVE	
	CETIRIZINE (N=1369)	PLACEBO (N=821)	CETIRIZINE (N=2679)	PLACEBO (N=1671)
UPPER RESPIRATORY VIRUS	0 (0.0%)	0 (0.0%)	4 (0.1%)	3 (0.2%)
ALLERGIC RHINITIS	0 (0.0%)	0 (0.0%)	4 (0.1%)	2 (0.1%)
CHEST PAIN	3 (0.2%)	1 (0.1%)	4 (0.1%)	1 (0.1%)
DERMATITIS,CONTACT (POISON IVY)	1 (0.1%)	3 (0.4%)	3 (0.1%)	3 (0.2%)
BLOODSHOT EYES	2 (0.1%)	1 (0.1%)	3 (0.1%)	2 (0.1%)
LARYNGITIS	1 (0.1%)	1 (0.1%)	3 (0.1%)	2 (0.1%)
HEARTBURN	0 (0.0%)	1 (0.1%)	3 (0.1%)	1 (0.1%)
CANDIDIASIS	1 (0.1%)	0 (0.0%)	3 (0.1%)	0 (0.0%)
STIFF NECK	0 (0.0%)	0 (0.0%)	3 (0.1%)	0 (0.0%)
ARTHRITIS	0 (0.0%)	1 (0.1%)	2 (0.1%)	3 (0.2%)
COLD SORES	2 (0.1%)	0 (0.0%)	2 (0.1%)	3 (0.2%)
DERMATITIS	0 (0.0%)	1 (0.1%)	2 (0.1%)	3 (0.2%)
HERPES SIMPLEX	1 (0.1%)	2 (0.2%)	2 (0.1%)	3 (0.2%)
LEG ACHE	0 (0.0%)	0 (0.0%)	2 (0.1%)	3 (0.2%)
FLU	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)
TENDONITIS	1 (0.1%)	2 (0.2%)	2 (0.1%)	2 (0.1%)
BRONCHITIS,ACUTE	1 (0.1%)	0 (0.0%)	2 (0.1%)	1 (0.1%)
BURSITIS	2 (0.1%)	1 (0.1%)	2 (0.1%)	1 (0.1%)
DRUG REACTION	1 (0.1%)	1 (0.1%)	2 (0.1%)	1 (0.1%)
NOSE BLEED	1 (0.1%)	0 (0.0%)	2 (0.1%)	1 (0.1%)
PAIN,SWELLING MOUTH	2 (0.1%)	0 (0.0%)	2 (0.1%)	1 (0.1%)
RASH-CONTACT DERMATITIS	2 (0.1%)	1 (0.1%)	2 (0.1%)	1 (0.1%)
ABDOMINAL PAIN	1 (0.1%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
ACNE CYST	0 (0.0%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
ALLERGIES	0 (0.0%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
FURUNCULUSIS	1 (0.1%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
INGROWN TOENAIL	0 (0.0%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
MENSTRUAL ABNORMALITY	0 (0.0%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
NECK MUSCLE SPASM	1 (0.1%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
OTITIS EXTERNA	0 (0.0%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
STREP THROAT	0 (0.0%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
SWOLLEN GLANDS	1 (0.1%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
VAGINAL YEAST INFECTION	0 (0.0%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
DIZZINESS	0 (0.0%)	2 (0.2%)	1 (0.0%)	5 (0.3%)
ANEMIA	0 (0.0%)	1 (0.1%)	1 (0.0%)	3 (0.2%)
SNEEZING	0 (0.0%)	2 (0.2%)	1 (0.0%)	3 (0.2%)

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STUDY : COMBINED CETIRIZINE PROTOCOLS.
 TABLE F00 : INCIDENCE OF ILLNESSES EMERGENT DURING PLACEBO-CONTROLLED STUDIES.

ILLNESSES	NDA		CUMULATIVE	
	CETIRIZINE (N=1369)	PLACEBO (N=821)	CETIRIZINE (N=2679)	PLACEBO (N=1671)
BLADDER INFECTION	0 (0.0%)	0 (0.0%)	1 (0.0%)	2 (0.1%)
MOOD-CHANGES	0 (0.0%)	1 (0.1%)	1 (0.0%)	2 (0.1%)
VAGINITIS	1 (0.1%)	2 (0.2%)	1 (0.0%)	2 (0.1%)
BEE STING	1 (0.1%)	0 (0.0%)	1 (0.0%)	1 (0.1%)
CANKER SORES IN MOUTH	0 (0.0%)	0 (0.0%)	1 (0.0%)	1 (0.1%)
DIAPHORESIS	0 (0.0%)	0 (0.0%)	1 (0.0%)	1 (0.1%)
DYSURIA	1 (0.1%)	0 (0.0%)	1 (0.0%)	1 (0.1%)
FINGER INFECTION	0 (0.0%)	1 (0.1%)	1 (0.0%)	1 (0.1%)
FOOT, INJURY	1 (0.1%)	0 (0.0%)	1 (0.0%)	1 (0.1%)
GINGIVITIS	0 (0.0%)	1 (0.1%)	1 (0.0%)	1 (0.1%)
IRRITABLE BOWEL	0 (0.0%)	0 (0.0%)	1 (0.0%)	1 (0.1%)
TMJ (TEMPOROMANDIBULAR JOINT DISEASE)	0 (0.0%)	0 (0.0%)	1 (0.0%)	1 (0.1%)
TOOTH INFECTION	1 (0.1%)	1 (0.1%)	1 (0.0%)	1 (0.1%)
ABNORMAL EKG	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
ANGINA	1 (0.1%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
ANOREXIA (NERVOSA)	1 (0.1%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
ARTHRITIS, KNEE	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
BONE SPUR	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
CHIPPED TOOTH	1 (0.1%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
CRAMPS, UNSPECIFIED	1 (0.1%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
DEPRESSION	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
DIABETES MELLITUS	1 (0.1%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
DRY THROAT	1 (0.1%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
EPIDIDIMITIS	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
ESOPHAGEAL REFLUX	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
EYE INFECTION	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
FLUSHING	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
GALLSTONES	1 (0.1%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
HERNIA, HIATAL	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
HERPES ZOSTER	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
HYPEREXTENSIVE JOINT	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
HYPOTHYROIDISM	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
IMPACTED WISDOM TEETH	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
INFLAMMATION, KNEE	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
KIDNEY STONES	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
MONONUCLEOSIS	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)

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STUDY : COMBINED CETIRIZINE PROTOCOLS.
 TABLE 800 : INCIDENCE OF ILLNESSES EMERGENT DURING PLACEBO-CONTROLLED STUDIES.

ILLNESSES	NDA		CUMULATIVE	
	CETIRIZINE (N=1369)	PLACEBO (N=821)	CETIRIZINE (N=2679)	PLACEBO (N=1671)
NASAL CONTUSION	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
NEURO-DERMATITIS	1 (0.1%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
PAIN,FACIAL	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
PHLEBITIS,SUPERFICIAL	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
PINCHED NERVE	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
PITYRIASIS ROSEA	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
PNEUMONIA	1 (0.1%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
PREMATURE CARDIAC BEATS	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
PREMENSTRUAL SYNDROME	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
PRESSURE TO MAXILLARY	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
RECTAL BLEEDING	1 (0.1%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
SALIVARY GLAND INFECTION	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
SCRATCH ON EYE	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
SPUTUM YELLOW	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
SUNBURN	1 (0.1%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
SWOLLEN BREASTS	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
SYNCOPIAL EPISODE(S)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
TORN MENISCUS	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
URINARY FREQUENCY	1 (0.1%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
VAGINAL MONILIA	1 (0.1%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
SPRAINS & STRAINS	0 (0.0%)	1 (0.1%)	0 (0.0%)	3 (0.2%)
CONSTIPATION	0 (0.0%)	1 (0.1%)	0 (0.0%)	2 (0.1%)
ENLARGED LYMPH NODE	0 (0.0%)	1 (0.1%)	0 (0.0%)	2 (0.1%)
JAW PAIN	0 (0.0%)	1 (0.1%)	0 (0.0%)	2 (0.1%)
KNEE INJURY	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)
LOW BACK SPASM	0 (0.0%)	2 (0.2%)	0 (0.0%)	2 (0.1%)
NERVOUSNESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)
PAIN,ABSCESS TOOTH	0 (0.0%)	1 (0.1%)	0 (0.0%)	2 (0.1%)
PALPITATIONS	0 (0.0%)	2 (0.2%)	0 (0.0%)	2 (0.1%)
ABSCESS,TOE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
ATAXIA	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
BACTERIAL INFECTION	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
BLOATED FEELING	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
BRONCHOSPASM	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
BRUISING	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
BURNS,ARM	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)

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STUDY : COMBINED CETIRIZINE PROTOCOLS.
 TABLE F08 : INCIDENCE OF ILLNESSES EMERGENT DURING PLACEBO-CONTROLLED STUDIES.

ILLNESSES	NDA		CUMULATIVE	
	CETIRIZINE (N=1369)	PLACEBO (N=821)	CETIRIZINE (N=2679)	PLACEBO (N=1671)
COXSACKIE VIRUS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
CYST ON WRIST	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
CYST, OVARIAN	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
DENTAL CARIES	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
DERMATITIS, ATOPIC	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
DRY SKIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
FALLOPIAN TUBE INFECTION	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
FINGER, INJURY	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
FOOT PAIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
FRACTURE, CLAVICLE	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
HAIRY CELL LEUKEMIA	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
HERNIA, INGUINAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
HYPOGLYCEMIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
INCONTINENCE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
INCREASED HEART RATE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
INNER EAR PROBLEMS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
ITCHY EUSTACHIAN TUBES	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
KIDNEY INFECTION	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
KNEE (PAIN & SWELLING)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
KNEES LOCKING	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
LEG CRAMPS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
NEURALGIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
PAIN/STIFFNESS IN NECK	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
PAIN, RIB	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
RUBELLA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
TONGUE SWELLING	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
TRAUMA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
TROUBLE SLEEPING	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
URINARY HESITANCY	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)

PATIENTS MAY BE INCLUDED IN MORE THAN ONE ILLNESS.

* EACH PATIENT IS COUNTED ONLY ONCE ON THIS LINE.

TABLE 3.1: MATCHING ADVERSE EXPERIENCE AND INTERCURRENT ILLNESS¹ EVENT TERMS: CETIRIZINE TREATED ADULT PATIENTS

Number of safety evaluable patients	3982		
Number of patients with adverse experiences (AE)	1743	(1743/3982)	43.8%
Number of patients with intercurrent illnesses	826	(826/3982)	20.7%
Number of patients with matching AE and intercurrent illness terms	71	(71/1743)	4.1%
Number of patients with matching terms who discontinued due to AE	2		
Number of patients with matching terms who discontinued due to intercurrent illness	2		

<u>Event Terms*</u>	<u>Number of Patients</u>
Headache	24
Pharyngitis/sore throat	10
Respiratory disorder/upper respiratory virus/cold/upper respiratory infection/bronchitis	7
Diarrhea	6
Fever/elevated temperature	6
Nausea	4
Earache/otitis media/ear congestion	4
Bronchospasm/respiratory distress/asthma	3
Coughing	2
Rash/contact dermatitis-rash	2
Eye Abnormality/conjunctivitis	1
Eczema/dermatitis	1
Infection fungal/vaginal yeast infection	1
Chronic sinusitis/sinusitis	1
Palpitations/premature cardiac beats	1
Conjunctivitis/blood shot eyes	1
Epistaxis/nose bleed	1
Herpes simplex/cold sores	1
Back pain	1
Hemorrhage rectum/rectal bleeding	1
Furunculosis	1
Migraine	1
Polyuria/urinary frequency	1
Chest pain	1
Anorexia	1
Myalgia/muscle soreness	1

¹ Intercurrent illness includes all illnesses which emerged after the onset of treatment with study drug
*Event terms separated by a slash (/) were considered similar terms by a Pfizer physician

TABLE 3.2: MATCHING ADVERSE EXPERIENCE AND INTERCURRENT ILLNESS¹ EVENT TERMS: PLACEBO TREATED ADULT PATIENTS

Number of safety evaluable patients	1671		
Number of patients with adverse experiences (AE)	610	(610/1671)	36.5%
Number of patients with intercurrent illnesses	320	(320/1671)	19.1%
Number of patients with matching AE and intercurrent illnesses terms	32	(32/610)	5.2%
Number of patients with matching terms who discontinued due to AE	4		
Number of patients with matching terms who discontinued due to intercurrent illnesses	1		

<u>Event Terms*</u>	<u>Number of Patients</u>
Headache	13
Nausea	6
Pharyngitis/sore throat	5
Respiratory disorder/cold	4
Urinary incontinence/incontinence	1
Urinary retention/urinary hesitancy	1
Bronchospasm/asthma	1
Back pain/low back spasm	1
Heartburn/dyspepsia	1
Fever/elevated temperature	1
Rash/contact dermatitis	1
Coughing	1
Myalgia/muscle soreness	1
Conjunctivitis	1
Infection/finger infection	1
Palpitations	1
Diarrhea	1
Chest pain	1
Urticaria/hives	1

¹ Intercurrent illness includes all illnesses which emerged after the onset of treatment with study drug
*Event terms separated by a slash (/) were considered similar terms by a Pfizer physician

illnesses:

For NDA database: cetirizine 11.7%, placebo 17.3%

For Cumulative database: cetirizine 16.5%, placebo 19.2%

There is a greater increase in the incidence patients reporting intercurrent illnesses during treatment with cetirizine than during placebo treatment when the cumulative database is compared to the NDA database.

The incidence of patients that discontinued the study due to intercurrent illnesses in placebo controlled studies (cumulative database) was 1.6% in cetirizine treated patients and 2.3% in placebo treated patients.

In response dated 5/25/95, the sponsor clarifies the following: "Of the 1743 cetirizine treated patients who reported one or more adverse experiences, 71 (4.1%) reported one or more intercurrent illnesses using the same or similar event terms. Of the 610 placebo treated patients who reported one or more adverse experiences, 32 (5.2%) reported one or more intercurrent illnesses using the same or similar event terms. Table 3.1, 3.2 (C-5/25/95)

7. Please submit the complete medical records for the adverse event report with Mnf. number 9300233.

Response: After numerous attempts the physician refuses to give further information on this case to the sponsor. The hand written copy of the physician report and the statement to the sponsor " I have no further information, I have already given info to FDA "is included. This information had been faxed to Dr. Ravitz, Division of Epidemiology, on February 16, 1994.

Reviewer's comments: The hand-written copy of the report follows. The physician report, as this reviewer reads it, states that:

78 y/o female with long history of HTN, DM, atrial fibrillation. She was started on Vistaril 10 hs for the last 2-3 days -stopped it then when restarted had multiple syncopal episodes with rib fractures. Documented torsades de pointes at hospital.

The recorded concomitant medication included the following medications for years:

Lanoxin po, Procainamide, Coumadin,
Hydrochlorothiazide, Potassium chloride, Bumex, and
Zantac.

The report notes that the patient required inpatient hospitalization. Relevant test: QT prolongation on EKG to

52 msec?. The patient took the vistaril for inability to sleep. The dose: 1 capsule po q hs. The therapy dates: 12/25. Therapy duration 12/31. Event onset:12/31/92. Event duration: 1 day. Did event abate after stopping drug?: Yes. Did event reappear after reintroduction?:N/A. Date of report: 2/7/93.

Stamped: Received on 93 Feb 16.

The patient had tolerated the concomitant medication regimen which included procainamide, lanoxin, diuretics and potassium supplements without a history of adverse events. We do not know the status of the patient's electrolytes at the time of torsades. In view that no additional information will be available in this case, it cannot be ruled out that hydroxyzine at normal doses did not contribute to the QT prolongation and torsades in this patient.

8. Please address the increased frequency of Category 9 adverse events (liver enzymes) in the erythromycin-cetirizine study for 4 out of 16 patients receiving the combination.

"Results falling outside the normal range were reviewed by the investigator for clinical significance and relationship to study drug. The abnormal results were later computer categorized as Category 9 were those that were considered to be clinically significant and possibly related to study medication. These in turn were blindly reviewed by a Pfizer physician and were either left as Category 9 or recategorized to one of the following: 5=documented lab. error, 6=likely due to concurrent illness, 7=likely due to concomitant medication."

See attached photocopy. (SU 4/25/95, vol 35.2, p.9 61)

SGPT (U/L) Values

Pt.	Base line	Cet Day 5	Comb Day 6	Comb Day 8	Comb Day 10	Wash Day 2	Wash Day 4	Wash Day 7	Wash Day 19	Eryth Day 5	Comb Day 6	Wash Day 2	Wash Day 7

Pt.	Base line	Ery Day 5	Comb Day 6	Comb Day 8	Comb Day 10	Wash Day 2	Wash Day 4	Wash Day 7	Wash Day 19	Cet Day 5	Comb Day 6	Wash Day 2

One of the subjects demonstrated a maximal elevation of SGPT < 2x the upper limit of normal, another subject showed a maximal SGPT elevation between 2 and 4 times the upper limit of normal, and the other two subjects had maximum elevations >4X the upper limit of normal. All subjects were asymptomatic, and no subject discontinued for abnormal liver function tests. Two subjects (nos. 6 and 102) experienced elevations of SGPT on the combination of drugs following single administration of both cetirizine and erythromycin; subject 102 experienced an elevated SGPT on erythromycin alone as well. One patient (no. 16) experienced an abnormal SGPT on the combination following cetirizine, but he discontinued from the study prior to the second regimen for personal reasons. Subject 1 had an abnormal SGPT on combination treatment following initial treatment with erythromycin, but not on cetirizine alone or on the combination following initial treatment with cetirizine. In general, the SGPT returned to normal when the combined drugs were stopped during the three week washout phase

Both cetirizine and erythromycin are known to be associated with abnormal transaminases in a small percent of patients. It is difficult to attribute the abnormalities observed in the small number of volunteers in this study to either the combination, cetirizine alone or erythromycin alone because of the sequential nature of the design and lack of concurrent placebo, erythromycin, and cetirizine controls. In addition, the abnormalities resolved during the washout period when both drugs were withdrawn. Therefore, we cannot attribute these abnormalities to concomitant administration of cetirizine and erythromycin. "

- As previously advised, your proposed name "Peactine" connotes usefulness in acute situations and implies lack of drowsiness. Your alternate proposed names "Ultreon" implies maximum strength or effectiveness as compared to related products and "Alacrin" appears to be derived from "alacrity" which denotes quickness and alertness. These three tradenames are not acceptable. Your alternate proposed name, "Zyrtec", is acceptable.

The sponsor accepted the trade name Zyrtec. Refer to proposed package insert.

- Your proposed annotated package insert has been revised. Please refer to the attachment and note that our recommended additions to the labeling are underlined and in bold typeface and our comments are in brackets, caps, and bold typeface.

The proposed package insert was included in this submission. Specific comments regarding the proposed labeling are included in Section 2 of this review.

In addition, we have the following comments and requests for information.

15. Please provide a summary of the population variability of cetirizine kinetics. This should include presentations of histograms by dose of cetirizine, C_{max} and AUC after single and multiple (steady-state) dosing.

The response to this question was included in the correspondence dated 5/12/95-BZ. Biopharm was consulted for the review of this section.

16. Which enantiomer form of cetirizine is formed when hydroxyzine is given to humans?

Response: BZ-5/12/95. has indicated that no chiral analysis has been performed to determine which enantiomer of cetirizine is formed in either blood or urine samples obtained from humans who have receives single or multiple doses of hydroxyzine."

17. Does each one of the cetirizine enantiomers bind to the same plasma protein?

Response: BZ-5/12/95. "Plasma protein binding studies have not been conducted with individual enantiomers of cetirizine, according to

18. What is known about the pharmacokinetics of the enantiomers in humans? Does interconversion occur?

Response: BZ-5/12/95. "Pharmacokinetic monitoring of the cetirizine enantiomers 28556 and 28557) was conducted in humans after a single oral dose of 2.5 mg of 28556 or 28557 or a single oral dose of 5 mg of cetirizine (NDA-Report 101; filed 4/25/95, vol 17 pages 11 1314-11 1736). . . . The mean plasma concentration of cetirizine was similar to the summed concentration of the two enantiomers when the enantiomers were given alone, indicating that there was no apparent interaction between the two isomers. . . . The cumulative urinary excretion of each of the individual enantiomers following the administration of cetirizine was approximately equal to the cumulative urinary excretion of each of the respective enantiomers when they were administered alone. . . . In urine samples, there was no evidence of interconversion of the enantiomers of cetirizine."

19. Has cetirizine binding to H_1 receptors ever been tested? If so, what are the results?

Response: BZ-5/12/95. "Draft data from [redacted] exists. An audited result is not available. The affinity of cetirizine and hydroxyzine was tested for H3 receptors in the guinea pig cerebral cortex. In this study, [3H]-N-alpha-methylhistamine was used as the radioligand and thioperamide was the positive control. Neither cetirizine nor hydroxyzine (both tested at 10 microM) inhibited significantly (<20%) the radioligand specific binding, whereas thioperamide (a selective H3 histamine antagonist) displayed an affinity of 15 nanoM, according to [redacted]."

20. What is the CNS and cardiac activity of cetirizine's metabolite? We note that in mice, the metabolite influences its general behavior at 2-4 times lower doses than cetirizine.

Response: BZ-5/12/95.

The results from two non-clinical pharmacology studies as well as the pharmacokinetics of the metabolite P026 are discussed in the sponsor's response to this question. Appropriate comments as to the adequacy of this response pertain to the pharmacology and biopharm reviewers.

As the medical reviewer understands this response, it appears that the P026 metabolite is twice as potent for the same route (i.p. or i.v.) as cetirizine, in terms of CNS effects in mice and at least four times as potent in terms of cardiac effects (bradycardia and decrease in blood pressure) in the rat. However, according to expected plasma concentrations of P026 in normal human volunteers (PK study P026 mean plasma peak concentration is approximately 18% of the cetirizine peak concentration), after multiple oral dosing at recommended doses, the cardiac and CNS effects from P026, would be negligible.

21. For future adverse events where the etiologic factor could be attributed to an immunologic or to an allergic reaction to cetirizine, please document the presence or absence of a positive history of an allergic or immunologic reaction to other piperazine related structures in these patients.

Response: BZ-5/12/95. "Where possible as part of the post marketing surveillance, Pfizer plans to review the data of the immunologic or allergic reactions to cetirizine which are spontaneously reported to Pfizer for a positive medical history of allergic or immunologic reactions to other particular piperazine-related products, specifically those compounds listed in Attachment D. This post-marketing surveillance information will be reported to the FDA."

In Attachment D, the following compounds are listed:

"Buclizine, Chlorcyclizine, Cyclizine, Fluphenazine, Hydroxyzine, Meclizine, Perphenazine, Prochlorperazine, Thiethylperazine, and Trifluoroperazine"

22. Because of the high degree of protein binding of cetirizine, please indicate and submit any in vivo or in vitro data that were generated by examining the displacement by highly bound drugs such as phenytoin, carbamazepin, or warfarin of cetirizine.

Response: BZ-5/12/95. "According to _____, no definite audited reports are available describing in vivo or in vitro binding data generated to determine the displacement of cetirizine by phenytoin, carbamazepine, or warfarin."

The sponsor reports an un-audited European in vitro study that was published in the form of an abstract, that reports that cetirizine binding was studied using equilibrium dialysis and radiolabelled cetirizine. The authors report that cetirizine is 88-90% bound mainly to human serum albumin. Inhibition studies indicate that cetirizine could bind to two main binding sites of albumin, to the diazepam site with highest affinity and to the warfarin site with the lowest affinity.

II. Relevant Additional Safety Update Information

- A. The case report forms of all patients discontinued for adverse events (vol 7, 8, 9, and 10), and intercurrent illnesses (vol 11 and 12) as well as the case report of a patient with a serious adverse events (vol 12) were reviewed, no new safety concerns were raised by the review of these case report forms.
- B. In the course of providing us with additional safety information regarding the foreign studies, Pharmia identified two additional deaths.

The study 119 was conducted in 1985 to study senile pruritus. Of 9 elderly patients that participated in this study, 2 patients died within 4 days of a clinic visit. All the available information that was provided to us by the sponsor on these two deaths was reviewed [N(BM) 6/14/95 and N(BM) 6/29/95].

The sponsor was then asked: when they had become aware of this trial, why it had not been submitted earlier and what were the standard operating procedures for monitoring reports from studies. Since blood pressure fluctuations had been noted in a group of elderly patients that had also been studied for senile pruritus from which 17 deaths had been previously reported, and there were also blood pressure fluctuations in the two recently reported deaths, the sponsor was asked to provide us with a further analysis of the NDA cumulative data, since this safety update and previous ones did not include information on vital signs. In this analysis we asked the sponsor to provide us with an integrated summary of vital sign data (BP and pulse) for cetirizine versus placebo for placebo controlled US studies of one week duration or longer and to show the data by dose, age (<65 years and 65 years and older), gender and race. The sponsor response to this request was dated 9/12/95.

In summary the 9/12/95 response states that: " was solely responsible for the monitoring, review of source documents, data analysis and preparation of study reports for these studies. In a meeting with the Agency on October 26, 1987, it was agreed that the Pfizer sponsored clinical trials would constitute the pivotal safety and efficacy trial to support the approval of the NDA. The study reports received by Pfizer would be considered "Other Trials" and submitted as individual study reports in order to provide full disclosure. clinical trial are processed in a manner similar to that of literature reports."

In the analysis, "the mean changes and mean percent changes

found in the cetirizine group are small and similar to the placebo group. The mean changes by dose do not suggest a relationship between cetirizine dose and change in vital sign parameter." **Appendix 1**

- B. Hydroxyzine/Meclizine and cardiovascular events (update) in Appendix F volume 35.4 -January 1, 1994 to April 19, 1995. The review identified 14 new hydroxyzine cases, one updated hydroxyzine case, and two new meclizine cases. Of these 16 were spontaneously reported and one was a literature report.

"The updated review of the new cases supports the previous conclusion that there is no indication that serious arrhythmias occur in association with hydroxyzine or meclizine when used in normal therapeutic doses in patients who are otherwise healthy." **Appendix 2.**

- C. Response to a consult request to the Division of Epidemiology and Surveillance, HFD-730 on Ketoconazole and Hydroxyzine drug interaction dated June 23, 1995.

Line-listing corresponding to the Spontaneous Reporting System reports where ketoconazole and Hydroxyzine are listed as concomitant drugs. Between 1982 and the present there have been 20 such reports in the SRS.

Demographics:

Outcome: 2 deaths; 5 hospitalizations; 1 disability

Origin: 18 domestic; 2 foreign

Sex: 6 female; 14 male

Age: range 6-90

Most often reported COSTART terms (2 or more cases each):

Liver function abnorm	5
Bilirubinemim	3
Phosphatase alk inc	3
Pruritus	3
Intracran hyperten	2
Jaundice cholestat	2
Rash	2
Rash mac pap	2

The ketoconazole labeling addresses hepatic adverse events. An interaction with hydroxyzine is not mentioned. In reviewing the report its important to remember the limitations associated with data derived from the Spontaneous Reporting System. **Appendix 3.**

- D. Update on cetirizine literature review in Appendix E, vol 4, SU 4/25/95 with copy of article in correspondence dated 8/8/95.

The photocopy of a case report suggestive of drug induced hepatitis is enclosed in **Appendix 4**.

Appendices

Appendix 1

TABLE 1: SUMMARY OF CHANGES IN VITAL SIGN RESULTS IN PLACEBO-CONTROLLED ADULT STUDIES

		---CETIRIZINE---					---PLACEBO---				
		N	MEAN BASELINE	----CHANGE FROM BASELINE ¹ ----			N	MEAN BASELINE	----CHANGE FROM BASELINE ¹ ----		
				MEAN	S.D.	% CHANGE			MEAN	S.D.	% CHANGE
AGE:											
< 65 YRS	SYSTOLIC BP	2100	117.59	-0.552	11.30	0.017	1355	117.43	-0.621	11.11	-0.004
	DIASTOLIC BP	2107	75.23	-0.503	9.35	0.498	1334	75.06	-0.457	9.99	0.222
	HEART RATE	2100	74.34	0.778	10.01	2.051	1330	73.77	0.555	9.90	2.058
≥ 65 YRS	SYSTOLIC BP	132	137.65	-0.174	16.33	0.547	96	139.88	-3.760	15.73	-2.020
	DIASTOLIC BP	132	80.11	0.023	13.29	0.906	96	80.78	-3.083	8.72	-3.190
	HEART RATE	133	74.92	-0.368	7.99	0.286	96	74.47	0.958	8.87	1.910
GENDER:											
MALE	SYSTOLIC BP	1115	120.42	-0.212	12.14	0.303	671	121.64	-1.064	11.51	-0.475
	DIASTOLIC BP	1114	76.30	-0.359	9.34	1.213	670	76.70	-0.558	9.50	-0.133
	HEART RATE	1114	73.31	0.797	10.12	2.151	669	72.84	0.414	10.43	2.421
FEMALE	SYSTOLIC BP	1125	117.13	-0.045	11.15	-0.204	760	116.55	-0.626	11.49	0.016
	DIASTOLIC BP	1125	74.66	-0.733	9.90	-0.162	760	74.33	-0.700	10.30	0.105
	HEART RATE	1127	75.43	0.623	9.70	1.707	757	74.68	0.731	9.27	1.719
RACE:											
WHITE	SYSTOLIC BP	1990	110.81	-0.725	11.77	-0.094	1240	110.95	-0.969	11.52	-0.326
	DIASTOLIC BP	1989	75.50	-0.667	9.79	0.440	1240	75.27	-0.656	10.20	0.002
	HEART RATE	1989	74.14	0.683	9.98	1.924	1236	73.67	0.679	9.87	2.248
BLACK	SYSTOLIC BP	160	121.22	1.331	10.86	1.414	119	120.27	1.412	12.65	1.802
	DIASTOLIC BP	160	77.41	0.131	7.93	0.613	118	77.19	0.153	8.50	0.986
	HEART RATE	162	76.10	1.901	9.45	3.246	118	75.62	0.127	10.06	1.229
OTHER	SYSTOLIC BP	90	113.54	0.478	10.16	0.757	72	116.56	-2.167	8.31	-1.621
	DIASTOLIC BP	90	72.47	0.889	8.57	2.170	72	75.50	-1.542	6.69	-1.774
	HEART RATE	90	76.54	-0.856	8.84	-0.372	72	73.33	-0.333	8.87	-0.029
TOTAL:	SYSTOLIC BP	2240	110.77	-0.530	11.65	0.040	1431	110.94	-0.832	11.49	-0.214
	DIASTOLIC BP	2239	75.51	-0.547	9.63	0.522	1430	75.44	-0.634	9.93	-0.007
	HEART RATE	2241	74.30	0.710	9.90	1.920	1426	73.81	0.582	9.83	2.048

¹ PATIENTS TO BE INCLUDED IN THIS TABLE REQUIRED TO HAVE A BASELINE AND ON TREATMENT VITAL SIGN CHANGE OF FINAL VISIT FROM BASELINE AND % CHANGE FROM BASELINE ARE CALCULATED FOR EACH PATIENT AND THEN MEANS OF THESE CHANGES DETERMINED

TABLE 2: SUMMARY OF CHANGES IN VITAL SIGN RESULTS IN PLACEBO-CONTROLLED ADULT STUDIES - BY DOSE AT FINAL DETERMINATION

	N	MEAN BASELINE	---CHANGE FROM BASELINE ¹ ---		
			MEAN	S.D.	% CHANGE
CETIRIZINE 5 MG:					
SYSTOLIC BP	360	116.61	-1.203	12.58	-0.430
DIASTOLIC BP	359	74.23	-0.585	9.89	2.698
HEART RATE	359	74.04	0.994	10.14	2.314
CETIRIZINE 10 MG:					
SYSTOLIC BP	1362	118.90	-0.515	11.20	0.835
DIASTOLIC BP	1362	75.74	-0.659	9.71	-0.871
HEART RATE	1364	74.31	0.490	10.08	1.743
CETIRIZINE 15 MG:					
SYSTOLIC BP	55	120.85	1.309	12.90	1.690
DIASTOLIC BP	55	77.85	0.509	11.02	1.725
HEART RATE	55	76.15	-1.236	8.73	-0.966
CETIRIZINE 20 MG:					
SYSTOLIC BP	463	119.83	-0.268	11.84	0.264
DIASTOLIC BP	463	75.56	-0.313	8.99	0.436
HEART RATE	463	74.65	1.367	9.28	2.515
PLACEBO:					
SYSTOLIC BP	1431	118.94	-0.832	11.49	-0.214
DIASTOLIC BP	1430	75.44	-0.634	9.93	-0.887
HEART RATE	1426	73.81	0.582	9.83	2.648

¹ PATIENTS TO BE INCLUDED IN THIS TABLE REQUIRED TO HAVE A BASELINE AND AT LEAST ONE TREATMENT VALUE WITH A CORRESPONDING CET. DOSE CHANGE OF FINAL VISIT FROM BASELINE AND % CHANGE FROM BASELINE ARE CALCULATED FOR EACH PATIENT AND THEN MEANS OF THESE CHANGES DETERMINED

FILE: CSFXBPB
DATE: 09/06/95 16:14:23

Appendix 2

APPENDIX F

Hydroxyzine/Meclizine and Cardiovascular Events (Update)

HYDROXYZINE / MECLIZINE AND CARDIOVASCULAR EVENTS: AN UPDATE

**Pfizer Inc
Safety Evaluation and Epidemiology
New York, New York
April 21, 1995**

Contents:

A Review of Cases

Appendix - Hydroxyzine/Meclizine and Cardiovascular Events. January 14, 1994

A Review of Cases

HYDROXYZINE / MECLIZINE AND CARDIOVASCULAR EVENTS: AN UPDATE

A previous review¹ of Pfizer's early alert safety database for cardiovascular adverse events reported for hydroxyzine and meclizine concluded that heart rate/rhythm events have occurred in association with overdoses of these two compounds, that such events may rarely occur in patients treated with hydroxyzine who appear predisposed to arrhythmias, and that there was no indication that these compounds were associated with serious arrhythmias when used at therapeutic doses in otherwise healthy patients. This review of new hydroxyzine and meclizine cases was conducted to determine if there was any recent evidence to the contrary; none was discovered.

The Pfizer early alert safety database is comprised of cases of adverse events spontaneously reported to Pfizer, cases reported from adverse event registries, reports of adverse events published in the medical literature, and cases of serious adverse events reported from clinical studies regardless of causality. The previous review covered hydroxyzine and meclizine cases entered into the database through December 31, 1993. For this current report the database was reviewed for new hydroxyzine and meclizine cases involving cardiovascular adverse events entered into the database from January 1, 1994 through April 19, 1995, and for any cases entered into the database prior to January 1, 1994 that had been updated based on receipt of new information to include cardiovascular adverse events. This review identified 14 new hydroxyzine cases, one updated hydroxyzine case, and two new meclizine cases. Of these, 16 cases were spontaneously reported and one was a literature case. All are summarized below.

HYDROXYZINE

Of the 15 hydroxyzine patients, six were female, four were males, and gender was unknown in five. Eight patients were adults aged 23 to 84 years (mean $\pm$ SD = 43.25 $\pm$ 21.42 years), one was approximately four years of age, one was approximately one year of age, and for five (one of whom was a nursing home patient) the age was unknown. The route of administration was reported to be orally in seven patients, intramuscularly in four patients, intravenously in three patients, and was unknown in one patient.

The updated case originally entered prior to January 1, 1994 (case # 8900941, originally reported as case # R3P290) involved a 61-year-old female with a history of epilepsy, Alzheimer's disease, and sub-arachnoid hemorrhage receiving therapy with warfarin, phenytoin, lorazepam, and clorazepate. She developed an otitis media, which was treated with erythromycin 500 mg twice daily, and after about ten days of therapy developed urticaria. The erythromycin was discontinued, and hydroxyzine 150 mg/day intramuscularly was started. On the third day of hydroxyzine therapy, she became semi-comatose with right facial paresis, flaccid limbs, hyper-reflexia, absence of the pupilla light reflex, hypotension (supine blood pressure = 90/70 mmHg), and "a decreased heart rate". Hydroxyzine was discontinued, and she recovered within two days.

The treating physician thought that the events were due to the combined effects of hydroxyzine, lorazepam, and clorazepate.

In one case, the events were associated with an intentional hydroxyzine overdose. The patient (case # 9501282) was a 25-year-old male who ingested fifty hydroxyzine 25 mg tablets (1,250 mg). He was hospitalized eight hours later for gastric lavage, at which time physical and laboratory examinations were described as "unremarkable" (blood pressure was 130/80 mmHg and chest x-ray was normal). He was transferred to the intensive care unit because of concern over potential seizures, and a few hours later suffered a cardiac arrest with asystole. Resuscitation for several minutes led to a return of a regular sinus rhythm. The patient was given an external pacemaker set at 50 beats/minute as a prophylactic measure. Four days later, when the pacemaker was removed, his heart rate fell to 45 beats/minute, which was successfully treated with one ampule of intravenous atropine. The patient was discharged in good condition.

In one case the events were associated with an accidental ingestion of hydroxyzine by a young child. The patient (case # 9503721) was a 13-month-old female who ingested between 500 mg and 625 mg of hydroxyzine tablets and developed generalized seizures, sinus tachycardia, mydriasis, intermittent apnea, and mild pyrexia. On admission, she was semi-comatose. Her plasma hydroxyzine concentration 8.5 hours after ingestion was 102.7 $\mu\text{g/mL}$. She received supportive care and seizure control therapy with intravenous physostigmine and diazepam, and lavage with activated charcoal, and completely recovered within 72 hours.

In five cases, the reported events could have been associated with concomitant therapy. The first of these (case # 9408568) involved a female patient of unknown age described as a "nursing home patient" receiving multiple unknown medications, hydroxyzine (indication, dosage, and duration of therapy unknown), and venlafaxine (75 mg/day for depression) who developed hypertonia and trismus. Warfarin (indication, dosage, and duration of therapy unknown) was also listed as a concomitant medication. She reportedly experienced unspecified "problems" in the nursing home, and was transported to an emergency room, where she "arrested". The hydroxyzine and venlafaxine were discontinued, and the hypertonia and trismus improved. She reportedly had a history of atrial fibrillation and was being treated with multiple medications that the reporter was unable to identify. Venlafaxine is reported to be associated with hypertonia and trismus, and, although not reported to be associated with cardiac arrest, it has also been reported to be associated with arrhythmias including extrasystoles, first-degree atrioventricular block, and bundle-branch block².

In two other patients whose events could have involved other medications hydroxyzine was administered as part of a pre-anesthesia regimen for dental surgery. The first of these patients (case # 9390388) was a 23-year-old female who received general anesthesia for extraction of wisdom teeth. She received hydroxyzine 100 mg orally and betamethasone (dose and route of administration unknown) followed by vecuronium bromide, propofol, and fentanyl intravenously. After five minutes, she developed a rash, tachycardia, and hypertension which resolved spontaneously. Skin tests were performed for all drugs administered and were positive

for hydroxyzine and vecuronium bromide. The second of these patients (case # 9501923) involved an approximately four-year-old male with a history of muscle weakness of unknown etiology who received anesthesia prior to a dental procedure. He was given hydroxyzine pamoate 50 mg and diazepam 10 mg mixed with honey, and then inhaled a mixture of 50% nitrous oxide and 50% oxygen. He also received 2.75 Carpules of lidocaine 2% with epinephrine 1:100,000 into the oral mucosa over five minutes. Over the next 50 minutes, the patient appeared twice to have exhibited "early signs of vomiting", but he did not vomit. He then again demonstrated a "rising and falling movement of the chest and stomach", and became apneic. Resuscitation was attempted, and he was found to have no carotid pulse. Paramedics were called, and he was transported to an emergency room. During transport, the paramedics again attempted to resuscitate the patient. He was received at the emergency room in asystole, and was resuscitated and maintained in sinus tachycardia, but his pupils were fixed and dilated. He was transferred to the pediatric intensive care unit, and expired two days later. Hydroxyzine blood concentrations five to six hours after administration were negative. Lidocaine and epinephrine concentrations were not reported. The medical examiner listed the probable cause of death as cardiopulmonary arrest with no precipitating factors. It was reported that he had received diazepam, hydroxyzine, and lidocaine with epinephrine twice before without incident.

The last two cases where the events could have been related to concomitant medication are not very well documented and were difficult to evaluate; however, in both of these the patients appeared to have had pre-existing cardiovascular disease and were receiving other medications which could have contributed to the reported events. In the first of these (case # 9503401) a patient of unknown age and gender with "a deficient heart state" and gastric cancer was treated with hydroxyzine and amiodarone and developed bradycardia which improved following discontinuation of hydroxyzine. In the second (case # 9503402) a patient of unknown age and gender with supraventricular tachycardia and hypertension treated with hydroxyzine 100 mg/day, nordazepam 7.5 mg/day, and nifedipine 20 mg/day experienced sinus tachycardia and "generalized flushing". No additional information is available for these cases, but amiodarone has been reported to be associated with bradycardia ³, and nifedipine has been reported to be associated with tachycardia and flushing ⁴.

In four patients hydroxyzine was administered as part of a pre-anesthesia regimen prior to general anesthesia. The first of these (case # 9503403) involved a 55-year-old female with no known illnesses receiving no known other medications who received hydroxyzine 150 mg intramuscularly and atropine 0.5 mg intramuscularly prior to surgery to repair a dog bite-induced open fracture of the wrist. Approximately 10 minutes later, she was reported to be "feeling bad", was conscious and "about to vomit". Her blood pressure was reported as "40", and she had an impalpable pulse, severe sweating, and pallor. A plasma expander infusion was started, and another 0.5 mg of atropine was administered intramuscularly. The reaction was reported to be immediate, with blood pressure of "70", and bradycardia (40 beats/minute). Another 0.75 mg of atropine was administered intravenously, and a "complete recovery" occurred within half an hour. The patient underwent surgery the next day without any premedication and without any problems. The second (case # 9503404) involved a 32-year-old male with no known illnesses

receiving no known other medications who received hydroxyzine 150 mg intramuscularly and atropine 0.5 mg intramuscularly prior to an appendectomy. Approximately five minutes later, he wanted to vomit, became very pale, was sweating, had an impalpable blood pressure, and bradycardia (40 beats/minute). A plasma expander infusion was started and his lower limbs were raised. He recovered and underwent the surgery about two hours later.

Two other cases which involved hydroxyzine as part of a pre-anesthesia regimen are not very well documented and difficult to evaluate. The first of these (case # 9503398) involved a 30-year-old male pre-medicated with hydroxyzine 50 mg/day for three days prior to "surgery" who developed "an acute major bronchospasm during surgery", followed by ventricular fibrillation leading to cardiac arrest, phase IV coma, and death. No additional information is available on this case.

The last case (case # 9503399) involving hydroxyzine as pre-anesthesia is also not well documented, but the patient appears to have had pre-existing cardiovascular disease which may have contributed to the reported events. This 84-year-old patient of unknown gender with a history of aortic sclerosis, mitral insufficiency murmur, and left anterior hemibloc received a single intramuscular injection of hydroxyzine 100 mg as premedication for eye cancer surgery, and developed bradycardia which regressed after treatment with atropine. No additional information is available for this case.

There were two cases that were not very well documented. These cases (case #s 9503397 and 9503400) involved two patients of unknown age and gender who experienced bradycardia following intravenous administration of hydroxyzine. No additional information is available for these cases.

The last hydroxyzine case involved a patient who received hydroxyzine and meperidine for pain. This case contained limited information and a possible relationship between the reported events and hydroxyzine and/or meperidine can not be entirely excluded. The patient (case # 9400513) was a 36-year-old female with an unknown medical history admitted to the hospital for a flare-up of previously documented gallstones. She was prescribed meperidine 100 mg and hydroxyzine 100 mg intravenously for pain. During administration, she became nauseated, lightheaded, developed a severe headache, and had temporary hypotension. The medication was stopped immediately. She appeared pale, uncomfortable, and anxious. There were no rashes or wheezing. Electrocardiogram revealed ischemia in leads III, V3, V4, and V5. She was placed on oxygen, put in the Trendelenburg position, and given methylprednisolone, epinephrine, and naloxone. She was transferred to the intensive care unit where she was found to have "an elevation in enzymes associated with a myocardial infarction" (specific details were not provided) and it was reported that "cardiac catheterization and echocardiography revealed a completely normal heart".

MECLIZINE

The first meclizine case (case # 9401063) involved a 47-year-old male with a history of hypertension who experienced a cardiac arrest "manifested as ventricular fibrillation" after being treated with meclizine (dose unknown) for vertigo for "a couple of weeks". He reportedly had been prescribed enalapril for his hypertension, but was not taking it at the time of his cardiac arrest. Cardiac work-up consisting of electrocardiograms before and after this episode were reported as normal. An echocardiogram, cardiac catheterization, and ergonovine provocation were all reported to be normal.

The second meclizine case (case # 9503262) was reported by a consumer, and involved a 45-year-old male with an unknown medical history who took two meclizine 25 mg chewable tablets before an airplane flight. Two to three hours into the flight, upon awakening he "passed out". He felt sick, and the cabin staff administered oxygen to help revive him. It was also reported that meclizine was not effective. No additional information is available for this case.

SUMMARY AND CONCLUSIONS

In summary, this updated review identified two meclizine cases and 14 hydroxyzine cases which involved cardiovascular adverse events entered into Pfizer's early alert safety database from January 1, 1994 to April 19, 1995, and one hydroxyzine case entered prior to January 1, 1994 which had been updated to include cardiovascular events. Sixteen were spontaneously reported cases and one was a literature case.

Among the hydroxyzine cases, two involved non-fatal overdoses. In six cases (the updated case and five new cases) the patients were taking concomitant medications (venlafaxine, vecuronium, propofol, fentanyl, lidocaine with epinephrine, amiodarone, nifedipine, lorazepam, and clorazepate) that have been reported to be associated with the types of events that were reported^{2,11}. There were four cases where hydroxyzine was part of a pre-anesthesia regimen prior to general anesthesia, but two of these cases were not very well documented and in one of them the patient may have had pre-existing cardiovascular disease which contributed to the reported event. Another two cases were not very well documented and were difficult to evaluate. In the last hydroxyzine case a patient with an unknown medical history appeared to have experienced a myocardial infarction while receiving hydroxyzine and meperidine, but a subsequent cardiac catheterization and echocardiography were normal.

In one meclizine case the patient had a history of hypertension for which enalapril had been prescribed, but he reportedly had not been taking the enalapril when he started meclizine therapy. Cardiac work-up before and after the event were reported as normal. The other meclizine case was reported by a consumer and is difficult to evaluate since it was not well documented.

The original review, which included cases entered into the database through December 31, 1993, identified 12 hydroxyzine cases and six meclizine cases involving heart rate/rhythm adverse

events or syncope. Among the hydroxyzine cases, two cases were poorly documented, one case involved syncope associated with a seizure, and five cases involved events which could have been due to other causes. In one case a relationship between hydroxyzine and arrhythmia could not be entirely excluded; however, the patient had received terfenadine (which is known to be associated with serious arrhythmias) three days prior to onset of the reported event. In three of the hydroxyzine cases the events were associated with intentional overdoses/suicide attempts, and involved tachycardia following ingestion of 625 mg, cardiac arrest following ingestion of 1,250 mg, and ventricular arrhythmias including torsades de pointes following ingestion of 31,300 mg.

For the meclizine cases discussed in the previous review, limited information was provided in five of the cases, which made evaluation difficult; however, in one of these cases the patient had an underlying illness which may have contributed to the events, and in another case the patient had experienced similar symptoms before. The remaining meclizine case involved an elderly female with a history of heart failure and liver disease who experienced torsades de pointes after she had increased her meclizine dose to about 2,500 mg/day over the preceding four to six weeks.

The previous review concluded that there is no indication that serious arrhythmias occur in association with hydroxyzine or meclizine when used in normal therapeutic doses in patients who are otherwise healthy. This updated review of new cases supports that conclusion.

References

- 1) Hydroxyzine/meclizine and cardiovascular events. Pfizer Inc; Clinical Safety; January 14, 1994.
- 2) Anon. EFFEXOR® (venlafaxine HCl - Wyeth-Ayerst). *Physician's Desk Reference (49th Ed)*. Medical Economics; Montvale, New Jersey; 1995; pg. 2664-2668.
- 3) Anon. Amiodarone hydrochloride. *American Hospital Formulary Service - Drug Information 94*. McEvoy GK, Litvak K, and Welsh OH (Eds). American Society of Hospital Pharmacists; Bethesda, Maryland; 1994; pg. 964-973.
- 4) Anon. Calcium channel blocking agents: systemic. *USP-DI: Drug Information for the Health Care Professional (14th Ed)*. United States Pharmacopeial Convention Inc; Rockville, Maryland; 1994; pg. 678-695.
- 5) Anon. DIPRIVAN® 1% (propofol - Stuart). *Physician's Desk Reference (49th Ed)*. Medical Economics; Montvale, New Jersey; 1995; pg. 2436-2441.
- 6) Anon. NORCURON® (vecuronium bromide - Organon). *Physician's Desk Reference (49th Ed)*. Medical Economics; Montvale, New Jersey; 1995; pg. 1751-1753.
- 7) Anon. Vecuronium bromide. *American Hospital Formulary Service - Drug Information 94*. McEvoy GK, Litvak K, and Welsh OH (Eds). American Society of Hospital Pharmacists; Bethesda, Maryland; 1994; pg. 832-838.
- 8) Anon. SUBLIMAZE® (fentanyl citrate - Janssen). *Physician's Desk Reference (49th Ed)*. Medical Economics; Montvale, New Jersey; 1995; pg. 1199-1201.
- 9) Anon. XYLOCAINE® (lidocaine HCl - Astra)/ XYLOCAINE® (lidocaine HCl - Astra) With Epinephrine. *Physician's Desk Reference (49th Ed)*. Medical Economics; Montvale, New Jersey; 1995; pg. 580-582.
- 10) Anon. Local anesthetics, parenteral, general statement. *American Hospital Formulary Service - Drug Information 94*. McEvoy GK, Litvak K, and Welsh OH (Eds). American Society of Hospital Pharmacists; Bethesda, Maryland; 1994; pg. 2112-2115.
- 11) Anon. Benzodiazepines general statement. *American Hospital Formulary Service - Drug Information 94*. McEvoy GK, Litvak K, and Welsh OH (Eds). American Society of Hospital Pharmacists; Bethesda, Maryland; 1994; pg. 1488-1494.

Appendix 3

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

JUN 23 1995

DATE:

FROM: Evelyn Farinas, RPh.
Postmarketing Safety Evaluator
Reports Evaluation Branch, HFD-735

THROUGH: Sandra Kweder, MD, Acting Director *DJK for RSC (2/2/15)*
Division of Epidemiology and Surveillance, HFD-730

TO: Dr. Ana Maria Saavedra
Division of Pulmonary Drugs Products
HFD-155

SUBJECT: Consult Request: Ketoconazole and Hydroxyzine
drug interaction.

INTRODUCTION

Following your telephone request, please find attached the line-listing corresponding to the Spontaneous Reporting System [SRS] reports where Ketoconazole and Hydroxyzine are listed as concomitant drugs. Between 1982 and the present, there have been 20 such reports in the SRS.

DEMOGRAPHICS

Outcome: 2 deaths; 5 hospit.; 1 disability
Origin: 18 domestic; 2 foreign
Sex: 6 female; 14 male
Age: range 6-90

Most often reported COSTART terms (2 or more cases each):

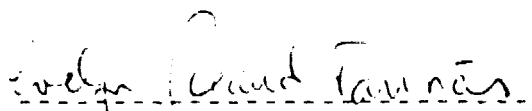
LIVER FUNC ABNORM	5
BILIRUBINEM	3
PHOSPHATASE ALK INC	3
PRURITUS	3
INTRACRAN HYPERTENS	2
JAUNDICE CHOLESTAT	2
RASH	2
RASH MAC PAP	2

DISCUSSION

The Ketoconazole labeling addresses both hepatic adverse events and several drug interactions associated with the use of Ketoconazole. The labeling includes a WARNING box which states: "When used orally, ketoconazole has been associated with hepatic toxicity, including some fatalities." The labeling also indicates that concomitant Ketoconazole use alters the metabolism of the following drugs: terfenadine, astemizole, loratadine, rifampin, coumarin, INH, cyclosporine, phenytoin, methylprednisolone, etc. Hydroxyzine was not mentioned.

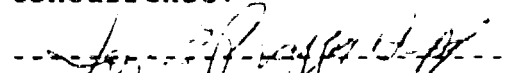
In reviewing this report, it is essential to remember limitations associated with data derived from the Spontaneous Reporting System. In some of these cases, the reported clinical data was incomplete, and there is no certainty that these drugs caused the reported reactions. Furthermore, a given reaction may actually have been due to an underlying disease process or to another coincidental factor. Because this data was generated using computer printouts, some of the numbers may reflect duplicates.

If I may be of further assistance, please call me at 594-5471.

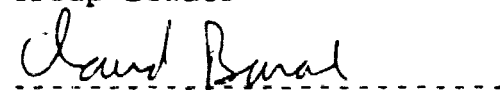


Evelyn R. Farinas, MGA, RPh

Concurrence:



Toni Piazza-Hepp, Pharm. D.
Group Leader



David Barash, RPh.
Chief

CC:

HFD-730/Acting Director
HFD-733/Graham/Acting Chief
HFD-735/Barash/Piazza-Hepp/Farinas/Chron/Consult

14-JUN-1995 14:05:40

Page 1

Drugs Included in FARINASEKETOC

Drugcode	Drug
FARINASEKETOC	KETOCONAZOLE
	MIZORAL
	MIZORAL 2X

Geog Area: ALL (DOM + FOR)

Costart(code): N/A

Drugcode1: FARINASEKETOC

Drugcode2: FARINASEHDXZ

Drugs Included in FARINASEHDRXZ

Drugcode	Drug
FARINASEHDRXZ	ATARAX
	EMAZAX
	HYDROXYZINE
	HYDROXYZINE HYDROCHLORIDE
	HYDROXYZINE PAMOATE
	MARAX
	VISTARIL

Geog Area: ALL (DOM + FOR)

Costart(code): N/A

Drugcode1: FARINASEKETOC

Drugcode2: FARINASEHDRXZ

Number of Cases Per Serious Outcome, By Age Category

Age Category	Total Cases	Total Serious	Total Died	Total Hospit	Total Disabled	Total Congen Anom	Total Life-Thr
0 - 9	2	1	0	1	0	0	0
10 - 19	0	0	0	0	0	0	0
20 - 29	2	2	0	2	0	0	0
30 - 39	3	0	0	0	3	0	0
40 - 49	3	1	0	0	1	0	0
50 - 59	2	0	0	0	0	0	0
60 - 69	3	2	2	1	0	0	0
70 - 79	3	1	0	1	0	0	0
80 - 120	1	1	0	1	0	0	0
MULL AGE	1	0	0	0	0	0	0
Totals:	20	8	2	6	1	0	0

Number Of Cases Per Serious Outcome, By Sex and Age Category

Sex	Age Category	Total Cases	Total Serious	Total Dfjed	Total Hospit	Total Disabled	Total Congen Anom	Total Life-Thr
Female	0 - 9	0	0	0	0	0	0	0
	10 - 19	0	0	0	0	0	0	0
	20 - 29	0	0	0	0	0	0	0
	30 - 39	1	0	0	0	0	0	0
	40 - 49	2	1	0	0	1	0	0
	50 - 59	1	0	0	0	0	0	0
	60 - 69	1	0	0	0	0	0	0
	70 - 79	1	1	0	1	0	0	0
	80 - 120	0	0	0	0	0	0	0
	NULL AGE	0	0	0	0	0	0	0
Totals:		6	2	0	1	1	0	0
Male	0 - 9	2	1	0	1	0	0	0
	10 - 19	0	0	0	0	0	0	0
	20 - 29	2	2	0	2	0	0	0
	30 - 39	2	0	0	0	0	0	0
	40 - 49	1	0	0	0	0	0	0
	50 - 59	1	0	0	0	0	0	0
	60 - 69	2	2	2	1	0	0	0
	70 - 79	2	0	0	0	0	0	0
	80 - 120	1	1	0	1	0	0	0
	NULL AGE	1	0	0	0	0	0	0
Totals:		14	6	2	5	0	0	0
Unknown	0 - 9	0	0	0	0	0	0	0
	10 - 19	0	0	0	0	0	0	0
	20 - 29	0	0	0	0	0	0	0
	30 - 39	0	0	0	0	0	0	0
	40 - 49	0	0	0	0	0	0	0
	50 - 59	0	0	0	0	0	0	0
	60 - 69	0	0	0	0	0	0	0
	70 - 79	0	0	0	0	0	0	0
	80 - 120	0	0	0	0	0	0	0
	NULL AGE	0	0	0	0	0	0	0
Totals:		0	0	0	0	0	0	0

Number of Cases Per Serious Outcome, By Year/Quarter

Year - Qtr	Total Cases	Total Serious	Total Died	Total Hospit	Total Disabled	Total Congen Anom	Total Life-Thr
1982 - 2	1	1	0	1	0	0	0
1983 - 3	1	0	0	0	0	0	0
1983 - 4	1	1	1	1	0	0	0
1985 - 3	1	1	1	0	0	0	0
1988 - 4	1	0	0	0	0	0	0
1989 - 3	1	0	0	0	0	0	0
1990 - 2	2	0	0	0	0	0	0
1990 - 4	1	0	0	0	0	0	0
1991 - 3	2	0	0	0	0	0	0
1991 - 4	1	0	0	0	0	0	0
1992 - 2	1	0	0	0	0	0	0
1992 - 3	2	1	0	0	1	0	0
1993 - 3	1	0	0	0	0	0	0
1993 - 4	1	1	0	1	0	0	0
1994 - 1	1	1	0	1	0	0	0
1994 - 2	1	1	0	1	0	0	0
1995 - 1	1	1	0	1	0	0	0
Totals:	20	6	2	6	1	0	0

Number Of Dechallenges/Rechallenges Per Serious Outcome

De/Rechall	Total Cases	Total Serious	Total Died	Total Hospit	Total Disabled	Total Congen Anom	Total Life-Thr
DECHALLENGE	6	2	0	2	0	0	0
RECHALLENGE	0	0	0	0	0	0	0
N/A	5	3	2	2	0	0	0
Totals:	11	5	2	4	0	0	0

Number Of Foreign, Study, Consumer and Literature Reports, By General Source

General Source	Total Cases	Total Foreign	Total Study	Total Consumer	Total Literature	Total Exclusions *
CDL	0	0	0	0	0	0
CHIROPRACTORS	0	0	0	0	0	0
CIOBS	0	0	0	0	0	0
COMMUNITY HEALTH CLINICS	0	0	0	0	0	0
CONSUMERS	0	0	0	0	0	0
CORONER'S OFFICE	0	0	0	0	0	0
DENTIST	0	0	0	0	0	0
DRUG TREATMENT CENTERS	0	0	0	0	0	0
FDA DISTRICTS	0	0	0	0	0	0
HEALTH CARE STUDENTS	0	0	0	0	0	0
LITERATURE	0	0	0	0	0	0
MANUFACTURER	15	2	0	1	0	3
MILITARY HOSPITAL	0	0	0	0	0	0
NON-FEDERAL HOSPITAL (NIN)	0	0	0	0	0	0
NURSES	0	0	0	0	0	0
OPTOMETRIST	0	0	0	0	0	0
OSTEOPATHS	0	0	0	0	0	0
OTHER: FOREIGN COUNTRIES	0	0	0	0	0	0
OTHER: HMO'S	0	0	0	0	0	0
OTHER: NURSING HOMES	0	0	0	0	0	0
PHARMACISTS	1	0	0	0	0	0
PHYSICIAN EXTENDERS/ASSISTANTS	0	0	0	0	0	0
PHYSICIANS	1	0	0	0	0	0
PLANNED PARENTHOOD CLINICS	0	0	0	0	0	0
PODIATRISTS	0	0	0	0	0	0
PUBLIC HEALTH SERVICE FACILITIES	0	0	0	0	0	0
SPECIAL PROJECTS	0	0	0	0	0	0
SPECIAL STUDY (IND)	0	0	0	0	0	0
SPECIAL STUDY (NDA)	1	0	1	0	0	1
STATE HEALTH DEPARTMENT	0	0	0	0	0	0
UNKNOWN	0	0	0	0	0	0
VA HOSPITAL	2	0	0	0	0	0
Totals:	20	2	1	1	0	4

Geog Area: ALL (DOM + FOR)

Costart(code): N/A

Drugcode1: FARINASEKETOC

Drugcode2: FARINASEHDXZ

* For Reports Included In This Analysis, Exclusions = Cases Having At Least One of the Sources FOR, STU, CON, LIT.

Number of Cases Per Serious Outcome, By Report Type

Report Type	Total Cases	Total Serious	Total Died	Total Hospit	Total Disabled	Total Congen Anom	Total Life-Thr
15-DAY	5	4	0	3	1	0	0
PERIODIC	11	2	2	1	0	0	0
DIRECT	4	2	0	2	0	0	0
UNKNOWN	0	0	0	0	0	0	0
Totals:	20	8	2	6	1	0	0

Numbers Of Cases Having 1, 2, 3 Or 4 Or More Drugs

<u>Total Cases</u>	<u>1 Drug</u>	<u>2 Drugs</u>	<u>3 Drugs</u>	<u>4 Or More Drugs</u>
20	0	2	4	14

Geog Area: ALL (DON + FOR)

Costart(code): N/A

Drugcode1: FARINASEKETOC

Drugcode2: FARINASEHDXZ

Number of Cases Per Serious Outcome, By Location Within Geographic Region

Region	Location	Total Cases	Total Serious	Total Died	Total Hospit	Total Disabled	Total Congen Anom	Total Life-Thr
FRGN	BELG	1	1	0	1	0	0	0
	FRAN	1	1	0	1	0	0	0
Totals:		2	2	0	2	0	0	0
MATL	PA	1	0	0	0	0	0	0
		1	0	0	0	0	0	0
Totals:		1	0	0	0	0	0	0
NE	MA	1	0	0	0	0	0	0
	NJ	1	0	0	0	0	0	0
Totals:		2	0	0	0	0	0	0
PAC	CA	4	1	0	1	0	0	0
		4	1	0	1	0	0	0
Totals:		4	1	0	1	0	0	0
SE	FL	4	2	1	1	1	0	0
	KY	1	0	0	0	0	0	0
	LA	1	0	0	0	0	0	0
	MS	1	0	0	0	0	0	0
	TN	1	0	0	0	0	0	0
Totals:		8	2	1	1	1	0	0
SW	MO	2	2	0	2	0	0	0
	TX	1	1	1	0	0	0	0
Totals:		3	3	1	2	0	0	0

Geo. Area: ALL (DOM + FOR) Costart(code): N/A

Drugcode1: FARINASEKETOC

Drugcode2: FARINASEHDX2

NOTE: A location of N/A refers to cases for which no location was entered.

Counts Of COSTARTs In Cases, With Most Frequent COSTART Terms Listed First

COSTART Term	Count
LIVER FUNC ABNORM	5
BILIRUBINEM	3
PHOSPHATASE ALK INC	3
PRURITUS	3
INTRACRAN HYPERTENS	2
JAUNDICE CHOLESTAT	2
RASH	2
RASH MAC PAP	2
ALOPECIA	1
ARRHYTHMIA	1
ATROPHY INJECT SITE	1
BRAIN SYND ACUTE	1
CARCINOMA LUNG	1
CONVULS	1
DIARRHEA	1
DRUG INTERACTION	1
DRY EYE	1
HYPOCALCEM	1
HYPOTENS	1
JAUNDICE	1
LIVER TENDER	1
PAIN ABDO	1
REACT AGGRAV	1
TORSADES DE POINTES	1
URTICARIA	1
VOMIT	1

Number Of Cases Per Serious Outcome, By Suspect And Other Drug

Sus/ Oth	Generic (Collapsed) Drug	Drug	Total Cases	Total Serious	Total Died	Total Hospit	Total Disabled	Total Congen Anom	Total Life-Thr
Susp	AMOXICILLIN	AMOXICILLIN	1	0	0	0	0	0	0
	CIPROFLOXACIN	CIPRO	1	0	0	0	0	0	0
	CIPROFLOXACIN	CIPROFLOXACIN	2	2	0	2	0	0	0
	GANCICLOVIR	CYTOVENE	1	0	0	0	0	0	0
	HYDROXYZINE	HYDROXYZINE HYDROCHLORID	1	0	0	0	0	0	0
	KETOCONAZOLE	KETOCONAZOLE	3	3	1	3	0	0	0
	KETOCONAZOLE	NIZORAL	7	2	1	1	0	0	0
	KETOCONAZOLE	NIZORAL 2X	1	0	0	0	0	0	0
	PENTAMIDINE	NEBUPENT	1	0	0	0	0	0	0
	TERFENADINE	SELDANE	3	2	0	1	1	0	0
	TRIAMCINOLONE	KENALOG	1	0	0	0	0	0	0
		Totals:	22	9	2	7	1	0	0
Oth	AZIDOTHYIMIDINE	RETROVIR	1	0	0	0	0	0	0
	AZI	RETROVIR	1	0	0	0	0	0	0
	BETAMETHASONE	CELESTONE	1	0	0	0	0	0	0
	BUTICONAZOLE NITRATE	BUTICONAZOLE NITRATE	1	1	0	1	0	0	0
	CEFADROXIL	DURICEF	1	0	0	0	0	0	0
	CLINDAMYCIN	CLEOCIN	1	0	0	0	0	0	0
	CLOTRIMAZOLE	MYCELEX	2	0	0	0	0	0	0
	CORTISONE	CORTISONE	1	0	0	0	0	0	0
	DESIPRAMINE	DESIPRAMINE HYDROCHLORID	1	0	0	0	0	0	0
	DEXAMETHASONE	DECADRON	1	1	1	1	0	0	0
	DIPIVEFRIN	PRCPINE	1	1	0	1	0	0	0
	DOXEPIIN	DOXEPIIN	2	0	0	0	0	0	0
	ESTROGENS	PREMARIN	1	0	0	0	0	0	0
	FLURAZEPAM	DALMANE	1	1	0	1	0	0	0
	HEPARIN	HEPARIN	1	0	0	0	0	0	0
	HYDROXYZINE	ATARAX	9	1	0	1	0	0	0
	HYDROXYZINE	HYDROXYZINE	8	5	0	4	1	0	0
	HYDROXYZINE	VISTARIL	2	2	2	1	0	0	0
	IBUPROFEN	IBUPROFEN	2	2	0	2	0	0	0
	KETOCONAZOLE	KETOCONAZOLE	3	2	0	2	0	0	0
	KETOCONAZOLE	NIZORAL	6	1	0	0	1	0	0
	LOPERAMIDE	IMODIUM	1	0	0	0	0	0	0
	MEPERIDINE	DEMEROL	1	1	1	0	0	0	0
	NAPROXEN	NAPROSYN	1	0	0	0	0	0	0
	NYSTATIN	NYSTATIN	1	1	1	1	0	0	0
	PREDNISONE	PREDNISONE	3	1	1	0	0	0	0
	RANITIDINE	ZANTAC	1	1	1	0	0	0	0
	TERFENADINE	SELDANE	1	0	0	0	0	0	0
	THIETHYLPERAZINE	TORECAN	1	0	0	0	0	0	0
	TRIAMCINOLONE	TRIAMCINOLONE	1	0	0	0	0	0	0
	VINCRIStINE	VINCRIStINE SULFATE	1	1	1	1	0	0	0
	ZALCITABINE	ZALCITABINE	2	2	0	2	0	0	0
	ZIDOVUDINE	RETROVIR	1	0	0	0	0	0	0
	ZOMEPIRAC SODIUM	ZOMAX	1	1	0	1	0	0	0
		Totals:	63	25	8	19	2	0	0

Geog Area: ALL (DOM + FOR)

Costart(code): N/A

Drugcode1: FARINASEKETOC

Drugcode2: FARINASEHDRXZ

Number Of Cases Per Serious Outcome, By Year Of Receipt

Year	Total Cases	Total Serious	Total Died	Total Hospit	Total Disabled	Total Congen Anom	Total Life-Thr
1982	1	1	0	1	0	0	0
1983	2	1	1	1	0	0	0
1985	1	1	1	0	0	0	0
1984	1	0	0	0	0	0	0
1989	1	0	0	0	0	0	0
1990	3	0	0	0	0	0	0
1991	3	0	0	0	0	0	0
1992	3	1	0	0	1	0	0
1993	2	1	0	1	0	0	0
1994	2	2	0	2	0	0	0
1995	1	1	0	1	0	0	0
Totals:	20	8	2	6	1	0	0

Number Of Cases Per Serious Outcome, By Bodysystem

Bodysystem	Total Cases	Total Serious	Total Died	Total Hospit	Total Disabled	Total Congen Anom	Total Life-Thr
BODY	4	3	1	1	1	0	0
CV	2	1	0	1	0	0	0
DIG	7	3	0	2	1	0	0
ENDO	0	0	0	0	0	0	0
HAL	0	0	0	0	0	0	0
HAN	4	1	0	1	0	0	0
MS	0	0	0	0	0	0	0
NER	4	3	1	3	0	0	0
RES	1	1	1	0	0	0	0
SKIN	8	3	0	2	1	0	0
SS	1	0	0	0	0	0	0
UG	0	0	0	0	0	0	0
Totals:	31	15	3	10	3	0	0

NDA 19835

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Number Of Cases Per Serious Outcome, By COSTART Within Bodysystem

Bodysystem	COSTART	Total Cases	Total Serious	Total Qied	Total Hospit	Total Disabled	Total Congen Anom	Total Life-Thr
BODY	ATROPHY INJECT SITE	1	0	0	0	0	0	0
	DRUG INTERACTION	1	1	0	1	0	0	0
	PAIN ABDO	1	1	0	0	1	0	0
	REACT /SGRAV	1	1	1	0	0	0	0
	Totals:	4	3	1	1	1	0	0
CV	ARRHYTHMIA	1	1	0	1	0	0	0
	HYPOTENS	1	0	0	0	0	0	0
	TORSADES DE POINTES	1	1	0	1	0	0	0
Totals:	3	2	0	2	0	0	0	
DIG	DIARRHEA	1	1	0	0	1	0	0
	JANIDICE	1	1	0	1	0	0	0
	JANIDICE CHOLESTAT	2	0	0	0	0	0	0
	LIVER FUNC ABNORM	5	1	0	1	0	0	0
	LIVER TENDER	1	1	0	0	1	0	0
	VOMIT	1	1	0	1	0	0	0
Totals:	11	5	0	3	2	0	0	
HMB	BILIRUBINEM	3	0	0	0	0	0	0
	HYPOCALCEM	1	1	0	1	0	0	0
	PHOSPHATASE ALK INC	3	0	0	0	0	0	0
Totals:	7	1	0	1	0	0	0	
NER	BRAIN SYND ACUTE	1	1	0	1	0	0	0
	CONVULS	1	1	1	1	0	0	0
	INTRACRAN HYPERTENS	2	1	0	1	0	0	0
Totals:	4	3	1	3	0	0	0	
RES	CARCINOMA LUNG	1	1	1	0	0	0	0
Totals:	1	1	1	0	0	0	0	
SKIN	ALOPECIA	1	0	0	0	0	0	0
	PRURITUS	3	1	0	0	1	0	0
	RASH	2	0	0	0	0	0	0
	RASH MAC PNP	2	2	0	2	0	0	0
	URTICARIA	1	0	0	0	0	0	0
Totals:	9	3	0	2	1	0	0	
SS	DRY EYE	1	0	0	0	0	0	0
Totals:	1	0	0	0	0	0	0	

Line Listing Summary Of Cases

Year	CaseNum	Image ID	Rpt Type	Age	Sex	Lor	Wfg Control No.		S/O Dose	Unit	Route	Durat (Days)	DC	RC
Serious Outcome			COSTART	Drug										
1982	C131771 (NOSP	N131771	NFR 15-DAY (JAUNDICE (LIVER FUNC ABNORM (BRAIN SYND ACUTE	89G	M	CA			S 0 0 0 0	200.00 .00 .00 .00 .00	AL PO PO PO PO	21057	Y	NA
1983	C166154	N166154	NFR 15-DAY (INTRACRAN HYPERTENS		M	MS	N432		S 0 0	.00 .00 .00	PO TOP PO			
1983	C177396 (NOSP (DIED	N177396	PERIODIC (CONVULS	062	M	FL	41400302		S 0 0 0 0	200.00 20.00 6.00 200.00 1.50	MG ML MG MG GM	PO PO PO PO IV	12 9 27 37	
1985	C164338 (DIED	N164338	PERIODIC (CARCINOMA LUNG (REACT AGGRA.	064	M	TX	N644		S 0 0 0 0	200.00 20.00 .00 225.00 150.00	MG MG MG MG MG	PO PO PO PO PO	2 159 16 16 16	NA
1988	C559684	N559684	DIRECT (RASH	057	F	FL			S 0 0 0 0	1.50 .00 .00 .00 .00	GM PO PO PO PO	1		
1989	C620699	N600699	PERIODIC (JAUNDICE CHOLESTAT (PHOSPHATASE ALK INC (BILIRUBINEM (LIVER FUNC ABNORM	070	M	MA	N964		S 0 0 0 0	200.00 .00 .00 .00 .00	MG PO PO PO PO	28	NA	NA
1990	C657697	N657697	PERIODIC (DRY EYE	040	M	CA	00313139		S 0 0 0 0	600.00 .00 .00 .00 .00	MG IV PO PO PO		NA	NA
1990	C661002	N661002	DIRECT (URTICARIA (PRURITUS	040	F	KY			S 0 0	.60 .00 .00	PO		NA	NA

Line Listing Summary Of Cases

Year	CaseNum	Image ID	Rpt Type	Age	Sex	Loc	Mfg Control No.		S/O Dose	Unit	Route	Durat (Days)	BC	RC
Serious Outcome			COSTART	Drug										
1990	C707343	N707343	PERIODIC (ATROPIN INJECT SITE	036	F	LA	0290041	(KENALOG (ATARAX (NIZORAL (CELESTONE	S 0 0 0	60.00 .00 .00 .00	MG IN	8	NA	NA
1991	C759135	N759135	PERIODIC (PRURITUS (LIVER FUNC ABNORM (PHOSPHATASE ALK INC (BILIRUBINEM	070	M	NJ	US9001061	(SELDANE (NIZORAL (ATARAX (DOXEPIN (PREDNISON	S S 0 0 0	.00 200.00 .00 .00 .00	MG PO PO	28 28	NA	NA
1991	C767201	N767201	PERIODIC (LIVER FUNC ABNORM	039	M	CA	N1511	(NIZORAL (IMODIUM (NAPROSYN (TIORECAN (ATARAX	S 0 0 0 0	200.00 .00 .00 .00 .00	MG PO	37	Y	NA
1991	C785575	N785575	PERIODIC (RASH	050	M	PA	AR161	(HYDROXYZINE HYDROCHLORIDE (NIZORAL	S 0	100.00 .00	MG PO	1	NA	NA
1992	C852627	N852627	PERIODIC (ALOPECIA	006	M	FL	NS240	(NIZORAL 2X (ATARAX (CORTISONE	S 0 0	.00 .00 .00	TOP	22	Y	NA
1992	C863064	N863064	PERIODIC (HYPOTENS	035	M	TN	US1921091NB	(NEBUPENT (RETROVIR (NIZORAL (HYDROXYZINE (MYCELEX	S 0 0 0 0	300.00 .00 .00 .00 .00	MG INH	1	Y	NA
1992	C870140	N870140	MFR 15-DAY (DISABLED (PAIN ABDO (PRURITUS (LIVER TENDER (D:ARRHEA	042	F	FL	9287657	(SELDANE (NIZORAL (HYDROXYZINE	S 0 0	.00 .00 .00	PO	1065	N	NA
1993	C1364372	N1360128	PERIODIC (JAUNDICE CHOLESTAT (PHOSPHATASE ALK INC (BILIRUBINEM (LIVER FUNC ABNORM	060	F	CA	N1606	(NIZORAL (DURICEF (PREMARIN (ATARAX	S 0 0 0	200.00 .00 .00 .00	MG PO	15	Y	NA

Line Listing Summary Of Cases

Year	CaseNum	Image ID	Rpt Type	Age	Sex	Loc	Mfg Control No.	S/O	Dose	Unit	Route	Durat (Days)	DC	RC
		Serious Outcome	COSTART				Drug							
1993	C1399836 (NOSP	N1403748 (RASH MAC PAP	DIRECT	028	M	NO	REF3712JAFR3712	S	500.00	MG	PO	95	Y	NA
							(CIPROFLOXACIN	O	.00					
							(HYDROXYZINE	O	.00					
							(IBUPROFEN	O	.00					
							(KETOCOMAZOLE	O	.00					
							(ZALCITABINE	O	.00					
1996	C1433747 (NOSP	N1439071 (RASH MAC PAP	DIRECT	028	M	NO	REF3712JAFR3712	S	500.00	MG	PO	86	Y	NA
							(CIPROFLOXACIN	O	.00					
							(HYDROXYZINE	O	.00					
							(IBUPROFEN	O	.00					
							(KETOCOMAZOLE	O	.00					
							(ZALCITABINE	O	.00					
1994	C1451429 (NOSP	N1462815 (INTRACRAN HYPERTENS (VOMIT	MFR 15-DAY	007	M	BELG	REF3712JAFR3712	S	20.00	MG	PO	7	NA	NA
							(KETOCOMAZOLE	O	.00					
							(HYDROXYZINE							
1995	C1542491 (NOSP	N1554908 (HYPOCALCEM (ARRHYTHMIA (DRUG INTERACTION (TORSADES DE POINTES	MFR 15-DAY	073	F	FRAN	94007559	S	120.00	MG	PO	15	Y	NA
							(SELDANE	S	400.00	MG	PO	14	Y	NA
							(KETOCOMAZOLE	O	.00					
							(BUTOCOMAZOLE NITRATE	O	.00					
							(HYDROXYZINE	O	.00					

Total Cases: 20

Comments For Cases

1

CaseNum: C131771 Image ID: M131771
BILI 4.7, SGPT 695, SGOT 230, ALP PHOS 523; ONYCHOMYCOSIS RESISTENT TO GRISEOFULVIN.

CaseNum: C166154 Image ID: M166154
BULGING FONTANELLE.

Listing Of Case Numbers and Initial and Followup Image ID Numbers

Initial Case Image ID	Followup Image ID	Followup Entry Date	Followup Release Date	CaseNum
131771	M332974			C131771
166154				C166154
177396	M364293			C177396
364338				C364338
559684				C559684
600699				C600699
657697				C657697
661002				C661002
707343				C707343
759135				C759135
767201				C767201
785575				C785575
852627	M882610			C852627
863064				C863064
870140				C870140
1360128				C1360128
1403748				C1399838
1439071				C1433747
1462815				C1451429
1554908	M0			C1542491
1554908	M1573588	03-APR-1995	05-APR-1995	C1542491

Total Cases: 20

Geog Area: ALL (DUI + FOR)

Costart(code): N/A

Drugcode1: FARINASEKETOC

Drugcode2: FARINASEHORYZ

*** NOTE: SUBMIT CASENUM/IMAGE ID PAIRS CN DATA REQUESTS, IN ASCENDING IMAGE ID ORDER. INCLUDE C AND M PREFIXES ***

Appendix 4

APPEARS THIS WAY
ON ORIGINAL

Cytolytic hepatic injury after cetirizine (Zyrtec®) administration

Several cases of hepatitis attributed to terfenadine (Teldane®) have been reported [1, 2]. However, no cases of hepatitis during treatment with cetirizine (Zyrtec®), a new non-anti-cholinergic type H1 antihistamine [3] have been reported apart from a moderate elevation in alanine aminotransferase (ALT) [1]. We are reporting a case of hepatitis during treatment with cetirizine.

A 46-year-old man with no history of alcohol intoxication, drug addiction, transfusion, or recent trip abroad, whose serum hepatic enzymes had been normal before introduction of the drug, was treated with 10 mg/day cetirizine (Zyrtec®), and no other drugs, for rhinorrhea and allergic tearing. A few months after the cetirizine was started he presented with jaundice, without fever or skin rash, itching, or abdominal pain. The results of the blood tests were: total bilirubin: 93 µmol/L; serum aspartate aminotransferase activity (AST): 553 IU/L (N < 25), ALT: 217 IU/L (N < 30), alkaline phosphatase (AP): 481 IU/L (N < 220), and gammaglutamyl transpeptidase (GGT): 445 IU/L (N < 38); leukocytes: 6200/mm³ of which 4% were eosinophilic polymorphonuclears and 2% monocytes. The results of the hepatitis A (anti-HAV IgM), B (HBs and anti-HBs antibody), and C (anti-HCV) virus serologies were negative. Serologies for cytomegalovirus and infectious mononucleosis, biliary tract ultrasound, and anti-tissue antibody study were not done. Administration of cetirizine was stopped 3 days after the jaundice started. Four days after cetirizine withdrawal, the rise in aminotransferases increased: ALT: 1040 IU/L, AST: 240 IU/L. One month after withdrawal, the hepatic enzyme values were normal (ALT: 23 IU/L, AST: 9 IU/L, AP: 201 IU/L).

Two months after recovery and 10 days after the accidental reintroduction of cetirizine there was further asymptomatic liver disease characterized by abnormal lab values: ALT 244 IU/L and AST: 74 IU/L. HCV serology and differential blood count were not done. Withdrawal of the drug was once again followed by complete normalization of the liver tests in 2 months.

This liver disorder was of the cytolytic type, occurred after several months of treatment with cetirizine, regressed when it was withdrawn, and reappearing when the drug was introduced once again. Even though all other diagnostic hypotheses (biliary lithiasis, autoimmune hepatitis, infectious mononucleosis) were not completely ruled out, positive reintroduction of cetirizine makes it appear likely that the drug was involved. Despite the absence of an abdominal ultrasound, the diagnosis of lithiasis migration is unlikely in view of the absence of biliary history, fever, and biliary-type pain in both episodes. Also, there were differential blood count anomalies suggesting infectious mononucleosis. Of the non-anti-cholinergic H1 type antihistamines, terfenadine [1], and oxatomide [4] may be responsible for hepatitis. On the other hand, no cases of hepatitis following ingestion of loratadine (Clarityne®) or astemizole (Hismanal®) have been published. Our case report is the first of hepatitis attributed to cetirizine. The action mechanism of H1 type antihistamine hepatotoxicity is unknown. Despite the absence of hypereosinophilia and skin rash, an allergic mechanism may be deduced from the short time to onset following reintroduction. This agrees with one case of terfenadine hepatitis [2]. The occurrence of unaccountable liver disorder in a patient taking H1 antihistamines should suggest a drug origin.

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sence de manifestations extra-hépatiques (fièvre, érythrodermie) sont en faveur d'une origine immuno-allergique. Cette observation permet d'attirer l'attention sur la possibilité d'une atteinte hépatique précoce secondaire à la prise d'acitretine.

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Atteinte hépatique cytolitique après administration de cétirizine (Zyrtec®). #10 "Hepatic injury after cetirizine administration"

Plusieurs cas d'hépatites attribuées à la terféndine (Tel-dane®) ont été rapportés (1, 2). En revanche, aucune hépatite n'a été publiée au cours d'un traitement par la cétirizine (Zyrtec®), un nouvel anti-histaminique de type H1 non anti-cholinergique (3), en dehors d'une augmentation modérée de l'alanine aminotransférase (ALAT) (1). Nous rapportons un cas d'hépatite survenue au cours d'un traitement par cétirizine.

Un homme de 46 ans, sans antécédent d'intoxication alcoolique, de toxicomanie, de transfusion ou de voyage récent à l'étranger, dont l'activité sérique des enzymes hépatiques était normale avant l'introduction du médicament, avait traité par 10 mg/j de cétirizine (Zyrtec®), sans autre médicament, pour une rhinorrhée et un larmoiement allergique. Quelques mois après l'introduction de la cétirizine, survint un ictère, sans fièvre ni éruption cutanée, prurit ou douleur abdominale. Les résultats biologiques sanguins étaient les suivants : bilirubinémie totale : 93 µmol/L ; activité sérique de l'aspartate aminotransférase (ASAT) : 533 UI/L (N < 25), de l'ALAT : 217 UI/L (N < 30), des phosphatases alcalines (PAL) : 481 UI/L (N < 220) et de la gamma-glutamyl transpeptidase (GGT) : 445 UI/L (N < 32) ; leucocytes : 6 200/mm³ dont 4 % de polymorphes éosinophiles et 2 % de monocytes. Les résultats des sérologies des virus des hépatites A (IgM anti-VHA), B (antigène HBs et anticorps anti-HBc) et C (anti-VHC) étaient négatifs. Les examens sérologiques du cytomégalovirus et de la mononucléose infectieuse, l'échographie des voies biliaires et la recherche d'anticorps anti-tissus ne furent pas effectués. L'administration de cétirizine fut arrêtée 3 jours après le début de l'ictère. Quatre jours après l'arrêt de la cétirizine l'augmentation des aminotransférases était accrue : ALAT : 1 040 UI/L, ASAT : 240 UI/L. Un mois après l'arrêt, les tests enzymatiques hépatiques étaient normaux (ALAT : 23 UI/L, ASAT : 9 UI/L, PAL : 201 UI/L).

Deux mois après la guérison et 10 jours après la réintroduction accidentelle de cétirizine apparut une nouvelle atteinte hépatique, asymptomatique, et caractérisée par une situation biologique : ALAT : 244 UI/L et ASAT : 74 UI/L. La sérologie du VHC et la numération formule sanguine ne furent pas effectuées. L'arrêt de l'administration du médicament fut à nouveau suivi d'une normalisation complète des tests hépatiques en 2 mois.

Il s'agit d'une atteinte hépatique de type cytolitique, survenant après plusieurs mois d'un traitement par cétirizine, régressant à son arrêt et réapparaissant au décours de la réintroduction du médicament. Même si toutes les autres hypothèses diagnostiques n'ont pas été totalement éliminées (lithiase biliaire, hépatite auto-immune, mononucléose infectieuse), la réintroduction positive de la cétirizine rend vraisemblable le rôle du médicament. Malgré l'absence d'échographie abdominale, le diagnostic d'une migration lithiasique est peu probable devant l'absence d'antécédent biliaire, de fièvre et de douleur de type biliaire lors des 2 épisodes. Par ailleurs, il n'y avait pas d'anomalie à la numération formule sanguine orientant vers une mononucléose infectieuse. Parmi les anti-histaminiques de type H1 non anti-cholinergiques, la terféndine (1, 2) et l'oxatamide (4), peuvent être responsables d'hépatites. En revanche, aucune hépatite survenant après la prise de loratadine (Clarityne®) ou d'astémizole (Hismanal®) n'a été publiée. Notre observation constitue le premier cas d'hépatite attribuée à la cétirizine. Le mécanisme d'action de l'hépatotoxicité des anti-histaminiques de type H1 n'est pas connu. Malgré l'absence d'hyperéosinophilie et d'éruption cutanée, un mécanisme allergique peut être évoqué dans notre observation d'après le délai de survenue plus court lors de la réintroduction. Ceci est en accord avec un cas d'hépatite à la terféndine (2). La survenue de perturbations hépatiques inexpliquées chez un patient prenant des anti-histaminiques de type H1 devrait faire penser à une origine médicamenteuse.

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Curiethérapie à haut débit de dose dans le traitement du cancer œsophagien.

Le traitement par radiothérapie externe (RE), chimiothérapie concomitante avec, dans certains cas, irradiation laser associée semble efficace dans le traitement non chirurgical à visée curative du cancer œsophagien (KCO) (1). La curiethérapie à haut débit de dose (CHDD) permet, comme la curiethérapie à faible débit, d'augmenter la dose délivrée à la tumeur sans majorer les complications relatives aux tissus sains, mais, en raison d'un temps court d'irradiation, avec un confort très supérieur à celui du « faible débit » (2). Nous rapportons les résultats préliminaires obtenus chez 9 patients atteints d'un carcinome épidermoïde œsophagien.

De 1990 à 1992, les patients ont été traités à visée curative et, en raison d'une contre-indication opératoire d'ordre général, par RE, chimiothérapie et CHDD complémentaire. Il s'agissait de 8 hommes et 1 femme, d'âge moyen 62 ans (extrêmes : 52-74 ans) atteints d'un carcinome épidermoïde œsophagien du tiers supérieur dans 2 cas, du tiers moyen dans 5 cas, du tiers inférieur dans 2 cas, à double localisation dans 1 cas. La lésion initiale était classée T1 N0 M0 dans 2 cas, T1 Nx M0 dans 1 cas, T3 N0 M0 dans 1 cas, T3 Nx M0 dans 1 cas, T3 N1 M0 dans 4 cas (classification de l'UICC 1987, complétée par les données endoscopiques dans 6 cas). Le traitement a consisté, dans tous les cas, en une RE délivrant 64 Gy en 32 fractions (4 faisceaux plus cyclothérapie), 2 cures de chimiothérapie à la 1^{re} et 3^e semaines de la RE (5 fluorouracile : 1 g/m² de J1 à J4 et cisplatyl : 25 mg/m² de J2 à J5) et, 3 semaines après la fin de la RE, une séance de CHDD réalisée, sous simple analgésie, avec le projecteur de source Curietron 192 HDR jusqu'en juin 1991 et IR 192 Nuclétron par la suite, délivrant 7 Gy/surface au moyen d'un applicateur œsophagien de type Savary-Gilliard-Bonvoisin de 12,8 mm de diamètre (2). Les patients ont tous bénéficié d'un contrôle endoscopique avec biopsies 1 mois après la CHDD et, par la suite, d'un suivi trimestriel : clinique, endoscopique, tomodensitométrique avec, dans certains cas, une endosonographie.

La tolérance du traitement par CHDD a été parfaite, sans aucun effet secondaire chez les 9 patients. La réponse locale en fin de traitement a été complète dans 8 cas sur 9 avec histologie œsophagienne normale, et partielle dans 1 cas avec persistance en fin de traitement d'une ulcération creusante avec tissu néoplasique résiduel (lésion classée initialement T3 N0 M0). Un seul malade a eu une complication iatrogène sous forme de métastases vertébrales multiples en regard des champs de RE sur rachis ostéoporotique. Les 9 patients sont en vie, avec une alimentation orale normale, sans dilatation œsophagienne et sans rechute dans 8 cas, avec un recul de 7 à 33 mois, supérieur à 24 mois dans 5 cas.

Ce travail confirme la facilité d'utilisation du projecteur de source de CHDD et la bonne tolérance immédiate du traitement (2), sans dysphagie ni douleurs au décours de la séance de CHDD (3). Aucun patient n'a eu de complication à type d'ulcère, sténose ou fistule œsophagiennes imputables à la CHDD, contrairement à ce qui a déjà été

rapporté (4). Si, pour Hishikawa et al., l'adjonction de la CHDD à la RE permet d'augmenter la survie des patients (5), cette étude, en raison d'un recul insuffisant et d'un nombre encore limité de patients traités, ne permet pas de préjuger du résultat carcinologique, des effets secondaires à long terme et du bénéfice en matière de survie de l'utilisation de la CHDD.

Si l'exérèse chirurgicale est considérée comme le traitement de choix pour les tumeurs œsophagiennes classées T1 et T2, les résultats très prometteurs de cette étude confirment que les cancers œsophagiens évolués (T3) bénéficient des associations thérapeutiques non chirurgicales et soulignent la nécessité d'une prise en charge pluridisciplinaire du cancer œsophagien. Des travaux prospectifs multicentriques sont nécessaires pour l'évaluation précise du bénéfice de la curiethérapie à haut débit de dose, d'application simple et bien tolérée, notamment en matière de réponse carcinologique œsophagienne, d'effets secondaires à long terme et de survie.

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Section 2

I. ANNOTATED PACKAGE INSERT

The reviewer's comments in this section were presented as a draft to Dr. Himmel as Group Leader and at the September 21, 1995 "in-house" meeting. Some clarifications were made to the text as suggested by Dr. Himmel. The text used in the submitted proposed labeling has been typed in a CG Times Scalable font and the reviewer's comments in a Courier 10 Cpi font.

ZYRTEC
cetirizine hydrochloride
Tablets
For Oral Use

DESCRIPTION

Cetirizine hydrochloride, the active component of ZYRTEC tablets, is an orally active and selective H₁-receptor antagonist. The chemical name is (±)-[2-[4-(p-chloro-α-phenylbenzyl)-1-piperazinyl]ethoxy] acetic acid, dihydrochloride. Cetirizine is a racemic compound with an empirical formula of C₂₁H₂₅ClN₂O₄·2HCl. The molecular weight is 461.8 and the chemical structure is shown below:

Cetirizine hydrochloride is a white, crystalline powder and is water soluble. ZYRTEC is formulated as a white (dye-free), film-coated, rounded-off rectangular shaped tablet for oral administration and is available in 5 and 10 mg strengths. Inert ingredients are: lactose; magnesium stearate; povidone; titanium dioxide; hydroxypropyl methylcellulose; polyethylene glycol; and corn starch.

CLINICAL PHARMACOLOGY

Mechanism of Actions: Cetirizine, a human metabolite of hydroxyzine is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H₁ receptors (1,2). The antihistaminic activity of cetirizine has been clearly documented in a variety of animal and human models (3-24). In vivo and ex vivo animal models have shown negligible anticholinergic and antiserotonergic activity (5,8,10,13,14,17). In clinical studies, however, dry mouth was more common with cetirizine than with placebo (89). In vitro receptor binding studies have shown no measurable affinity for other than H₁ receptors (16). Autoradiographic studies with radiolabeled cetirizine in the rat have shown negligible penetration of the brain (25). Ex vivo experiments in the mouse have shown that systemically administered cetirizine does not significantly occupy cerebral H₁ receptors (16).

Pharmacokinetics: Cetirizine is rapidly absorbed after oral administration of a tablet, which had bioavailability similar to an oral solution (26). Food had no effect on the extent of cetirizine absorption, but T_{max} was delayed by 1.7 hours and C_{max} was decreased by 23% in the presence of food (27). A mass balance study in 6 healthy male volunteers indicated that 70% of the administered radioactive dose was recovered in the urine and 10% in the feces, for a combined total recovery of

about 80% (28). Approximately 50% of the administered radioactive dose was excreted in urine as unchanged drug (28). Most of the rapid increase in peak plasma radioactivity is associated with parent drug indicating low first pass metabolism (28). Cetirizine is metabolized to a very limited extent by oxidative o-dealkylation to a metabolite (28,29) with negligible antihistaminic activity (30).

Cetirizine exhibits linear kinetics over the dosage range of 5 to 60 mg (31,32). In pharmacokinetic studies in 146 healthy volunteers, the mean $\pm$ SD terminal half-life was 8.3 ± 1.8 hours, oral clearance was 54 ± 13 mL/min, and the apparent volume of distribution was 0.50 ± 0.08 L/kg (33). No accumulation was observed for cetirizine following daily doses of 10 mg, for 10 days (34). The steady-state maximum plasma concentration was 311 ± 40 ng/mL and was achieved within 1.0 ± 0.5 hour (34). Individual histograms of cetirizine C_{max} and AUC showed unimodal distributions with a two- to four fold variability in healthy subjects (100). Plasma protein binding of cetirizine is 93 ± 0.3 % and was independent of concentration in the range of 0.025 to 1.0 mcg/mL (29); this concentration range covers the therapeutic plasma levels.

Reviewer's comments:

In this section, a limited description of the human PK of cetirizine's enantiomers based on foreign study results may be appropriate. It would be up to Biopharm's recommendations.

SPECIAL POPULATIONS

Effect of Age: Following a single 10 mg oral dose, half-life increased by about 50% and clearance decreased by 40% in 16 elderly subjects as compared to the 14 normal subjects (35). The decrease in cetirizine clearance in these elderly volunteers was directly correlated to their decreased renal function.

Effect of Gender: No gender-related differences were observed in the kinetics of cetirizine between 86 white adult males and 3 white adult females (36).

Effect of Race: No race-related differences were observed in the kinetics of cetirizine between 86 white adult males and 11 black adult males (36).

Renally Impaired Patients: The kinetics of cetirizine were studied following multiple oral daily doses of 10 mg for 7 days in 7 normal volunteers (creatinine clearance 89-128 mL/min), 8 patients with mild renal function impairment (creatinine clearance 42-77 mL/min) and 7 patients with moderate renal function impairment (creatinine clearance 11-31 mL/min) (37). The pharmacokinetics of the drug were similar in patients with mild impairment and normal volunteers. Moderately renally impaired patients had a 3-fold increase in half-life and 70% decrease in clearance compared to normal volunteers (37). Accumulation of cetirizine was also more pronounced in patients with moderate impairment (37).

Following a single oral 10 mg dose of cetirizine, 5 patients on hemodialysis (creatinine clearance less than 7 mL/min) had a 3 fold increase in half-life accompanied by a 70% decrease in clearance. Cetirizine was not completely cleared by hemodialysis as less than 10% of the administered dose was removed during the dialysis session (37).

Dosing adjustment is necessary in patients with moderate or severe renal impairment and patients on dialysis. (See also DOSAGE AND ADMINISTRATION).

Hepatically Impaired Patients: Following single oral doses of 10 mg and 20 mg cetirizine administered to 6 and 10 patients, respectively, with chronic liver diseases (hepatocellular, cholestatic, and biliary cirrhosis), resulted in a 50% increase in half-life along with a 40% decrease in clearance compared to 16 healthy subjects (37,38,39).

Dosing adjustment may be necessary in hepatically impaired patients. (See also DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Theophylline: A multiple dose study in 24 healthy male volunteers showed that the pharmacokinetics of cetirizine (20 mg QD for 3 days) and theophylline (400 mg QD for 3 days) were not altered when they were given in combination (40).

Pseudoephedrine: A multiple dose study showed no significant differences in any pharmacokinetic parameters for either cetirizine (20 mg QD) or pseudoephedrine (120 mg Q12h) when they were concomitantly administered to 24 healthy male subjects for 6 days (41).

Antipyrine: Cetirizine 10 mg QD was administered for 9 days to 10 healthy male volunteers. Following coadministration on the ninth day with 250 mg antipyrine, no changes were observed in plasma clearance or elimination half-life of antipyrine. Therefore, cetirizine does not alter the oxidative metabolizing enzyme activity in the liver (42).

Ketoconazole: In a multiple-dose study involving 16 healthy male volunteers, the pharmacokinetics of cetirizine (20 mg QD) and ketoconazole (400 mg QD) were not altered when they were given in combination (43).

Erythromycin: In a multiple-dose study involving 16 healthy male volunteers, the pharmacokinetics of cetirizine (20 mg QD) and erythromycin (500 mg Q8h) were not altered when they were given in combination (44).

Cimetidine: In a double-blind, randomized, single-dose, crossover study, cetirizine 20 mg was administered to 6 healthy volunteers concomitantly with placebo or 400 mg cimetidine. Neither cetirizine plasma concentrations nor wheal and flare measurements at 2 and 4 hours post dose were significantly different after cimetidine and placebo treatment (45).

Pharmacodynamics: Studies in normal volunteers show that ZYRTEC at doses of 5 and 10 mg strongly inhibits the skin wheal and flare caused by the intradermal injection of histamine (17-20,22,23,46-48). The onset of activity after a single 10 mg dose occurs within 20 minutes in 50% of subjects and in 95% of subjects within one hour (49,50), and this activity persists for at least 24 hours (17,22,46,49). In a 35 day study in children ages 5 to 12, no tolerance to the antihistaminic effects of ZYRTEC was found (51).

Reviewer's comments:

The labeling should somehow clarify that the antihistaminic effect that this article supports is the ability of the drug to continue to suppress the formation of wheal and flare reaction after a histamine cutaneous injection after 35 days of cetirizine treatment in the same way than after a single dose. The study design and endpoints measured are not adequate to support no tolerance to the antihistaminic effects as a clinical endpoint.

The following change is proposed:

In a 35 day study in children ages 5 to 12, no tolerance to Zyrtec's ability to suppress histamine induced wheal and flare reaction was found (51).

The referenced underlined article was submitted in Appendix G, pages 9 648-655, volume 35.4. Watson, et al: Cetirizine: A pharmacokinetic and pharmacodynamic evaluation in children with seasonal allergic rhinitis. Journal of Allergy and Clinical Immunology 84:457-464, 1989.

In this study, a population of 19 children (5-12), received cetirizine 5 mg (10 patients) or 10 mg (9 patients) over a period of 35 days, after a 7 day wash out period with placebo. Pseudoephedrine was used as a rescue medication.

Pharmacodynamic endpoints: cutaneous wheal and flare inhibition of histamine skin tests after a single dose and at the end of treatment and change in weekly investigator assessed symptom scores from baseline.

Due to the fact that the study was designed primarily as a PK PD study, a small number of children were enrolled. It did not have a concurrent placebo arm. The 5 and 10 mg cetirizine capsules were administered in a randomized, double blind manner. The investigators knew that during the wash-out period patients were receiving placebo and that during the study period they were receiving active medication.

The initial improvement in investigator assessed total symptom scores following a single dose compared to baseline, was not lost over a the following weekly evaluations. The authors state that "the 10 mg dose appeared to have more rapid onset of action in controlling rhinitis symptoms than did the 5 mg dose, but both doses provided excellent relief of symptoms through out the 35 days of dosing."

At the end of the article the authors state that "the

efficacy of cetirizine in the treatment of allergic rhinitis needs to be confirmed in a larger, placebo-controlled, noninvasive study in children."

The effects of intradermal injection of various other mediators or histamine releasers are also inhibited by cetirizine (17,23,47,48,52), as is cold-induced urticaria (53).

Reviewer's comments:

The title for the article that is referenced in the above underlined statement is: "Skin reactivity to cold in patients suffering from cold urticaria before and after a single oral administration of cetirizine 2HCL." This study was submitted as part of the NDA vol 52, 8 276. It was not part of the material reviewed by this reviewer. The proposed labeling statement emphasizes cetirizine's inhibition of the clinical condition of cold induced urticaria. Even though a single dose of cetirizine is reported as inhibiting cold induced reactivity or in other words wheal and flare formation, in patients with cold urticaria, this single dose study by itself should not be considered enough evidence to support this clinical claim.

The following change is proposed:

The effects of intradermal injection of various other mediators or histamine releasers are also inhibited by cetirizine (17,23,47,48,52), as is skin reactivity to cold in patients with cold-induced urticaria (53).

Reviewer's comments:

It would seem appropriate from the clinical research standpoint that a description of the observed differences in antihistaminic effects by cetirizine's enantiomers in humans should be part of this section.

The following sentence is recommended:

The ability of cetirizine's enantiomers to inhibit wheal and flare reactions in humans differs; no activity has been demonstrated for the L (-) enantiomer.

Refer to the results of UCB study 101, vol 35.17 pages 11 1314-1736.

In mildly asthmatic subjects, ZYRTEC at 5 to 20 mg blocked bronchoconstriction due to nebulized histamine, with virtually total blockade after a 20 mg dose (24). In addition, the late phase recruitment of eosinophils, neutrophils and basophils, components of the allergic inflammatory

response, are inhibited by ZYRTEC following cutaneous antigen challenge (54-58).

Four randomized double-blind, placebo-controlled trials were conducted in healthy subjects to assess the psychomotor/psychophysical effects (as measured by the multiple sleep latency test, simulated assembly line task, Stroop word test, and the critical flicker frequency test) of ZYRTEC versus hydroxyzine or diphenhydramine. These studies showed that ZYRTEC was generally not significantly different from placebo but was different from hydroxyzine and diphenhydramine which produced significantly decreased test performance (59-62, 103).

Reviewer's comments:

The above underlined paragraph should be deleted.

The overview and analysis submitted in the safety update of 4/25/95 does not adequately support the above underlined paragraph. The fact that the conclusions for the above paragraph are derived from the single dose phase of 3 studies included in the pooled analysis presented in reference 103 is not stated. In addition, it is not stated that the conclusions based on the pooled cognitive test performance results may not predict what would be expected after multiple dosing in clinical practice.

Although the labeling refers to the results from 4 studies in the above paragraph only the data from 3 of them is pooled in the analysis that is presented in the 4/25/95 submission as reference 103 to support these statements. An additional study is referenced but not used in the analysis. In the other two studies that are referenced in the 4/25/95 submission as reference 103 that also measure performance, no statistically significant differences between cetirizine and diphenhydramine or hydroxyzine are reported. A summary of the overview and analysis that supports the above underlined paragraph as included in reference 103 in the 4/25/95 safety update follows.

Reference 103, the overview and analysis of cetirizine performance studies was submitted in the safety update of 4/25/95 in vol 35.4, Appendix G, pages 9 759-769. In it, the data from 3 studies was pooled and analyzed (Gengo-cognitive function, Walsh-SALT I and SALT II). These were cross over, placebo controlled trials. The single dose phase of these studies was chosen for the analysis. A correlation was made between the perception of drowsiness while on drug (using VAS -visual analog for sedation) compared to placebo and the scores of the cognitive tests while on drug compared to placebo. The pooled analysis presented in this safety update does not report a statistical value for this comparison. A series of tables (scatter plots) are included and portray the individual

patient values. Although in the majority of cetirizine treated patients the perceived alertness and performance results compare favorably to the results obtained during placebo treatment, there are individual patients that report to feel less alert and have cognitive scores that are lower on cetirizine than when they were on placebo, particularly in the 3.5 -4 hr time, post study drug.

In reference to the results of the individual study reports listed in reference 103, Table 1, in only 2 out of 3 studies there was a significant difference between cetirizine and hydroxyzine (Walsh (SALT I) study, for the simulated assembly line task and between cetirizine and diphenhydramine (Walsh (SALT II) study, for the simulated assembly line task. The study on cognitive function by Gengo does not report a significant difference between cetirizine and hydroxyzine, using the flash-fusion frequency and the stroop word score.

There are two other studies that are also included in Table 1 but are not included in the analysis presented in this section. These are the Dement (Sleep Latency) and the Gengo (Driving Performance). In the first one no statistically significant differences were reported between treatments (hydroxyzine, placebo and cetirizine) for the Stanford Sleepiness test and the visual analog for sedation (VAS). There were no statistical differences reported between hydroxyzine and cetirizine for the vigilance performance test. In the Gengo (Driving Performance), there were significantly less number of correct answers given by patients on 20 mg of cetirizine than those on placebo for DSS (digit symbol substitution), No significant differences are reported between treatments (which include diphenhydramine) for the trails B tracking (TBT); no significant differences are reported between diphenhydramine and cetirizine for the simulated accident avoidance (SAA) or the driving reaction time (DRT).

In four clinical studies in healthy volunteers, no clinically significant mean increases in QTc were observed in ZYRTEC treated subjects (32, 43, 44, 63).

Reviewer's comments:

Proposed change:

In three clinical studies in healthy male adult volunteers, no clinically significant mean increases in QTc were observed in ZYRTEC treated subjects (32, 44, 63).

The proposed changes imply that the reviewer recommends that the results of the cetirizine-ketoconazole interaction

Report # 92CK 16-0603 be discussed separately. The discussion to support this proposed change will follow.

Reference is made to the MOR dated February 27, 1994 for the review of the studies: Report # 90CK16-0497 (ref. 39) and #92CK16-0604 (ref.44).

A separate summary MOR review of the study Report #93CK16-0624 reference 63, is included in **Appendix 1**. The study report was submitted in the 4/25/95 safety update submission in Section K.1.

In view of the limited characterization of PK in women in this NDA and that women have a higher incidence of reported torsades de pointes, it would be relevant to note that the following studies were conducted in male volunteers.

Since additional retrospective analysis was requested and -- conducted on the Pediatric studies conducted so far, these should also be part of a separate discussion in the labeling. This paragraph should clarify that the following data refers to studies conducted in adults.

In the first study, a placebo-controlled crossover trial, ZYRTEC was given at doses up to 60 mg per day, 6 times the maximum clinical dose for 1 week, and no significant QTc prolongation occurred (32). In the second study (43), a crossover trial, ZYRTEC and erythromycin were given alone and in combination. The effect of ZYRTEC 20 mg alone on QTc (Hodges corrections) was statistically estimated as a small decrease from baseline of 5.1 msec (-1.3%) after 5 days of therapy.

Reviewer's comments:

It is recommended that the QTc changes included in the labeling be expressed using the Bazzet correction which is more familiar to most physicians. If the Hodges correction is going to be used, the inclusion of a description of the Hodges correction and a reference (published article, not an abstract) that supports the superiority of Hodges method over the Bazzet in the heart rate range studied would be acceptable.

The adjective small should be deleted and the change reported as found.

There was no significant drug interaction effect on QTc with the combination of ZYRTEC 20 mg and erythromycin (43).

Reviewer's comments:

It is this reviewer's understanding that reference #43 refers as is listed in the annotations to the cetirizine-ketoconazole interaction study, or study report # 92CK-0603. Therefore, the annotated reference should be #44 instead of

#43.

In the third trial (44), also a crossover study, ZYRTEC and ketoconazole were given alone and/or in combination. The effect of ZYRTEC 20 mg alone on QTc was statistically estimated as a small increase from baseline of 8.2 msec (1.8%) after 10 days of therapy. The estimated effect of the combination on QTc change from baseline (16.1 msec) was equal to the sum of the individual component effects. Thus, there was no significant drug interaction effect on QTc with the combination of ZYRTEC and ketoconazole. In the fourth study (63), a placebo-controlled parallel trial, ZYRTEC was given alone or in combination with azithromycin. Results of this trial showed no significant increase in QTc associated with ZYRTEC 20 mg alone or in combination with azithromycin.

Reviewer's comments:

The underlined sentences should form part of a separate paragraph.

In the fourth study (63), a placebo-controlled parallel trial, ZYRTEC was given alone or in combination with azithromycin. Results of this trial showed no significant increase in QTc associated with ZYRTEC 20 mg alone or in combination with azithromycin.

Reviewer's comments:

The proposed label should describe the third study.

A separate summary MOR review of the study Report #93CK16-0624 reference 63, is included in **Appendix 1**. The study report was submitted in the 4/25/95 safety update submission in Section K.1.

In the third trial (44), also a crossover study, ZYRTEC and ketoconazole were given alone and/or in combination.

Reviewer's comments:

As noted above, this reviewer proposes to describe separately the results of this trial. Reference is made to the MOR dated 2/27/94 for this study Report # 92CK16-0603. As noted earlier the appropriate annotated reference for this study should be #43 instead of #44.

The following change is proposed for this sentence:

In a clinical study in healthy male volunteers (43), also a

crossover study, ZYRTEC and ketoconazole were given alone and/or in combination.

The effect of ZYRTEC 20 mg alone on QTc was statistically estimated as a small increase from baseline of 8.2 msec (1.8%) after 10 days of therapy. The estimated effect of the combination on QTc change from baseline (16.1 msec) was equal to the sum of the individual component effects.

Reviewer's comments:

The following changes are recommended:

The effect of ZYRTEC 20 mg alone on the mean increase in QTc from baseline was statistically estimated to be 8.2 msec (1.8%) after 10 days of therapy. The estimated effect of the combination on mean QTc change from baseline (16.1 msec) was equal to the sum of the individual component effects.

The adjective small should be deleted and the change reported as found. The reported change refers to the mean increase in QTc from baseline. This was mentioned at the beginning of the original paragraph, but since a separate paragraph is proposed, the reference to the mean increase in QTc from baseline should be added for clarity.

As noted earlier, it is recommended that the QTc changes included in the labeling be expressed using the Bazget correction which is more familiar to most physicians. If the Hodges correction is going to be used, the inclusion of a description of the Hodges correction and a reference (published article, not an abstract) that supports the superiority of Hodges method over the Bazget in the heart rate range studied would be acceptable.

Thus, there was no significant drug interaction effect on QTc with the combination of ZYRTEC and ketoconazole.

Reviewer's comments:

It is proposed that the above sentence should read:

There was no significant pharmacokinetic drug interaction effect on QTc with the combination of ZYRTEC and ketoconazole.

It is not clear to the reviewer if the drug interaction effect refers to the PK parameters on QTc. It was clear from the referenced MOR review of 2/27/94, that for change in QTc AUC and QTcmax, the estimated overall cetirizine, ketaconazole and combination effects were significantly

different to placebo. From the PK stand point the only positive significant correlation in this study was between cetirizine and QTcmax versus drug clearance. Since no significant effects were obtained with the drug combination on changes in QTc, it was considered that it would imply a lack of interaction of cetirizine metabolites with ketoconazole.

Reviewer's comments:

The addition of the following paragraph is recommended: .

In the retrospective analysis of ECGs obtained from 202 children ages 6-11, that were treated with Zyrtec for four weeks in a placebo controlled clinical study, the mean change in QTc adjusted for baseline differences was 9.94 msec (Bazett) for Zyrtec 10 mg, - 2.52 msec for Zyrtec 5 mg and 1.77 msec for placebo when the ECGs recorded within 11-17 days of first dose were compared to baseline. The statistical analyses did not demonstrate significant differences between treatment groups, or treatment related effects in QTc by dose corrected by weight, gender or race. Reference is made to original MOR of NDA 20346 and to the summary review of the requests related to the ECG analysis that were submitted to NDA 19835 in the safety update dated 4/25/95. These are summarized and discussed in Appendix 2.

Clinical Studies: Eleven multicenter, randomized, double-blind, placebo-controlled clinical trials were conducted in the United States. Five studies in seasonal allergic rhinitis were conducted for up to 4 weeks in duration (64); four studies in perennial allergic rhinitis for up to 8 weeks in duration (65,66); and two studies in chronic idiopathic urticaria each for 4 weeks in duration (67). Doses of 5-20 mg per day were studied. In general, most patients were controlled on a 10 mg dose. Five (5) mg was the minimally effective dose and 20 mg did not give added effectiveness compared with 10 mg.

Reviewer's comments:

The following recommended highlighted paragraph takes into consideration the Sponsor's suggestions in terms of dosing but describes the studies that support efficacy. This is important because it gives a fair sense to the prescribing physician of this issue.

Eleven multicenter, randomized, double-blind, placebo-controlled clinical trials were conducted in the United States; 7 of these support effectiveness, 3 in seasonal allergic rhinitis (1 to 4 weeks in duration), 2 in perennial allergic rhinitis for up to 8 weeks in duration, and 2 in chronic idiopathic urticaria of 4 weeks in duration. Doses of 5-20 mg per day were studied. In general, most patients were controlled on a 10 mg dose.

Five (5) mg was the minimally effective dose and 20 mg did not give added effectiveness compared with 10 mg.

A less desirable alternative that may be more agreeable to the Sponsor and that conveys the information would be to only describe the 7 trials that supported efficacy. The paragraph would then read: Seven multicenter, randomized, double-blind, placebo-controlled clinical trials conducted in the United States support effectiveness, 3 in seasonal allergic rhinitis (1 to 4 weeks in duration), 2 in perennial allergic rhinitis for up to 8 weeks in duration, and 2 in chronic idiopathic urticaria of 4 weeks in duration. Doses of 5-20 mg per day were studied. In general, most patients were controlled on a 10 mg dose. Five (5) mg was the minimally effective dose and 20 mg did not give added effectiveness compared with 10 mg.

INDICATIONS AND USAGE

Seasonal Allergic Rhinitis: ZYRTEC is indicated for the relief of symptoms associated with seasonal allergic rhinitis due to allergens such as ragweed, grass and tree pollens. Symptoms treated effectively include sneezing, rhinorrhea, nasal pruritus, ocular pruritus, tearing and redness of the eyes (68).

Perennial Allergic Rhinitis: ZYRTEC is indicated for the relief of symptoms associated with perennial allergic rhinitis due to allergens such as dust mites, animal dander and molds. Symptoms treated effectively include sneezing, rhinorrhea, post-nasal discharge, nasal pruritus, ocular pruritus and tearing (69).

Chronic Urticaria: ZYRTEC is indicated for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria. It significantly reduces the occurrence, severity and duration of hives and significantly reduces pruritus (70).

CONTRAINDICATIONS

ZYRTEC is contraindicated in those patients with a known hypersensitivity to it or any of its ingredients, or to its parent compound, hydroxyzine.

PRECAUTIONS

Activities Requiring Mental Alertness: In clinical trials, the occurrence of somnolence has been reported in some patients taking ZYRTEC; due caution should therefore be exercised when driving a car or operating potentially dangerous machinery. Concurrent use of ZYRTEC with alcohol or other CNS depressants should be avoided because additional reductions in alertness and additional impairment of CNS performance may occur.

Drug-drug interactions: No clinically significant drug interactions have been found with theophylline, pseudoephedrine,

ketoconazole, erythromycin and cimetidine (40,41,43-45). In clinical trials, there did not appear to be an increased incidence of adverse experiences in patients administered ZYRTEC and beta-agonists, non-steroidal anti-inflammatory drugs, oral contraceptives, corticosteroids, H₂-antagonists, cephalosporins, penicillins, thyroid hormones and thiazide diuretics (71).

Reviewer's comments:

Comments to the following statement if any should be made by Biopharm:

No clinically significant drug interactions have been found with theophylline, pseudoephedrine, ketoconazole, erythromycin and cimetidine (40,41,43-45)

However, it should be noted that in clinical trials, for theophylline users both placebo and cetirizine treated patients the incidence of study discontinuation (6.45% and 5.0% respectively due to adverse experiences was higher than for non users (2.73% and 2.39%). However, the total number patients exposed was small, there were 124 cetirizine and 80 placebo patients. The reasons for study discontinuation for these patients is not readily available in the submission. In the individual listing in the submission for discontinued patients, concomitant drugs were not included.

The following changes are recommended for the following statement:

In clinical trials, there did not appear to be an increased incidence of adverse experiences in patients administered ZYRTEC and beta-agonists, oral contraceptives, corticosteroids, and thiazide diuretics (71).

Supportive data regarding the following statement: In clinical trials, there did not appear to be an increased incidence of adverse experiences in patients administered ZYRTEC and beta-agonists, non-steroidal anti-inflammatory drugs, oral contraceptives, corticosteroids, H₂-antagonists, cephalosporins, penicillins, thyroid hormones and thiazide diuretics (71) is included in the safety update 4/25/95, Vol 35.4, pages 9 656-735. The tables of incidence and median exposure of medication categories are included in **Appendix 3**.

In the supportive data set, the incidence of exposure to thyroid, H₂ inhibitors, cephalosporin and penicillin is less than 2% for cetirizine treated patients (2,676) in placebo controlled studies, or less than 100 patients for each drug. In this reviewer opinion this is a very small data set from

which to derive meaningful conclusions unless a proper statistical analysis is made and found to be otherwise. Even though the total incidence of adverse events may be similar for patients concurrently receiving these drugs, the incidence of specific adverse events may be more or less than expected and it is difficult to ascertain the true clinical meaning. As an example: in thyroid treated patients the incidence of cetirizine treated patients reporting fatigue was 9.09% (4/44) and 3.92% (2/51) for placebo treated patients. Dry mouth was also reported twice as frequently on cetirizine treated patients.

For NSAID users (cetirizine and placebo) the reported incidence of adverse events is higher than for non users. Refer to table in **Appendix 3**. NSAID users that received cetirizine report a higher incidence of somnolence, fatigue and dry mouth than placebo treated patients also using NSAID and cetirizine-non NSAID user, treated patients. The reported rates for these adverse events in placebo treated patients, NSAID users and non users, were very similar. With an incidence of exposure of 14% for NSAID use in cetirizine treated patients and 16.9% in placebo treated patients, the increased incidence of somnolence, mouth dry and fatigue in cetirizine treated patients that were also treated with NSAID should be part of the labeling.

Carcinogenesis, mutagenesis and impairment of fertility: No evidence of carcinogenicity was observed in a 2-year carcinogenicity study in rats (72) at dietary doses up to 20 mg/kg/day (15 times the recommended human dose on a mg/m²/day basis). An increased incidence of benign liver tumors was found in a 2-year carcinogenicity study in male mice (73) at a dietary dose of 16 mg/kg/day (6 times the recommended human dose on a mg/m²/day basis). The clinical significance of these findings during long-term use of ZYRTEC is not known. Cetirizine was not mutagenic in Ames test, and not clastogenic in human lymphocyte assay, mouse lymphoma assay, and in vivo micronucleus test in rats (74-77). No impairment of fertility was found in a fertility and general reproductive performance study in mice (78,79) at a dose of 64 mg/kg/day (26 times the recommended human dose on a mg/m²/day basis).

Pregnancy Category B: Cetirizine has not been shown to be teratogenic in mice, rats and rabbits at doses up to 96, 225, and 135 mg/kg/day (or 40, 180, and 216 times the recommended human dose on a mg/m²/day basis), respectively (80-82). There are no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, ZYRTEC should be used in pregnancy only if clearly needed.

Nursing Mothers: Retarded pup weight gain was found in mice during lactation (79) when dams were given cetirizine at 96 mg/kg/day (40 times the recommended human dose on a mg/m²/day basis). Studies in beagle dogs indicate that approximately 3% of the dose is excreted in milk (83). Cetirizine has been reported to be excreted in human breast milk (102). Because many drugs are excreted in human milk, use of ZYRTEC in nursing mothers is not recommended.

Geriatric Use: The safety and efficacy of ZYRTEC has been demonstrated in patients 65 years and older (84). As with the general population, clearance of ZYRTEC is reduced in proportion to creatinine clearance (35).

Pediatric Use: In more than 588 children aged 6 to 11 years, ZYRTEC was administered in doses from 1.25 to 10 mg. In these studies ZYRTEC was well-tolerated at doses up to 10 mg (85,86). The safety of ZYRTEC in children under the age of 6 years has not yet been established. ZYRTEC is not indicated for the treatment of children under the age of 12 years.

Reviewer's comments:

Although the statement that more than 588 have received Zyrtec is probably correct, the data received in the safety update of 4/25/95, 588 patients form this dataset. These patients received 1.5 to 10 mg of cetirizine for up to 5 weeks. Reference is made to safety update section D.3, vol 35.2, page 9 32-33. Unless the chosen one it is the customary way for labeling the number of patients that were studied, the following changes to the above underlined statement are recommended:

In clinical trials where 588 children aged 6-11 years participated, ZYRTEC was administered in doses from 1.25 to 10 mg up to 5 weeks. These patients had a mean body weight of 75 lbs (range 34-232).

Reviewer's comments:

Following the Division's recommendations based on the Pediatric Rule the following statement should be deleted:

ZYRTEC is not indicated for the treatment of children under the age of 12 years.

ADVERSE REACTIONS

Controlled and uncontrolled clinical trials included more than 6000 patients, with more than 3900 receiving ZYRTEC at doses of 5 to 20 mg per day; the duration of treatment ranged from 1 week to 6 months (87). In addition, there were more than 1400 ZYRTEC treated patients in foreign clinical trials.

Reviewer's comments:

The following change is recommended:

Controlled and uncontrolled clinical trials included more than 6000 patients, with more than 3900 receiving ZYRTEC at doses of 5 to 20 mg per day; **in adults** the duration of treatment ranged from 1 week to 6 months, **with a mean duration of exposure of 30 days.**

Reviewer's comments:

There were 3982 adult patients in the cumulative database that were exposed to cetirizine for up to 6 months. The mean duration of exposure to cetirizine in the cumulative database was 30.1 days. The total number of adult patients exposed to cetirizine for more than 12 week and up to 6 months was 237. Refer to Table F1.C, vol 35.3, included in Appendix 4.

Reviewer's comments:

This reviewer could not find the reference to the number of patients listed as having received cetirizine as part of foreign clinical trials. The reference for the total number of adult patients treated with cetirizine is not part of the 4/25/95 safety update. In the 6/7/95 N (BM), the number of patients that received cetirizine in the 17 trials that were submitted in the 4/25/95 safety update was recorded as 385. The following statement should have an annotated reference or it should be deleted:

there were more than 1400 ZYRTEC treated patients in foreign clinical trials.

Most adverse reactions reported during therapy with ZYRTEC were mild or moderate (88). In placebo-controlled trials, the incidence of discontinuations due to adverse reactions in patients receiving ZYRTEC 5 mg or 10 mg was not significantly different from placebo (2.9% vs 2.4%, respectively) (89).

Reviewer's comments:

The following change is recommended:

In placebo-controlled trials, the incidence of discontinuations due to adverse reactions in patients

receiving ZYRTEC 5 mg or 10 mg was not significantly different from placebo (2.6% (11/430) and 3.0% (44/1489) for 5 and 10 mg of cetirizine respectively versus 2.4% (37/1521) for placebo treated patients).

In reference 89, the recorded number of discontinued patients in placebo-controlled, fixed-dose studies that received cetirizine 5 or 10 mg is listed as 2.9% (59/2034). In the following section (D.5.c, vol 35.2 page 9 37) the recorded number of discontinued patients in placebo-controlled, fixed-dose studies is listed as 2.6% (11/430) for 5 mg of cetirizine, 3.0% (44/1489) for 10 mg cetirizine and 2.4% (37/1521) for placebo treated patients.

The most common adverse reactions at the recommended doses were headache and somnolence (89). The incidence of headache associated with ZYRTEC was not different from placebo (89). The incidence of somnolence associated with ZYRTEC was dose related (90) and, predominantly, mild to moderate (88). The incidence of somnolence in fixed dose studies was 6% in placebo, 11% at 5 mg and 14% at 10 mg (90).

Reviewer's comments:

The following changes are recommended:

The incidence of somnolence in fixed dose studies was 6% in placebo, 11% at 5 mg and 14% at 10 mg. **These were significantly different from placebo (90).**

The reference for this change is also the annotated reference #90 (SU 4/25/95, vol 35.2 page 9 38).

Discontinuations due to somnolence for ZYRTEC (91) were not significantly different from placebo (1.0% vs 0.6%, respectively). In addition, fatigue and dry mouth were also considered treatment-related adverse reactions. There was no difference by age, race, gender or by body weight with regard to the incidence of adverse reactions (92-94).

Table 1 lists adverse experiences which were reported for ZYRTEC 5 and 10 mg in controlled clinical trials in the United States (89).

Table 1. Adverse Reactions Reported in Placebo-Controlled United States ZYRTEC Trials (Maximum Dose of 10mg) at Rates of 1% or Greater

(Percent Incidence)

Adverse Experience	ZYRTEC (N= 2034)	Placebo (N= 1612)
Headache	17.6%	17.9%
Somnolence	13.7	6.3
Fatigue	5.9	2.6
Dry Mouth	5.0	2.3
Nausea	2.5	2.9
Pharyngitis	2.0	1.9
Dizziness	2.0	1.2
Insomnia	1.4	1.2
Epistaxis	1.2	0.6
Coughing	1.0	0.6
Abdominal Pain	1.0	0.9
*Dyspepsia	0.8	1.6
Pruritus	0.3	1.2

Reviewer's comments:

The following change to the above table is recommended:

Delete the rows for dyspepsia and pruritus.

Note: dyspepsia is misspelled in the table. The incidence rates of dyspepsia and pruritus do not need to be included in the above table, since the intent was to include only those adverse events that had an incidence of 1% or greater in the cetirizine treated group.

The following events were observed infrequently (equal to or less than 1%), in 3982 patients who received ZYRTEC in U.S. trials, including an open study of six months duration (88); a causal relationship with ZYRTEC administration has not been established.

Application Site: application site reaction, injection site inflammation

Autonomic Nervous System: anorexia, urinary retention, flushing, saliva increased

Cardiovascular: palpitation, tachycardia, hypertension, arrhythmia, cardiac failure

Central and Peripheral Nervous Systems: paresthesia, confusion, hyperkinesia, hypertonia, migraine, tremor, vertigo, cramps legs, ataxia, dysphonia, coordination abnormal, hyperesthesia, hypoesthesia, myelitis, paralysis, ptosis, speech disorder, twitching, visual field defect

Endocrine: thyroid disorder

Gastrointestinal: appetite increased, dyspepsia, abdominal pain, diarrhea, flatulence, constipation, vomiting, stomatitis ulcerative, tongue disorder, tooth caries aggravated, stomatitis, tongue discoloration, tongue edema, gastritis, hemorrhage rectum, hemorrhoids, melena, hepatic function abnormal

Genitourinary: polyuria, urinary tract infection, cystitis, dysuria, hematuria, urine abnormal

Hearing and vestibular: earache, tinnitus, deafness, ototoxicity

Metabolic/Nutritional: thirst, edema, dehydration, diabetes mellitus

Note: thirst is misspelled in this listing.

Musculoskeletal: myalgia, arthralgia, bone disorder, arthrosis, tendon disorder, arthritis, muscle weakness

Psychiatric: insomnia, nervousness, depression, emotional lability, concentration impaired, anxiety,

depersonalization, paroniria, thinking abnormal, agitation, amnesia, libido decreased, euphoria

Resistance Mechanism: healing impaired, herpes simplex, infection, infection fungal, infection viral

Respiratory System: epistaxis, rhinitis, coughing, respiratory disorder, bronchospasm, dyspnea, upper respiratory tract infection, hyperventilation, sinusitis, sputum increased, bronchitis, pneumonia

Reproductive: dysmenorrhea, menstrual disorder, breast pain female, intermenstrual bleeding, leukorrhea, menorrhagia, pregnancy unintended, vaginitis, testes disorder

Reticuloendothelial: lymphadenopathy

Skin: pruritus, rash, skin disorder, skin dry, urticaria, acne, dermatitis, rash erythematous, sweating increased, alopecia, angioedema, furunculosis, bullous eruption, eczema, hyperkeratosis, hypertrichosis, photosensitivity reaction, photosensitivity toxic reaction, rash maculo-papular, seborrhea, purpura

Special Senses: taste perversion, taste loss, parosmia

Vision: eye abnormality, vision abnormal, eye pain, conjunctivitis, xerophthalmia, glaucoma, ocular hemorrhage

Body as a Whole: weight increase, back pain, malaise, pain, chest pain, fever, asthenia, edema generalized, edema periorbital, edema peripheral, rigors, edema legs, face edema, hot flushes, abdomen enlarged, allergic reaction, nasal polyp

Occasional instances of transient, reversible hepatic transaminase elevations have occurred during cetirizine therapy (95).

Reviewer's comment:

The following changes to the above underlined statement are recommended:

Occasional instances of transient, reversible hepatic transaminase elevations have occurred during cetirizine therapy. The incidence of abnormal hepatic transaminases in all cetirizine treated patients that were considered to be clinically significant and possibly related to study medication was: SGOT 27/ 2979 (1%) and SGPT 52/2926 (2%); for placebo treated patients it was: SGOT 6/1525 (0%) and for SGPT 12/1480 (1%). Regardless of attributable cause, the incidence of abnormal SGOT, more than twice the upper limit of normal, appears to be similar in cetirizine and placebo treated patients (0.4%); for SGPT the incidence is (0.3%) for cetirizine versus (0.1%) in placebo treated patients.

The incidence of abnormal hepatic transaminases in all cetirizine treated patients that were considered to be clinically significant and possibly related to study medication was: SGOT 27/ 2979 (1%) and SGPT 52/2926 (2%) -SU 4/25/92, vol 35.2, page 9 58. For placebo treated these incidences were: SGOT 6/1525 (0%) and for SGPT 12/1480 (1%), Table F 23.B in SU 4/25/95, vol 35.3, page 9 322.

The majority of the SGOT and SGPT abnormalities regardless of attributable causality are generally less than twice the upper limit of normal. Regardless of attributable cause, the incidence of abnormal SGOT more than twice the upper limit of normal appear to be similar in cetirizine and placebo treated patients (0.4%), for SGPT the incidence is (0.3%) versus (0.1%) -SU 4/25/95, vol 35.2 page 9 60.

In foreign marketing experience the following additional rare, but potential severe adverse events have been reported: hemolytic anemia, thrombocytopenia, orofacial dyskinesia, severe hypotension, anaphylaxis, hepatitis, glomerulonephritis, stillbirth, and cholestasis (96).

In a six-week, placebo-controlled study of 186 patients with allergic rhinitis and mild to moderate asthma, ZYRTEC 10 mg QD improved rhinitis symptoms and did not alter pulmonary function. This study

supports the safety of administering ZYRTEC to allergic rhinitis patients with mild to moderate asthma (101).

DRUG ABUSE AND DEPENDENCE

There is no information to indicate that abuse or dependency occurs with ZYRTEC.

OVERDOSAGE

Overdosage has been reported with ZYRTEC. In one patient who took 150 mg of ZYRTEC,

the patient was somnolent but did not display any other signs or abnormal blood chemistry or hematology results (97). Should overdose occur, treatment should be symptomatic or supportive, taking into account any concomitantly ingested medications. There is no known specific antidote to ZYRTEC. ZYRTEC is not effectively removed by dialysis, and dialysis will be ineffective unless a dialyzable agent has been concomitantly ingested (37). The minimal lethal oral dose in rodents is approximately 100 times the maximum recommended clinical dose on a mg/m² basis and the liver was the target organ of toxicity (98).

DOSAGE AND ADMINISTRATION

The recommended initial dose of ZYRTEC is 5 or 10 mg, depending on symptom severity. Most patients in clinical trials started at 10 mg (99). ZYRTEC is given as a single daily dose, with or without food. The time of administration may be varied to suit individual patient needs.

In patients with decreased renal function (creatinine clearance 11-31 ml/min), patients on hemodialysis (creatinine clearance less than 7 mL/min), and in hepatically impaired patients, a dose of 5 mg QD is recommended.

HOW SUPPLIED:

ZYRTEC tablets are white (dye free), film coated, rounded-off rectangular shaped containing 5 mg or 10 mg cetirizine hydrochloride.

5 mg tablets are engraved with "PFIZER" on one side and with "550" on the other. Bottles of 100: (NDC 0069-5500-66)

10 mg tablets are engraved with "PFIZER" on one side and with "551" on the other. Bottles of 100: (NDC 0069-5510-66)

Cetirizine is licensed from UCB, Pharma Inc.

STORAGE: Store at room temperature 59° to 86°F (15° - 30°C).

Appendix 1

Protocol No.: 93CK16-0624

Study No.: 93-N-0096

Title: A multiple dose study to evaluate the pharmacokinetics and/or ECG effects on concomitant administration of a course of azithromycin therapy with cetirizine

Study design: Randomized, multiple dose, open (except that the cardiologist reading the ECGs was blinded), parallel group study. Subjects were randomized to one of three treatment groups, which received the following regimes during an 11-day period of drug administration:

Group A	Day 1:	placebo QD
	Days 2-6:	20 mg cetirizine QD
	Day 7:	500 mg azithromycin QD/20 mg cetirizine QD
	Days 8-11:	250 mg azithromycin QD/20 mg cetirizine QD
Group B	Day 1:	placebo QD
	Days 2-6:	20 mg cetirizine QD
	Day 7:	20 mg cetirizine QD
	Days 8-11:	20 mg of cetirizine QD
Group C	Day 1:	placebo QD
	Days 2-6:	placebo QD
	Day 7:	placebo QD
	Days 8-11:	placebo QD

ECGs were recorded on Days 1, 6, and 11 immediately prior to dosing and 1, 2, 3, 4, 6, 8, 10, 12 and 16 hours post-dose. ECGs were also recorded prior to dosing, 1 and 24 hrs post-dose on days 2 and 7, and 24 hours after the Day 11 dose (morning of Day 12).

Blood samples for the determination of plasma cetirizine and azithromycin levels were obtained immediately prior to dosing and 1, 2, 3, 4, 6, 8, 10, 12 and 16 hours post-dose on Days 6 and 11. Blood samples were obtained pre-dose and 1 hr post-dose on days 1, 2 and 7, and additionally 24 hours post-dose on Days 2 and 7. A final blood sample was obtained 24 hours after the Day 11 dose (morning of Day 12).

Analysis: ECGs. For study Days 6 and 11 separately, the following variables were computed for changes from baseline in the electrocardiographic QT interval,

using Hodges correction. AVGCHG (the mean of the 11 changes over hour 0-24), AUCCHG (the area under the change curve from hour 0 to 24 calculated by the trapezoidal rule), MAXCHG (the maximum of the 11 changes (sign included) over hour 0-24), HR2CHG (change at hour 2 only). These ECG parameters were analyzed comparatively among treatments using analysis of variance procedures appropriate to a repeated measures model. For each on-drug ECG recording in each subject (including Days 2, 6, 7 and 11) the percent change from baseline in Hodges QTc was determined, and the number of occurrences of prolongations of 10% or greater over baseline was computed for each treatment group.

PK. The following pharmacokinetic parameters were determined for cetirizine on Day 6 and 11, for subjects in Group A and B: AUC (24), Cmax, Tmax and T1/2. These parameters, excluding T1/2, were also calculated for azithromycin on Day 11, for subjects on Group B. **Statistical analyses were performed only for the cetirizine data.** An analysis of variance was performed on log transformed cetirizine PK parameters in subjects in Group B, for Day 11 vs Day 6. Geometric mean ratios of the parameters for Day 11 versus Day 6 and 90% confidence intervals for these ratios were obtained by reexponentiation of the results of the analysis. The same analysis was used to make the following additional comparisons of cetirizine parameters: 1) Day 6 values for Group A versus Day 6 values for Group B and 2) Day 11 values for Group A versus Day 11 values for Group B.

Results: Forty two healthy male subjects entered and completed the study. There were 14 subjects in each of the three treatment groups. **All three treatment groups showed small mean increases from baseline after 5 and 10 doses of study drug with respect to each of the four derived QTc variables (with the exception of HR2CHG for the cetirizine only group, which was a small decrease from baseline), but differences among groups were not statistically significant for any analysis.**

Mean AVGCHG at Study Day 6 was an increase of 0.27 msec in the combination treatment group (which represents cetirizine alone given for 5 days) and an increase of 0.69 msec in the cetirizine only group. Combining these two mean changes yields a mean increase from baseline in Hodges QTc after 5 doses of cetirizine of 0.48 msec compared to a 1.62 msec in the placebo group. At Study Day 11, the mean AVGCHG of 2.41 msec for combination treatment, 2.01 msec for cetirizine and 1.33 msec for placebo were not significantly different among groups. The treatment day interaction in the repeated analysis of variance, which measures the difference among treatment groups with respect to the changes in QTc from Day 6 to Day 11, was not statistically significant. The results for AUCCHG,

MAXCHG, and HR2CHG parallel the results described above for AVGCHG.

The incidence of prolongation of 10% or greater over baseline Hodges QTc in the three treatment groups did not suggest any effect of cetirizine or the combination on QT intervals. Up to Study Day 6, only one subject in the placebo group experienced a prolongation of 10% or greater over baseline. For the period after Study Day 6, three subjects in the cetirizine only group and a subject in the placebo group had a single occurrence each of a Hodges QTc prolongation of 10% or greater than baseline. The maximum prolongation over baseline recorded for individuals while taking placebo and cetirizine and placebo were 16% and 14%, respectively. In the cetirizine/azithromycin combination group, no subject had a prolongation in Hodges QTc that was 10% or greater.

Three subjects (21%) in Group A (cetirizine/azithromycin) reported dizziness, and one subject (7%) in Group B (cetirizine alone); none of the subjects in the placebo group reported dizziness. Tachycardia was reported by two subjects (14%) in Group B and one subject (7%) in Group C (placebo).

Four subjects (two in Group A and two in Group B) had elevated SGOTs and SGPTs that were clinically significant and possibly related to study medication (Category 9). In the investigator's opinion, these elevation (maximum recorded SGOT and SGPT values were 67 mu/mL, and 107 mu/ml, respectively) were not clinical significant. In three of the four subjects these values declined to within the normal range at a follow up determination.

There were no significant differences in mean cetirizine AUC (24), C max or Tmax on Day 11 compared to Day 6, among subjects in Group B, indicating that steady state had been reached by Day 6 or before. No differences were found in cetirizine pharmacokinetic parameter between Group A and Group B for Day 6. It is assumed that steady state was reached by Day 6 or before in these two groups. There were no significant differences in Day 11 values of cetirizine AUC (24), Cmax or Tmax in group a compared with Group B, indicating that the addition of azithromycin does not affect steady state plasma concentration of cetirizine.

The results from the combination azithromycin-cetirizine cannot be compared to the results using azithromycin alone. However, according to the sponsor

the results using the combination are comparable with single dose administration data (azithromycin) from other studies.

Sponsor's conclusion:

The results indicate that cetirizine 20 mg QD administered for ten 10 does not affect the QT interval. There is no indication that concomitant administration of azithromycin and cetirizine produces any significant changes in QT interval. No pharmacokinetic interaction occurs when subjects who are taking cetirizine and have attained steady state levels of the drug are additionally administered the five-day recommended dosage regimen of azithromycin. Cetirizine alone and in combination with azithromycin was well tolerated in this study.

Reviewer's comments:

After reviewing the study the following questions were faxed to the Sponsor August 4, 1995. For clarity th'e questions are bolded and a summary of the response that was submitted and the amendment to the NDA dated, 8/11/95, follows.

1. **Please provide the corresponding ECG values in the format of Appendix F.2 in vol 14, for the following ECGs with QTc prolongations that are listed in Table 1.5, vol 1:**

**Cetirizine pt. # 25 Treatment Day 9 (Study Day 10) Hour 0
Day 10 : QTc 410 (Bazzet), 12.02% increase QTc Bazzet**

**Cetirizine pt. #38 Treatment Day 3 (Study Day 4) Hour 6
Day 4: QTc 436 (Bazzet), 10.66% increase QTc Bazzet**

**Cet/Azi pt. #35 Treatment Day 9 (Study Day 10) Hour 0
Day 10: QTc 427 (Bazzet), 17.96% increase QTc Bazzet**

**Cet/ Azi pt. #39 Treatment Day 9 (Study Day 10) Hour 0
Day 10: QTc 431 (Bazzet), 12.53% increase QTc Bazzet**

**Placebo pt. #12 Treatment Day 9 (Study Day 10) Hour 0
Day 10: QTc 435 (Bazzet), 12.40% increase QTc Bazzet**

**Placebo pt. # 33 Treatment Day 9 (Study Day 10) Hour 0
Day 10: QTc 433 (Bazzet), 13.05% increase QTc Bazzet**

Please explain why the corresponding ECG values for the above patients were not included in the Appendix F.2 listing and what was the reason for obtaining these ECGs out of the regular protocol schedule. Please submit the listings for any other ECGs obtained out of the regular protocol

schedule. Please explain why they were obtained and why they were not included in the Appendix F.2 listing.

The investigator made 104 additional ECG's that were not required by the protocol schedule; the protocol allowed it to ensure the safety of the subjects. Prior to the study the investigator informed Pfizer that they would obtain ECGs at 0 hrs on days 9 and 10 for all 42 subjects. This accounts for 83 of the 104 unscheduled ECGs (subject #9 did not have day 9 hour 0 ECG). Additionally, 12 ECGs were obtained on unscheduled days. A specific safety reason was described for only one of these subjects (Subject #38, Day 4, Hour 6) and the reason given was because on an increase QTc from baseline. Of the remaining 9 ECGs, all were repeat ECGs made back to back with a schedule recording. No specific safety reason was given for 7 of these ECGs and 2 ECGs were obtained because the investigator noted a greater than 20% increase change from baseline (Subject #6, Day 11, Hour 6 on placebo; and Subject #13, Day 11, Hour 0, on combination). In both instances the repeat ECG was normal and the cardiologist's blinded reading did not indicate greater than 20% increase in QTc.

All the analyses presented as well as that of the derived variables were based on the scheduled ECGs. The analysis of QTc prolongations over 10% predicted included days other than 6 and 11, but only included the scheduled ECGs. The Appendix F.2 data listing was intended to provide the actual data used in the data analysis and therefore did not include "unscheduled" ECGs.

The inclusion of "unscheduled" QTc readings in the analysis would only have affected the account of 10% prolongations over baseline Hodges presented in Tables 3 and 4 of the summary. This analysis was rerun including the 10% on treatment extra QTc's and no additional 10% prolongations (based on the Hodges QTc's) were found.

In regard to Table 1.5 in volume 1 of the safety update 4/25/95, all QTc readings, including the unscheduled reading were included. Although this deviation from the analysis should have been noted in the response, the results do not impact the conclusions of the study.

2. **Please provide us with an analysis for Max QTc change (MAXCHG) using the Bazett formula as was provided in Table E.1.3 using the Hodges formula.**

Attached see Table E.2.2

The largest values for MAXCHG for Day 6 and 11 were observed in the placebo treated group. The significant statistical change is observed between the cetirizine group and the combination, result from the lower change in the cetirizine group for Day 6 and an apparent larger change from Day 6 to Day 11 compared to the other groups. This results do not indicate any effect of cetirizine alone or in combination with azithromycin on the maximum change from baseline Bazzet QTc.

Reviewer's comments:

After reviewing the data submitted (8/11/95) as response to our fax the following are noted:

1. From the group of unscheduled ECGs, those that had a Bazzet QTc prolongation of 10% or greater were included in the response to Question 1 of our approvable letter. —
2. The sponsor should have noted the existence of the 104 unscheduled ECGs in the study report and in their initial response.

The following Tables list the # of patients with QTc prolongations of 10% or greater along with those patient that in addition had a QTc of 440 msec or longer by treatment days.

Placebo treatment:

Days	# patients with QTc prolongation 10% or greater	# ECGs, QTc 10% or greater	# ECGs, QTc>440
1-5	6	14	5
6-9	3	3	0
10	7	11	4

After reviewing the individual patient data, for Days 1-5 in placebo treated patients there is one subject #36 that accounts for 4/5 of the ECGs with QTc of 440msec or longer, and of 5 ECGs that have a QTc with a 10% prolongation ore greater (range from 10.9% to 16.7% over baseline).

Cetirizine treated patients:

Days	# of patients with QTc prolongation 10% or greater	# ECGs, QTc 10% or greater	# ECGs, QTc >440
1-5	4	4	1
6-9	3	3	0
10	7	12	5

Combination treatment:

Days	# of patients with QTc prolongation 10% or greater	# ECGs, QTc 10% or greater	# ECGs, QTc >440
5*	5	6	3
6-9	5	5	1
10	4	7	2

* Please note that from days 1-5 inclusive patients were receiving only cetirizine

In the attached Table E.2.2., the statistical difference between cetirizine and the combination is $p=0.02$ for the treatment effect from Day 6 to Day 11. We would have expected the patients for both cetirizine and combination to have approximate equal Day 6 change, since the two groups were receiving the same drug for those 5 days of treatment. However, the cetirizine only group had a lower increase in QTc, than the combination, in this reviewer agrees with the Sponsor's interpretation for Day 6, since in addition the baseline QTc for cetirizine was 425 msec and for the combination it was 429 msec.

However, when the treatment effect from Day 6 to Day 11 is calculated, (Day 11-Day 6) cetirizine group it is 13.41 msec, versus the -1.43 in the combination and 3.14 in the placebo treated group. Using the Hodges correction as depicted in Table E.1.3. p11 550 vol 35.14, the maxchange (Day 11-Day6) for cetirizine treated patients was 6.79, versus 0.43msec for the combination and 1.79 for placebo. The mean increase for cetirizine treated patients in the cetirizine -ketaconazole study (Hodges) at 10 days of treatment was 8.2 msec. The results of this study suggest that the combination of cetirizine/azithromycin is favorable in decreasing the expected increase in QTc that has been observed in cetirizine treated

PROTOCOL 95CK16-0624: A MULTIPLE DOSE STUDY TO DETERMINE THE INTERACTION OF CETIRIZINE WITH AZITHROMYCIN IN YOUNG HEALTHY MALES

TABLE E.2.2
STATISTICAL ANALYSIS OF MAXCHG: MAXIMUM QTc CHANGE FROM BASELINE FROM HOUR 0 TO 24.
QT CORRECTED BY BAZETT FORMULA

OBSERVED MEAN CHANGE FROM BASELINE ± STD DEVIATION BY TREATMENT (MSEC)

TREATMENT PERIOD	PLACEBO	CETIRIZINE	CETIRIZINE/COMBINATION ¹	P-VALUE OVERALL ²	ESTIMATED CETIRIZINE EFFECTS ³	ESTIMATED COMBINATION EFFECT
(NO. SUBJ)	(14)	(14)	(14)			
BASELINE	425.71 ± 19.66	425.43 ± 14.16	429.43 ± 14.70			
DAY 6 CHANGE	40.14 ± 17.35	28.79 ± 14.94	36.07 ± 13.79	.156	-7.71 (P=.135)	
DAY 11 CHANGE	43.29 ± 16.22	42.50 ± 19.45	34.64 ± 16.05	.364	-0.79 (P=.906)	-8.64 (P=.201)
TREATMENT EFFECTS FROM DAY 6 TO DAY 11 (DAY 11 - DAY 6)						
	3.14 ± 20.72	13.71 ± 13.53	-1.43 ± 13.49			

ANALYSIS OF VARIANCE (SAS TYPE III MS)

EFFECT	DF	MEAN SQUARE	F-RATIO	P-VALUE	P-VALUES FOR DIRECT PAIRWISE COMPARISONS OF TREATMENT EFFECTS FROM DAY 6 TO DAY 11	
					CETIRIZINE	COMBINATION
TREATMENT	2	361.00	0.87	.4262		
SUBJ(TREAT)	39	414.14	3.13	.0003		
DAY	1	355.43	4.19	.0473		
TREAT*DAY ⁴	2	422.25	3.19	.0522	PLACEBO	0.0936
ERROR	39	132.44			CETIRIZINE	0.4618
						0.0104

¹SUBJECTS RECEIVED CETIRIZINE ALONE UP TO STUDY DAY 6 AND THEN RECEIVED CETIRIZINE + AZITHROMYCIN STARTING ON DAY 7.

²FROM ONE-WAY ANOVA F-TEST.

³FOR DAY 6 THE ESTIMATED CETIRIZINE EFFECT IS (.5 X CETIRIZINE MEAN + .5 X COMBINATION MEAN) MINUS PLACEBO MEAN. FOR DAY 11 THE ESTIMATED EFFECTS ARE THE RESPECTIVE PAIRWISE DIFFERENCES FROM PLACEBO.

⁴CORRESPONDS TO THE OVERALL DIFFERENCE IN TREATMENT EFFECTS FROM DAY 6 TO DAY 11.

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patients after 10 days of treatment.

This study lacked a treatment arm that started patients on azithromycin and then added the cetirizine. In addition it was not a cross over study. The results in terms of changes on QTc can only be stated as suggestive. The possibility of an interaction of azithromycin with the enantiomer of cetirizine that according to animal studies is more extensively metabolized by the liver, could be considered. However, the data in this study does not support at this time, a definite QTc change with the azithromycin interaction that should be included in the labeling.

3. Please provide us with follow up values for SGOT and SGPT for patient # 17. The last reported values were SGOT=61 and SGPT=107 mu/mL. If these are not available, please explain. Please contact the investigator to obtain a follow up in this patient.

No additional information was obtained after contacting the investigator.

Reviewer's comments:

It had been noted in the cetirizine database the 1-2% increases in liver transaminases. In the cetirizine/erythromycin study 4 cases were noted out of 16 subjects. In this study, 1/14 subjects develop the increase in enzymes by Day 5 of treatment on cetirizine alone before receiving the combination, 2/14 on cetirizine alone by Day 11 and one on the combination by Day 11. No patient treated with placebo has an elevation in liver transaminases that is considered to be of category 9. In three of the 4 subjects we have values returning to normal after the drug is discontinued at the end of the study.

As noted elsewhere in the reviewer's comments to the labeling, the statement regarding elevation of liver transaminases needs to be more specific than the one proposed by the Sponsor.

4. Please provide us with the individual patient listing for concomitant medications in this study.

The only additional concomitant medication in this study was Keri Lotion by two subjects.

Appendix 2

PEDS-4: Multicenter [(12), Albany, N.Y.; Minneapolis, MN; Dallas, TX; Aurora, CO; San Diego, CA; Atlanta, GA; Overland Park, KS; Sylvania, OH; East Meadow, NY; Bend, OR; Oregon, CA; Gainesville, FL], randomized, double-blind, multicenter, parallel study. Patients (6-11 yrs old) were treated for 4 weeks, during the ragweed pollen season. The randomization was stratified by entry weight to ensure patients 25 kg (55 lbs) or greater and patients less than 25 kg will be equally distributed, across all 3 treatment groups: cetirizine 5 mg Q.A.M., cetirizine 10 mg Q.A.M., or placebo. --

"The protocol required that ECGs be recorded at the week 2 visit, but many were recorded at the end of week 3 or week 4. In many cases recordings were made at week 2 and repeated at the end of treatment. Accordingly, an endpoint analysis was conducted on the change from baseline to the last ECG recorded.

All cases were included in this analysis regardless of time on treatment to last ECG, including discontinued patients, providing both a baseline and endpoint value were available. Five patients (2 placebo cases, 1 cetirizine 5 mg case and 2 cetirizine 10 mg cases) had their full ECG recorded more than two days after the last dose of medication and one patient's baseline ECG was obtained during treatment. A subset analysis was also conducted which excluded these cases to account for any possible biases related to the withdrawal of study drug. Also, in order to conform to the protocol, a subset analysis was conducted which included only those ECGs recorded 11 to 17 days after the first dose (i.e., within ± 3 days of the end of week 2 visit on day 14). If more than one ECG was recorded, the recording made closest to day 14 of treatment was included. Since some study sites consistently recorded ECGs at the end of treatment only, all their follow-up ECG data did not conform to the 11 to 17 day window. Therefore, these sites (92NO042, 92NO043 AND 92NO044) were completely excluded from the 11 to 17 day window analysis."

"The mean change from baseline and percent change from baseline for Peds-4 included in the report filed on September 2, 1993 using the Bazzet's correction. At that time it included ECGs within 48 hrs after the last dose. In this submission the analyses were revised to exclude any

ECGs recorded more than 24 hrs after the last dose."

1. Includes patients with QT recorded in the 11 to 17 day window after the first dose of study drug
2. Includes all patients for the endpoint change (i.e. the last recorded).
3. Includes all patients for the maximum change.

Analysis 3 was added to this response as a supplement. Analysis 1 and 2 differed from the original in that 2 or 3 patients were reduced from the original analysis and in several instances where a patient had multiple ECGs, a different endpoint may have been selected."

Change from baseline for ECGs recorded within days 11-17 of first dose from Table 2.1:

Number of patients	Placebo 40	Cet 5 mg 35	Cet 10 mg 44	p-value
QTc (Bazett) Baseline	425.05 +/- 25.47	417.36 +/- 25.33	420.54 +/- 22.34	0.061
Change	-0.79 +/- 24.25	-0.08 +/- 35.67	10.32 +/- 25.18	
(p-value within)	0.833	0.970	0.015	
Adjusted change	1.77	-2.52	9.94	

Change from baseline for ECGs recorded last or maximum ECG recorded on treatment (11-17 Days ECGs), from Table 2.2:

Number of patients	Placebo 64	Cet 5 mg 64	Cet 10 mg 65	p-value
QTc (Bazett) Baseline	418.93 +/- 24.88	421.02 +/- 25.98	421.15 +/- 21.31	0.006
Change	-5.89 +/- 27.21	-2.84 +/- 31.52	10.22 +/- 24.84	
(p-value within)	0.107	0.887	0.002	
Adjusted change	4.92	-2.40	10.73	

Distribution of percent change from baseline for ECGs recorded within days 11-17 of first dose, from Table 2.4:

	under 5%	5- <10%	10- <20%
Placebo-# of pts.	32	6	2
Row %	80%	15%	5%
5 mg cet	27	4	4
Row %	77.14%	11.43%	11.43%
10 mg cet	31	7	6
Row %	70.45%	15.91%	13.64%

Reviewer's comments:

There is a persistent increase in QTc change from baseline observed in the 10 mg treated cetirizine patients of approximately 10 msec for the group of patients that had their ECGs within 11 to 17 post dose, Table 2.1. This prolongation in QTc is also observed for the maximum QTc prolongation in ECGs for cetirizine treated patients when all patients were considered, Table 2.2.

The above noted differences in cetirizine treated patients are not statistically significant against placebo, but it is consistent in both analyses. It is important to consider that this study was not originally designed to detect such differences.

Appendix 3

Table: Incidence and median exposure of medication categories during placebo controlled studies; SU 4/25/95, vol 35.4, Appendix G, page 9 657

1

POOLED CETIRIZINE PROTOCOLS
 TABLE : INCIDENCE AND MEDIAN EXPOSURE OF MEDICATION CATEGORIES DURING PLACEBO-CONTROLLED STUDIES.

MEDICATION CATEGORIES	--- CETIRIZINE --- (N=2679)		----- PLACEBO ----- (N=1671)	
	INCIDENCE	EXPOSURE (DAYS)	INCIDENCE	EXPOSURE (DAYS)
NSAID	376 (14.0%)	4.0	282 (16.9%)	4.0
CORTICOSTEROIDS	190 (7.1%)	7.0	123 (7.4%)	7.0
BIRTH CONTROL	185 (6.9%)	29.0	142 (8.5%)	26.0
BETA AGONIST	179 (6.7%)	27.0	97 (5.8%)	22.0
THIAZIDE & RELATED AGENTS	93 (3.5%)	22.0	67 (4.0%)	21.0
THYROID	44 (1.6%)	15.5	51 (3.1%)	20.0
PENICILLINS	44 (1.6%)	8.0	33 (2.0%)	8.0
H2 INHIBITOR	20 (0.7%)	16.0	14 (0.8%)	15.0
CEPHALOSPORIN	11 (0.4%)	8.0	7 (0.4%)	7.0

PATIENTS MAY BE INCLUDED IN MORE THAN ONE CATEGORY.

• EACH PATIENT IS COUNTED ONLY ONCE ON THIS LINE.

PROGRAM: CSF1CNMC SAS IN C.J.ML
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Table: Incidence and median exposure of medication categories during all studies; SU 4/25/95, vol 35.4, Appendix G, page 9 658

POOLED CETIRIZINE PROTOCOLS
 TABLE : INCIDENCE AND MEDIAN EXPOSURE OF MEDICATION CATEGORIES DURING ALL STUDIES.

MEDICATION CATEGORIES	--- CETIRIZINE --- (N=3982)	
	INCIDENCE	EXPOSURE (DAYS)
NSAID	603 (15.1%)	5.0
BIRTH CONTROL	345 (8.7%)	15.0
BETA AGONIST	245 (6.2%)	24.0
CORTICOSTEROIDS	222 (5.6%)	7.0
THIAZIDE & RELATED AGENTS	125 (3.1%)	10.0
PENICILLINS	92 (2.3%)	10.0
THYROID	68 (1.7%)	15.0
H2 INHIBITOR	26 (0.7%)	14.5
CEPHALOSPORIN	25 (0.6%)	11.0

PATIENTS MAY BE INCLUDED IN MORE THAN ONE CATEGORY.

* EACH PATIENT IS COUNTED ONLY ONCE ON THIS LINE.

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658

PROGRAM: CSFICMPC SAS IN C.ML
 DATE : 11APR95 TIME: 9:16

Table: Incidence of adverse experiences in patients treated with cetirizine or placebo in placebo-controlled studies; SU 4/25/95, vol 35.4, Appendix G, page 9 667

TABLE : INCIDENCE OF ADVERSE EXPERIENCES IN PATIENTS TREATED WITH CETIRIZINE OR PLACEBO
IN PLACEBO-CONTROLLED STUDIES

ADVERSE EXPERIENCES	INCIDENCE IN SAFETY EVALUABLE PATIENTS			
	NSAID USER		NON-NSAID USER	
	CETIRIZINE NO. PTS. (%)	PLACEBO NO. PTS. (%)	CETIRIZINE NO. PTS. (%)	PLACEBO NO. PTS. (%)
TOTAL NO. OF PATIENTS	376	282	2393	1589
NO. OF PTS. WITH ADVERSE EXPERIENCES	251 (66.76%)	178 (63.12%)	907 (39.38%)	432 (31.10%)
HEADACHE	179 (47.61%)	122 (43.26%)	273 (11.85%)	180 (12.96%)
SOMNOLENCE	71 (18.88%)	18 (6.38%)	334 (14.50%)	87 (6.26%)
FATIGUE	27 (7.18%)	7 (2.48%)	128 (5.56%)	36 (2.59%)
MOUTH DRY	23 (6.12%)	8 (2.84%)	112 (4.86%)	31 (2.23%)
NAUSEA	10 (2.66%)	8 (2.84%)	56 (2.43%)	46 (3.31%)
DIZZINESS	6 (1.60%)	5 (1.77%)	41 (1.78%)	18 (1.30%)
PHARYNGITIS	12 (3.19%)	11 (3.90%)	35 (1.52%)	20 (1.44%)
INSOMNIA	5 (1.33%)	4 (1.42%)	29 (1.26%)	18 (1.30%)
EPISTAXIS	6 (1.60%)	3 (1.06%)	21 (0.91%)	8 (0.58%)
COUGHING	3 (0.80%)	4 (1.42%)	23 (1.00%)	7 (0.50%)
NERVOUSNESS	5 (1.33%)	2 (0.71%)	21 (0.91%)	12 (0.86%)
ABDOMINAL PAIN	6 (1.60%)	5 (1.77%)	18 (0.78%)	10 (0.72%)
DYSPEPSIA	3 (0.80%)	4 (1.42%)	21 (0.91%)	21 (1.51%)
RESPIRATORY DISORDER	7 (1.86%)	4 (1.42%)	17 (0.74%)	11 (0.79%)
RHINITIS	3 (0.80%)	1 (0.35%)	16 (0.69%)	9 (0.65%)
EARACHE	4 (1.06%)	2 (0.71%)	14 (0.61%)	8 (0.58%)
DIARRHEA	3 (0.80%)	2 (0.71%)	14 (0.61%)	15 (1.08%)
EYE ABNORMALITY	4 (1.06%)	0 (0.00%)	13 (0.56%)	6 (0.43%)
BACK PAIN	7 (1.86%)	7 (2.48%)	9 (0.39%)	4 (0.29%)
MALISE	4 (1.06%)	2 (0.71%)	12 (0.52%)	4 (0.29%)
APPETITE INCREASED	1 (0.27%)	1 (0.35%)	14 (0.61%)	4 (0.29%)
WEIGHT INCREASE	2 (0.53%)	1 (0.35%)	11 (0.48%)	5 (0.36%)
PAIN	4 (1.06%)	5 (1.77%)	7 (0.30%)	1 (0.07%)
PALPITATION	1 (0.27%)	1 (0.35%)	10 (0.43%)	4 (0.29%)
PARESTHESIA	3 (0.80%)	1 (0.35%)	8 (0.35%)	2 (0.14%)
PRURITUS	0 (0.00%)	2 (0.71%)	11 (0.48%)	20 (1.44%)
DYSMENORRHEA	7 (1.86%)	5 (1.77%)	3 (0.13%)	1 (0.07%)
RASH	3 (0.80%)	2 (0.71%)	7 (0.30%)	6 (0.43%)

-- (CONTINUED) --

Appendix 4

Tables F1C and F1D in SU 4/25/95, vol 35.3

TABLE F1.C: NUMBER OF PATIENTS EXPOSED TO DRUG BY DURATION OF EXPOSURE, BY FINAL DOSE - ADULT STUDIES

DURATION OF EXPOSURE	MDA (NUMBER OF PATIENTS)					CUMULATIVE (NUMBER OF PATIENTS)					N/A
	TOTAL	5 MG	10 MG	15 MG	20 MG	TOTAL	5 MG	10 MG	15 MG	20 MG	
UP TO 2 WEEKS	407	127	162	4	114	1540	192	736	4	268	340
3 - 4 WEEKS	551	87	367	6	91	1141	124	697	6	112	202
5 - 12 WEEKS	371	83	143	49	96	980	239	461	49	206	25
13 WKS-6 MONTHS	236	30	74	0	124	237	39	74	0	124	0
NOT AVAILABLE	3	0	1	0	2	84 ¹	0	79	0	2	3
TOTAL NUMBER OF PATIENTS	1568	335	747	59	427	3982	594	2047	59	712	570 ²
MEAN DURATION OF EXPOSURE (DAYS)	41.2	31.3	31.3	39.0	66.7	30.1	34.8	25.7	39.0	49.8	15.2

¹ FOR 84 PATIENTS (84N0055 PATIENT 71, 85N0051 PATIENT 8 AND 86N0199, PATIENT 8, PROTOCOL C-89001: 78 PATIENTS AND PROTOCOL L-0103: 3 PATIENTS) THE DURATION OF EXPOSURE COULD NOT BE DETERMINED.

² 526 PATIENTS (L-0103) HAD FINAL DOSE UNKNOWN WITH A PROTOCOL SPECIFIED MAXIMUM POSSIBLE TITRATED DOSE OF 20 MG.
44 PATIENTS (L-0192) HAD FINAL DOSE UNKNOWN WITH A PROTOCOL SPECIFIED MAXIMUM POSSIBLE TITRATED DOSE OF 10 MG.

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DATE: 04/10/95 10:34:56

Appendix 5

Proposed Amendment to the revised labeling for NDA 19835 drafted
in the 9/21/95 "in house meeting

Memo

From: Ana M. Saavedra-Delgado, M.D.
To: Marty Himmel, M.D.
Subject: Proposed amendment to the revised labeling for NDA
19835 drafted in the 9/21/95 "in-house" meeting
Date: September 27, 1995

"Following cutaneous antigen challenge, the late phase recruitment of eosinophils, neutrophils and basophils, components of the allergic inflammatory response, is inhibited by Zyrtec."

The following change is proposed:

"In studies conducted for up to twelve hours following cutaneous antigen challenge, the late phase recruitment of eosinophils, neutrophils and basophils, is inhibited by Zyrtec."

The references for the sponsor's statement are attached. Only the summary for studies CP-18, CP19 and CP20 were readily available. Copies of the two referenced literature articles, #57 and #58 are attached. In addition, the reviewer references study 104, that was submitted in the 4/25/95 submission in vol 18.

The summary report of study CP-18 appears to be the same study described in reference #57: J Allergy Clin Immunol:83(5):905-912, 1989.

The two published articles by the Baltimore group use the same skin chamber technique. In both studies 20 mg of cetirizine was used; in #57 for 2 days and in #58 for 3 days and they both had placebo controls. In #57 the cell infiltration was studied for up to 8 hrs and in study #58 for up to 12 hours. Statistical significant reduction of eosinophil and neutrophil infiltration was achieved for the pooled results of hours 6-8 in study #57. At 8 hours there was significant reduction in neutrophil and eosinophil infiltration. The results in basophils followed the same trend but perhaps due to small numbers they were not statistically significant.

In study #58 the group extends the observation for up to 12 hours and other two antihistamines are studied. In this study the statistical significant changes on cell infiltration are observed at 10-12 hrs for eosinophils and basophils and 8-12 hours for neutrophils.

In study #58, wheal and flare were measured at hourly intervals for up to 12 hours and cetirizine significantly inhibited the immediate reaction to cutaneous antigen challenge (up to 3 hours) but did not alter the late phase cutaneous reactivity as measured by wheal and flare (4-12 hours).

Study 104 studied cetirizine 15 mg bid for 4.5 days in a cross-over design comparing it to prednisolone 20 mg for 4.5 days and placebo. The investigators attempted to use the skin window technique but was not effective. Skin biopsy at 6 and 24 hours were obtained. Biopsies were read blindly. No statistical significant effect was noted with cetirizine in terms of the number of eosinophils or neutrophils at 6 or 24 hours compared to placebo. Prednisolone significantly inhibited the number of eosinophils compared to placebo in the skin biopsies. Neutrophils were also reduced but the difference was not statistically significant.

In summary, the above results do support Zyrtec's inhibition of cellular infiltration at the skin following cutaneous antigen challenges of eosinophils, neutrophils and basophils in studies conducted up to 12 hours post antigen challenge. However, even though the cellular infiltration is inhibited, the cutaneous manifestation of late phase reactivity, i.e. wheal and flare, does not appear to be inhibited.

The elimination of the phrase "component of allergic inflammatory response" is proposed because even though these cell types indeed are component of the inflammatory response, for the reader, the statement could imply that cetirizine inhibits this response.

Section 3.

I. Revised Labeling for NDA 19835 dated September 29, 1995

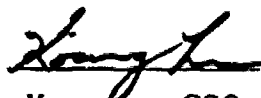
OCT 2 1995

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 29, 1995
FROM: Koung Lee
SUBJECT: NDA 19-835 Revised Cetirizine Tablet Labeling
TO: NDA 19-835 Zyrtec (cetirizine 5 and 10 mg) tablet

A labeling meeting was held on September 21, 1995 to revise Pfizer's April 25, 1995 proposed labeling for Zyrtec Tablet. Present at the meeting were Drs. Robert Temple, John Jenkins, Martin Himmel, Mehul Mehta, Joseph Sun, Mark Vogel, Bradley Gillespie, Anamaria Saavedra-Delgado, Mr. Bob Barron, Mr. Koung Lee, and Ms. Cathie Schumaker. Ms. Schumaker made the labeling revisions during the meeting using the PROXIMA to allow the team to see the changes as they were being made.

The Red Strike Out and Strike Out functions on WordPerfect 6.0 were used to identify the revisions. The Red Strike Out function changes the color of the letters to red on the monitor but the letters come out highlighted (eg., ZYRTEC) when printed on the laser jet printer. The Strike Out function prints the way it appears on the monitor (eg., ZYRTEC). After the revisions were made, the labeling was printed and circulated for concurrence from the team. The revised labeling was then faxed to Pfizer on September 29, 1995 with the request to submit to the NDA revised labeling with the recommended changes.

 10.2.95
Koung Lee, CSO

ATTACHMENT - REVISED LABELING

cc: Orig. NDA 19-835

HFD-155/Div. Files

HFD-155/C. Schumaker /9-29-95

HFD-155/M. Himmel

HFD-426/M.Mehta

HFD 155/J.Sun

HFD 155/A.Saavedra-Delgado

HFD 426/B.Gillespie

HFD 155/M.Vogel

HFD-150/B.Barron

HFD-155/K.Lee

ANNOTATED PACKAGE INSERT

ZYRTEC

cetirizine hydrochloride

Tablets

For Oral Use

DESCRIPTION

Cetirizine hydrochloride, the active component of ZYRTEC tablets, is an orally active and selective H₁-receptor antagonist. The chemical name is (±)-[2-[4-(p-chloro-α-phenylbenzyl)-1-piperazinyl]ethoxy] acetic acid, dihydrochloride. Cetirizine hydrochloride is a racemic compound with an empirical formula of C₂₁H₂₇ClN₄O₂·2HCl. The molecular weight is 461.82 and the chemical structure is shown below:

Cetirizine hydrochloride is a white, crystalline powder and is water soluble. ZYRTEC is formulated as a white (dye-free), film-coated, rounded-off rectangular shaped tablet for oral administration and is available in 5 and 10 mg strengths. Inert ingredients are: lactose; magnesium stearate; povidone; titanium dioxide; hydroxypropyl methylcellulose; polyethylene glycol; and corn starch.

CLINICAL PHARMACOLOGY

Mechanism of Actions: Cetirizine, a human metabolite of hydroxyzine is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H₁ receptors (1,2). The antihistaminic activity of cetirizine has been clearly documented in a variety of animal and human models (3-24). *In vivo* and *ex vivo* animal models have shown negligible anticholinergic and antiserotonergic activity (5,8,10,13,14,17). In clinical studies, however, dry mouth was more common with cetirizine than with placebo (89). *In vitro* receptor binding studies have shown no measurable affinity for other than H₁ receptors (16). Autoradiographic studies with radiolabeled cetirizine in the rat have shown negligible penetration of the brain (25). *Ex vivo* experiments in the mouse have shown that systemically administered cetirizine does not significantly occupy cerebral H₁ receptors (16).

Pharmacokinetics: Cetirizine is rapidly absorbed after oral administration of a tablet, which had bioavailability similar to an oral solution (26). Food had no effect on the extent of cetirizine absorption, but T_{max} was delayed by 1.7 hours and C_{max} was decreased by 23% in the presence of food (27). A mass balance study in 6 healthy male volunteers indicated that 70% of the administered radioactive dose was recovered in the urine and 10% in the feces, for a combined

total recovery of about 80% (28). Approximately 50% of the administered radioactive dose was excreted in urine as unchanged drug (28). Most of the rapid increase in peak plasma radioactivity is associated with parent drug indicating low first pass metabolism (28). Cetirizine is metabolized to a very limited extent by oxidative o-dealkylation to a metabolite (28,29) with negligible antihistaminic activity (30).

Cetirizine exhibits linear kinetics over the dosage range of 5 to 60 mg (31,32). In pharmacokinetic studies in 146 healthy volunteers, the mean $\pm$ SD terminal half-life was 8.3 ± 1.8 hours, oral clearance was 54 ± 13 mL/min, and the apparent volume of distribution was 0.50 ± 0.08 L/kg (33). No accumulation was observed for cetirizine following daily doses of 10 mg $\mp$ for 10 days (34). The steady-state maximum plasma concentration was 311 ± 40 ng/mL and was achieved within 1.0 ± 0.5 hour (34). Individual histograms of cetirizine C_{max} and AUC showed unimodal distributions with a two- to four- fold variability in healthy subjects (100). Plasma protein binding of cetirizine is 93 ± 0.3 % and was independent of concentration in the range of 0.025 to 1.0 mcg/mL (29); this concentration range covers the therapeutic plasma levels.

SPECIAL POPULATIONS

Effect of Age: Following a single 10 mg oral dose, half-life increased by about 50% and clearance decreased by 40% in 16 elderly subjects as compared to the 14 normal subjects (35). The decrease in cetirizine clearance in these elderly volunteers appeared to be related was directly correlated to their decreased renal function.

Effect of Gender: No gender-related differences were observed in the kinetics of cetirizine between 86 white adult males and 3 white adult females (36). The effect of gender on cetirizine pharmacokinetics has not been adequately studied.

Effect of Race: No race-related differences were observed in the kinetics of cetirizine between 86 white adult males and 11 black adult males (36).

Renally Impaired Patients: The kinetics of cetirizine were studied following multiple oral daily doses of 10 mg for 7 days in 7 normal volunteers (creatinine clearance 89-128 mL/min), 8 patients with mild renal function impairment (creatinine clearance 42-77 mL/min) and 7 patients with moderate renal function impairment (creatinine clearance 11-31 mL/min) (37). The pharmacokinetics of the drug were similar in patients with mild impairment and normal volunteers. Moderately renally impaired patients had a 3-fold increase in half-life and 70% decrease in clearance compared to normal volunteers (37). Accumulation of cetirizine was also more pronounced in patients with moderate impairment (37).

Patients (N=5) on hemodialysis (creatinine clearance less than 7 mL/min) given a single oral 10 mg dose of cetirizine, 5 patients on hemodialysis had a 3 fold increase in half-life accompanied by a 70% decrease in clearance compared to normals. Cetirizine was not completely cleared by hemodialysis as less than 10% of the administered dose was removed during the dialysis session (37).

Dosing adjustment is necessary in patients with moderate or severe renal impairment and patients on dialysis. (See also DOSAGE AND ADMINISTRATION).

Hepatically Impaired Patients: Following single oral doses of 10 mg and 20 mg cetirizine administered to 6 and 10 patients, respectively, ~~6 and 10 patients~~ with chronic liver diseases (hepatocellular, cholestatic, and biliary cirrhosis); ~~given 10 or 20 mg of cetirizine as a single oral dose resulted in had~~ a 50% increase in half-life along with a

40% decrease in clearance compared to 16 healthy subjects (37,38,39).

Dosing adjustment may be necessary in hepatically impaired patients. (See also DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

~~Formal pharmacokinetic interaction studies were conducted with cetirizine and pseudoephedrine, antipyrine, ketoconazole, erythromycin, and azithromycin. No pharmacokinetic interactions were observed. In a multiple dose study of theophylline (400 mg, once daily) and cetirizine, there was a small (16%) decrease in clearance of cetirizine.~~

~~Theophylline: A multiple dose study in 24 healthy male volunteers showed that the pharmacokinetics of cetirizine (20 mg QD for 3 days) and theophylline (400 mg QD for 3 days) were not altered when they were given in combination (40).~~

~~Pseudoephedrine: A multiple dose study showed no significant differences in any pharmacokinetic parameters for either cetirizine (20 mg QD) or pseudoephedrine (120 mg Q12h) when they were concomitantly administered to 24 healthy male subjects for 6 days (41).~~

~~Antipyrine: Cetirizine 10 mg QD was administered for 9 days to 10 healthy male volunteers. Following coadministration on the ninth day with 250 mg antipyrine, no changes were observed in plasma clearance or elimination half-life of antipyrine. Therefore, cetirizine does not alter the oxidative metabolizing enzyme activity in the liver (42).~~

~~Ketoconazole: In a multiple dose study involving 16 healthy male volunteers, the~~

pharmacokinetics of cetirizine (20 mg QD) and ketoconazole (400 mg QD) were not altered when they were given in combination (43).

~~Erythromycin:~~ In a multiple-dose study involving 16 healthy male volunteers, the pharmacokinetics of cetirizine (20 mg QD) and erythromycin (500 mg Q8h) were not altered when they were given in combination (44).

~~Cimetidine:~~ In a double-blind, randomized, single-dose, crossover study, cetirizine 20 mg was administered to 6 healthy volunteers concomitantly with placebo or 400 mg cimetidine. Neither cetirizine plasma concentrations nor wheal and flare measurements at 2 and 4 hours post-dose were significantly different after cimetidine and placebo treatment (45).

Pharmacodynamics: Studies in normal volunteers show that ZYRTEC at doses of 5 and 10 mg strongly inhibits the skin wheal and flare caused by the intradermal injection of histamine (17-20,22,23,46-48). The onset of this activity after a single 10 mg dose occurs within 20 minutes in 50% of subjects and in 95% of subjects within one hour (49,50), and this activity persists for at least 24 hours (17,22,46,49). In a 35 day study in children ages 5 to 12, no tolerance to the antihistaminic [suppression of wheal and flare response] effects of ZYRTEC was found (51). The effects of intradermal injection of various other mediators or histamine releasers are also inhibited by cetirizine (17,23,47,48,52), as is [response to a cold challenge in patients with] cold-induced urticaria (53). In mildly asthmatic subjects, ZYRTEC at 5 to 20 mg blocked bronchoconstriction due to nebulized histamine, with virtually total blockade after a 20 mg dose (24). In addition, [in studies conducted for up to 12 hours following cutaneous antigen challenge] the late phase recruitment of eosinophils, neutrophils and basophils, components of the allergic inflammatory response, [flare] inhibited by ZYRTEC at a dose of 20 mg following

cutaneous antigen challenge (54-58).

Four randomized double-blind, placebo-controlled trials were conducted in healthy subjects to assess the psychomotor/psychophysical effects (as measured by the multiple sleep latency test, simulated assembly line task, Stroop word test, and the critical flicker frequency test) of ZYRTEC versus hydroxyzine or diphenhydramine. These studies showed that ZYRTEC was generally not significantly different from placebo but was different from hydroxyzine and diphenhydramine which produced significantly decreased test performance (59-62, 103).

In four clinical studies in healthy adult males volunteers, no clinically significant mean increases in QTc were observed in ZYRTEC treated subjects (32,43,44,63). In the first study, a placebo-controlled crossover trial, ZYRTEC was given at doses up to 60 mg per day, 6 times the maximum clinical dose for 1 week, and no significant mean QTc prolongation occurred (32). In the second study (43), a crossover trial, ZYRTEC 20 mg and erythromycin (500 mg every 8 hours) were given alone and in combination. The effect of ZYRTEC 20 mg alone on QTc (Hodges corrections) was statistically estimated as a small decrease from baseline of 5.1 msec (-1.3%) after 5 days of therapy. There was no significant drug interaction effect on QTc seen with the combination of ZYRTEC 20 mg and erythromycin or with ZYRTEC alone (43). In the third trial (44), also a crossover study, ZYRTEC 20 mg and ketoconazole (400 mg per day) were given alone and/or in combination. The effect of ZYRTEC 20 mg ~~caused~~ alone on QTc was statistically estimated as a small mean increase in QTc from baseline of 8.2 msec (1.8%) ~~with~~ ~~Bazett value) after 10 days of therapy. Ketoconazole also increased QTc by about~~ ~~(Bazett value). The combination caused an increase of (the Bazett value) about equal to~~ ~~the sum of the individual effects.~~ The estimated effect of the combination on QTc change from baseline (16.1 msec) was equal to the sum of the individual component effects. Thus, there was no significant drug interaction effect on QTc with the combination of

ZYRTEC and ketoconazole. In the fourth study (63), a placebo-controlled parallel trial, ZYRTEC 20 mg was given alone or in combination with azithromycin (500 mg as a single dose on the first day followed by 250 mg once daily). Results of this trial showed There was no significant increase in QTc associated with ZYRTEC 20 mg alone or in combination with azithromycin.

In a six-week, placebo-controlled study of 186 patients with allergic rhinitis and mild to moderate asthma, ZYRTEC 10 mg QD improved rhinitis symptoms and did not alter pulmonary function. This study supports the safety of administering ZYRTEC to allergic rhinitis patients with mild to moderate asthma (101).

Clinical Studies: Eleven multicenter, randomized, double-blind, placebo-controlled clinical trials were conducted in the United States. Five studies in seasonal allergic rhinitis were conducted for up to 4 weeks in duration (64); four studies in perennial allergic rhinitis for up to 8 weeks in duration (65,66); and two studies in chronic idiopathic urticaria each for 4 weeks in duration (67). Doses of 5-20 mg per day were studied. In general, most patients were controlled on a 10 mg dose. Five (5) mg was the minimally effective dose and 20 mg did not give added effectiveness compared with 10 mg.

Nine multicenter, randomized, double-blind, clinical trials comparing cetirizine 5 or 20 mg to placebo in patients with seasonal or perennial allergic rhinitis were conducted in the United States. Five of these showed significant reductions in symptoms of allergic rhinitis. In seasonal allergic rhinitis (one to 4 weeks in duration) and 2 in perennial allergic rhinitis (for up to 8 weeks in duration). Two 4-week multicenter, randomized, double-blind, clinical trials comparing cetirizine 5 or 20 mg to placebo in patients with chronic idiopathic urticaria were also conducted and showed significant improvement in symptoms of chronic idiopathic urticaria. In general, the 10 mg dose was more effective than the 5 mg dose and the 20 mg dose gave no added effect.

INDICATIONS AND USAGE

Seasonal Allergic Rhinitis: ZYRTEC is indicated for the relief of symptoms associated with seasonal allergic rhinitis due to allergens such as ragweed, grass and tree pollens. Symptoms treated effectively include sneezing, rhinorrhea, nasal pruritus, ocular pruritus, tearing and redness of the eyes (68).

Perennial Allergic Rhinitis: ZYRTEC is indicated for the relief of symptoms associated with perennial allergic rhinitis due to allergens such as dust mites, animal dander and molds. Symptoms treated effectively include sneezing, rhinorrhea, post-nasal discharge, nasal pruritus, ocular pruritus and tearing (69).

Chronic Urticaria: ZYRTEC is indicated for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria. It significantly reduces the occurrence, severity and duration of hives and significantly reduces pruritus (70).

CONTRAINDICATIONS

ZYRTEC is contraindicated in those patients with a known hypersensitivity to it or any of its ingredients, or to its parent compound, hydroxyzine.

PRECAUTIONS

Activities Requiring Mental Alertness: In clinical trials, the occurrence of somnolence has been reported in some patients taking ZYRTEC; due caution should therefore be exercised when driving a car or operating potentially dangerous machinery. Concurrent use of ZYRTEC with alcohol or other CNS depressants should be avoided because additional reductions in alertness and additional

impairment of CNS performance may occur.

Drug-drug interactions: No clinically significant drug interactions have been found with theophylline at a low dose, ~~azithromycin~~, pseudoephedrine, ketoconazole, or erythromycin and emetidine (40,41,43-45). ~~There was a small decrease in the clearance of cetirizine caused by a 400 mg dose of theophylline; it is possible that larger doses could have a larger effect.~~ In clinical trials, there did not appear to be an increased incidence of adverse experiences in patients administered ZYRTEC and beta-agonists, non-steroidal anti-inflammatory drugs, oral contraceptives, corticosteroids, H₂-antagonists, cephalosporins, penicillins, thyroid hormones and thiazide diuretics (71).

Carcinogenesis, mutagenesis and impairment of fertility: No evidence of carcinogenicity was observed in a 2-year carcinogenicity study in rats (72) at dietary doses up to 20 mg/kg/day (15 times the recommended human dose on a mg/m²/day basis). An increased incidence of benign liver tumors was found in a 2-year carcinogenicity study in male mice (73) at a dietary dose of 16 mg/kg/day (6 times the recommended human dose on a mg/m²/day basis). The clinical significance of these findings during long-term use of ZYRTEC is not known. Cetirizine was not mutagenic in Ames test, and not clastogenic in human lymphocyte assay, mouse lymphoma assay, and in vivo micronucleus test in rats (74-77). No impairment of fertility was found in a fertility and general reproductive performance study in mice (78,79) at a dose of 64 mg/kg/day (26 times the recommended human dose on a mg/m²/day basis).

Pregnancy Category B: Cetirizine has not been shown to be ~~was not~~ teratogenic in mice, rats and rabbits at doses up to 96, 225, and 135 mg/kg/day (or 40, 180, and 216 times the recommended human dose on a mg/m²/day basis), respectively (80-82). There are no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, ZYRTEC should be used in pregnancy only if clearly needed.

Nursing Mothers: Retarded pup weight gain was found in mice during lactation (79) when dams were given cetirizine at 96 mg/kg/day (40 times the recommended human dose on a mg/m²/day basis). Studies in beagle dogs indicate that approximately 3% of the dose is excreted in milk (83). Cetirizine has been reported to be excreted in human breast milk (102; ~~Because many drugs are excreted in human milk, use of ZYRTEC in nursing mothers is not recommended.~~

Geriatric Use: The safety and efficacy of ZYRTEC has been demonstrated in patients 65 years and older (84). ~~As with the general population, clearance of ZYRTEC is reduced in proportion to creatinine clearance (35). (See CLINICAL PHARMACOLOGY section)~~

Pediatric Use: Safety and effectiveness in the pediatric population has not been established. In more than 588 children aged 6 to 11 years, ZYRTEC was administered in doses from 1.25 to 10 mg. In these studies ZYRTEC was well tolerated at doses up to 10 mg (85,86). ~~The safety of ZYRTEC in children under the age of 6 years has not yet been established. ZYRTEC is not indicated for the treatment of children under the age of 12 years.~~

ADVERSE REACTIONS

Controlled and uncontrolled clinical trials included more than 6000 patients, with more than 3900 receiving ZYRTEC at doses of 5 to 20 mg per day; the duration of treatment ranged from 1 week to 6 months, ~~with a mean of exposure of 100 days.~~ (87). In addition, there were more than 1400 ZYRTEC-treated patients in foreign clinical trials.

Most adverse reactions reported during therapy with ZYRTEC were mild or moderate (88). In placebo-controlled trials, the incidence of discontinuations due to adverse reactions in patients receiving ZYRTEC 5 mg or 10 mg was not significantly different from placebo (2.9% vs 2.4%, respectively) (89).

The most common adverse reactions that occurred more frequently on cetirizine than placebo was somnolence. ~~the recommended doses were headache and somnolence (89). The incidence of headache associated with ZYRTEC was not different from placebo (89). The incidence of somnolence associated with ZYRTEC was dose related, (90) and, predominantly, mild to moderate (88). The incidence of somnolence in fixed dose studies was 6% in placebo, 11% at 5 mg and 14% at 10 mg (90). Discontinuations due to somnolence for ZYRTEC (91) were uncommon, not significantly different from placebo (1.0% on Zyrtec vs 0.6% on placebo, respectively). In addition, Fatigue and dry mouth were also appeared to be considered treatment-related adverse reactions. There was no difference by age, race, gender or by body weight with regard to the incidence of adverse reactions (92-94).~~

Table 1 lists adverse experiences which were reported for ZYRTEC 5 and 10 mg in controlled clinical trials in the United States ~~(89)~~ and that were more common on ZYRTEC than placebo.

Table 1. Adverse Reactions Reported in Placebo-Controlled United States ZYRTEC Trials (Maximum Dose of 10mg) at Rates of $\pm$ 2% or Greater

(Percent Incidence)

Adverse Experience	ZYRTEC (N=2034)	Placebo (N=1612)
Headache	17.6%	17.9%
Somnolence	13.7	6.3
Fatigue	5.9	2.6
Dry Mouth	5.0	2.3
Nausea	2.5	2.9
Pharyngitis	2.0	1.9
Dizziness	2.0	1.2
Insomnia	1.4	1.2
Epistaxis	1.2	0.6
Coughing	1.0	0.6
Abdominal Pain	1.0	0.9
Dyspnea	0.8	1.6
Pruritus	0.7	1.2

In addition, headache and nausea occurred in more than 2% of the patients, but were more common on placebo.

The following events were observed infrequently (equal to or less than $\pm$ 2%), in 3982 patients who received ZYRTEC in U.S. trials, including an open study of six months duration (88); a causal relationship with ZYRTEC administration has not been established.

~~Application Site: application site reaction, injection site inflammation~~

Autonomic Nervous System: anorexia, urinary retention, flushing, saliva increased
~~salivation~~

Cardiovascular: palpitation, tachycardia, hypertension, ~~arrhythmia~~, cardiac failure

Central and Peripheral Nervous Systems: insomnia, paresthesia, confusion, hyperkinesia, hypertonia, migraine, tremor, vertigo, cramps legs, ataxia, dysphonia, ~~abnormal~~ coordination ~~abnormal~~, hyperesthesia, hypoesthesia, myelitis, paralysis, ptosis, ~~speech disorder~~, twitching, visual field defect

Endocrine: ~~thyroid disorder~~

Gastrointestinal: increased appetite ~~increased~~, dyspepsia, abdominal pain, diarrhea, flatulence, constipation, vomiting, ~~ulcerative stomatitis~~ ~~ulcerative~~, ~~tongue disorder~~, aggravated tooth caries ~~aggravated~~, stomatitis, tongue discoloration, tongue edema, gastritis, ~~rectum~~ hemorrhage ~~rectum~~, hemorrhoids, melena, abnormal hepatic function ~~abnormal~~

Genitourinary: polyuria, urinary tract infection, cystitis, dysuria, hematuria, ~~urine~~ ~~abnormal~~

Hearing and vestibular: earache, tinnitus, deafness, ototoxicity

Metabolic/Nutritional: thirst, ~~edema~~, ~~dehydration~~, diabetes mellitus

Musculoskeletal: myalgia, arthralgia, ~~bone disorder~~, arthrosis, ~~tendon disorder~~, arthritis,

muscle weakness

Psychiatric: insomnia, nervousness, depression, emotional lability, impaired concentration ~~impaired~~, anxiety, depersonalization, paroniria, ~~abñormal~~ thinking ~~abnormal~~, agitation, amnesia, ~~decreased~~ libido ~~decreased~~, euphoria

Resistance Mechanism: ~~healing impaired, herpes simplex, infection, infection fungal, infection viral~~

Respiratory System: epistaxis, rhinitis, coughing, ~~respiratory disorder~~, bronchospasm, dyspnea, upper respiratory tract infection, hyperventilation, sinusitis, increased sputum ~~increased~~, bronchitis, pneumonia

Reproductive: dysmenorrhea, ~~menstrual disorder~~, ~~female~~ breast pain ~~female~~, intermenstrual bleeding, leukorrhea, menorrhagia, ~~pregnancy unintended~~; vaginitis, ~~testes disorder~~

Reticuloendothelial: lymphadenopathy

Skin: pruritus, rash, ~~skin disorder~~, ~~dry~~ skin dry, urticaria, acne, dermatitis, rash erythematous, ~~increased~~ sweating ~~increased~~, alopecia, angioedema, furunculosis, bullous eruption, eczema, hyperkeratosis, hypertrichosis, photosensitivity reaction, photosensitivity toxic reaction, ~~maculo-papular~~ rash maculo-papular, seborrhea, purpura

Special Senses: taste perversion, taste loss, parosmia

Vision: ~~eye abnormality, vision abnormal~~, blindness, loss of accommodation, eye pain, conjunctivitis, xerophthalmia, glaucoma, ocular hemorrhage

Body as a Whole: increase weight ~~increase~~, back pain, malaise, ~~pain, chest pain~~, fever, asthenia, ~~generalized edema~~ ~~generalized~~, periorbital edema ~~periorbital~~, ~~peripheral edema~~ ~~peripheral~~, rigors, legs edema ~~legs~~, face edema, hot flushes, enlarged abdomen ~~enlarged~~, ~~allergic reaction~~, nasal polyp

Occasional instances of transient, reversible hepatic transaminase elevations have occurred during cetirizine therapy ~~(95)~~. There was a single report of possible drug-induced hepatitis with significant transaminase elevation (500 to 1000 IU/L) and elevated bilirubin.

In foreign marketing experience the following additional rare, but potential severe adverse events have been reported: hemolytic anemia, thrombocytopenia, orofacial dyskinesia, severe hypotension, anaphylaxis, hepatitis, glomerulonephritis, stillbirth, and cholestasis ~~(96)~~.

~~In a six-week, placebo-controlled study of 186 patients with allergic rhinitis and mild to moderate asthma, ZYRTEC 10 mg QD improved rhinitis symptoms and did not alter pulmonary function. This study supports the safety of administering ZYRTEC to allergic rhinitis patients with mild to moderate asthma (101).~~

DRUG ABUSE AND DEPENDENCE

There is no information to indicate that abuse or dependency occurs with ZYRTEC.

OVERDOSAGE

Overdosage has been reported with ZYRTEC. In one patient who took 150 mg of ZYRTEC, the patient was somnolent but did not display any other signs or abnormal blood chemistry or hematology results⁽⁹⁷⁾. Should overdose occur, treatment should be symptomatic or supportive, taking into account any concomitantly ingested medications. There is no known specific antidote to ZYRTEC. ZYRTEC is not effectively removed by dialysis, and dialysis will be ineffective unless a dialyzable agent has been concomitantly ingested⁽³⁷⁾. The minimal lethal oral dose in rodents is approximately 100 times the maximum recommended clinical dose on a mg/m² basis and the liver was the target organ of toxicity⁽⁹⁸⁾.

DOSAGE AND ADMINISTRATION

The recommended initial dose of ZYRTEC is 5 or 10 mg, depending on symptom severity. Most patients in clinical trials started at 10 mg⁽⁹⁹⁾. ZYRTEC is given as a single daily dose, with or without food. The time of administration may be varied to suit individual patient needs.

In patients with decreased renal function (creatinine clearance 11-31 mL/min), patients on hemodialysis (creatinine clearance less than 7 mL/min), and in hepatically impaired patients, a dose of 5 mg QD is recommended.

HOW SUPPLIED:

ZYRTEC tablets are white (dye free), film coated, rounded-off rectangular shaped containing 5 mg or 10 mg cetirizine hydrochloride.

5 mg tablets are engraved with "PFIZER" on one side and with "550" on the other. Bottles of 100: (NDC 0069-5500-66)

10 mg tablets are engraved with "PFIZER" on one side and with "551" on the other. Bottles of 100: (NDC 0069-5510-66)

Cetirizine is licensed from UCB, Pharma Inc.

STORAGE: Store at room temperature 59° to 86°F (15° - 30°C).

II. Reviewer's comments and regulatory recommendations

The medical reviewer has views and concerns that differ from those reflected in the revised labeling dated September 29, 1995. The MO draft review of the labeling dated September 12, 1995 may not have portrayed these issues adequately. The following comments are included to clarify these issues.

1. Electrocardiographic effect.

Reference is made to the MOR dated 2/27/1994 that reviewed cetirizine's electrocardiographic effect on QTc. In the review of this safety update submission that includes the results of the analysis of the PEDS-4 electrocardiographic data and the cetirizine -azithromycin study, a consistent statistical significant change in mean QTc over baseline is not demonstrated. However, there are a number of other indicators that support that cetirizine can prolong the QTc alone and in combination with ketoconazole. These are: individual patient data in SAR-8, SARA/LORA, 90CK16-0497, and 92CK16-0603; PEDS-4 (11-17 day group analysis); increase in frequency of >10% prolongation in patients receiving the combination in the cetirizine-ketoconazole study, and to a lesser extent in the cetirizine-erythromycin study.

In the other side of the spectrum, we have a case reported spontaneously of a patient that developed torsades de pointes, received on 4/22/93. A 73 y/o female that had a history of supraventricular tachycardia was placed on dysopyramide. She had a documented history of QT interval prolongation post-disopyramide. For allergic symptoms, the patient was placed on 10 mg cetirizine daily for 13 days. For symptoms of fever and viral illness she was placed on lysinesprin, paracetamol and josamycin, 2 days prior to the event. The case was evaluated by Dr. Woosley and we concurred with him that torsades was most likely due to dysopyramide, perhaps precipitated by hypokalemia. However, it is not clear what is potential role that the addition of 10 mg cetirizine may have to produce torsades when it is added to a multidrug regimen in a patient treated with antiarrhythmics that produce slow repolarization, in a situation where electrolyte control is not closely monitored.

Cetirizine is indicated for the treatment of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria. It would be marketed to a very wide section of the population, by for the most part primary care physicians that will not consider the current revised labeling of the

drug to indicate that there could be any problems for this "allergy" drug, that they may need to be concerned about. However, there are indications, that there could be, given the common use of multidrug therapy for whom physicians may consider that this drug would be a safe, very low risk choice.

Unless the drug labeling provides a distinct and clear warning of the drug's potential to prolong the QTc in susceptible patients at recommended doses, i.e. black box, the medical reviewer recommends the non approval of the drug based on the drug's electrocardiographic effects.

2. Liver transaminase elevations

Reference is made to the sponsor's response to question 6.c. of the NDA approvable letter, in Section 1 of this review and to the individual patient data provided in that section:

"Mean changes in laboratory results for patients treated with cetirizine and placebo in placebo controlled studies were analyzed and are shown in Table 22.A. There were statistically significant differences between treatment groups for change from baseline in SGOT, SGPT, and creatinine. The mean change for SGOT was 0.84 U/L for the cetirizine group compared to -0.05 U/L for placebo ($p < 0.02$). The mean change for the SGPT from baseline for the cetirizine treatment group was 1.35 U/L compared to -0.19 U/L for placebo ($p < 0.001$). The creatinine mean change from baseline was 0 for creatinine treated patients and 0.13 mg/dl for placebo treated patients."

According to the sponsor's Table 22.A (cumulative database), these mean changes from baseline represent the following mean percent changes from baseline:

N	Cetirizine	N	Placebo
2488	SGOT=11.64%	1511	SGOT=5.96%
2421	SGPT=15.6%	1451	SGPT=6.85%
2500	T.bili=6.9%	1527	T.bili=6.8%
2497	creatinine=1.84%	1523	creatinine=2.85%
2423	BUN=3.80%	1448	BUN=4.53%

Table 22.B summarizes the changes in laboratory results by dose as found in the NDA versus the cumulative database. When the cumulative database is compared to the NDA database, in the cumulative database the mean percent changes from baseline decreased for SGOT and SGPT for the 5 and 10 mg dose but not for the 20 mg dose where the mean percent change from baseline increased or stayed the same.

Table 22.E summarizes the changes in laboratory results by race as found in the NDA versus the cumulative database. Although the numbers for non-white patients are small compared to the white patient population in the cumulative database, for SGPT, the mean percent change from baseline in the cumulative database is larger for blacks, 17% (N=228) and "others", 17.5% (N=109) versus 14.8% in the white population (N=2546). In addition, the mean percent change from baseline in SGPT in black patients increased from 12.7% to 17% from the NDA to the cumulative database, which was opposite to the decrease in the other two groups; twice the number of patients were studied in the cumulative database

versus the NDA database.

"Evaluation of the incidence of abnormal liver function tests in patients with normal baseline tests in placebo-controlled studies show that cetirizine is associated with elevations in SGOT and SGPT but not total bilirubin or alkaline phosphatase. Abnormalities are generally less than twice the upper limit of normal. The incidence of abnormal SGOT and SGPT more than twice the upper limit of normal appear to be similar in cetirizine and placebo-treated patients." (SU 4/25/95, vol 32, 9 60).

The above data needs to be interpreted in terms of the mean duration of exposure (30.1 days-cumulative database) and the populations studied. If the decision is made to approve this drug, the revised labeling should reflect the fact that no placebo controlled studies have been conducted beyond eight weeks and that there may be individuals that may be more susceptible to these effects (if not populations). In addition, the incidence of these elevations should be included. A Phase IV commitment from the sponsor should be obtained to study these effects particularly in the non-white populations on a long term basis, i.e. 3-6 months.

3. Comparison of human PK of cetirizine's enantiomers following treatment with hydroxyzine to human PK data following treatment with cetirizine tablet.

We refer to our request to the sponsor in item 16 of cetirizine's approvable letter dated 2/21/95. In that request we asked which enantiomer form of cetirizine is formed when hydroxyzine is given to humans. In their response (BZ 5/15/95) the sponsor reported that this data was not available.

Hydroxyzine is reported to be a racemic mixture (USP-23, 1995). According to its chemical structure it would be assumed that its chiral center would be maintained, and that most likely a mixture of the two enantiomers of cetirizine would be formed in humans (no data is available). However, even if the two enantiomers are formed, we have no data as to whether there would be the same or a different ratio of exposure to the enantiomers in patients following treatment with hydroxyzine than when cetirizine is given.

The data from two clinical sponsored studies (4/25/95 101 and 102) suggest that for the same route and dose there are statistical and clinical significant differences between the two enantiomers in the inhibition of the cutaneous histamine challenge as well as the in the response to nasal histamine challenge in normal volunteers.

Reference is made to the Pharm-Tox Ammedment Review dated

10/11/95. In rats the liver is the primary target of treatment effects. The systemic exposure to the (-) enantiomer, 28557 is considerably less than to the (+) enantiomer, 28556. In the four week studies, the toxic effects were similar for the two enantiomers but the degree of toxicity was greater for 28556 than for 28557. Effects were more marked in males than in females. Systemic exposure was similar in males and females but renal excretion was substantially greater in females. In dogs there is no liver toxicity.

The sponsor has maintained that adequate data has been submitted to support the use of cetirizine at the recommended doses and that its safety profile should stand by itself without making a reference to hydroxyzine. However, particularly in terms of evaluation of safety after long term exposure (>12 weeks-33 weeks) to cetirizine the available data is minimal (around 200 patients). There are no placebo controlled studies of more than 8 weeks in duration in the cumulative database.

The fact that we do not know if the PK profile of the cetirizine enantiomers in patients receiving hydroxyzine is the same as in the patients receiving cetirizine, puts in question the rationale for using the long term safety profile of hydroxyzine to base safety decisions for cetirizine.

With the limited long term safety data available on cetirizine, if the long term safety data for hydroxyzine is going to be use in its place, this reviewer recommends that the sponsor should provide a comparison of the data of human PK on cetirizine's enantiomers after oral dosing with hydroxyzine and cetirizine prior to making a decision in favor of the drug's approval.

4. Incidence of reported adverse events.

The medical reviewer recommended that for the adverse event table in the revised labeling events at the 1% level would be reported. The following were the main reasons for this recommendation: Reference is made to MO review dated 2/23/94. In the majority of placebo controlled studies conducted in the US, the record of adverse experiences that was reported to the sponsor came from the report of the patients to the investigators and not from the daily records in diary cards. This method could have underestimated the frequency of these events. In addition, and to a lesser extend the fact that intercurrent illnesses were tabulated and kept as a separate database and they are not reported in the labeling, could also make the adverse event data in the table look better than it would be. If the decision is made

to approve the drug, then it would be appropriate to include in the labeling how the adverse event data was derived for the majority of patients in the database as well as a description of the most common intercurrent illnesses and their reported incidence in placebo controlled studies.

CC: Original NDA-19835

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Medical Officer Review

NDA 19835

Drug: Cetirizine tablets (Zyrtec)

Sponsor: Pfizer

Date: October 17, 1995

Subject: Response to the NDA approvable letter dated February 21, 1995 and proposed physician package insert included in the SU dated 4/25/95

Medical Officer Reviewer: Ana M. Saavedra-Delgado, M.D.

Correspondence:

A. Saavedra-Delgado MD
10/17/95

The medical officer has completed the review of material included in the following correspondence.

- SU 4/25/95 Final Safety Update, volumes 1-30
Includes response to questions 1-11 of the
cetirizine approvable letter of 2/21/95
- BZ 5/12/95 Response to items 15-22 of the 2/21/95
approvable letter
- C 5/25/95 Response to items 1 and 3 of FDA facsimile
dated 5/11/95
- N(BM) 6/7/95 Response to item 2 of FDA facsimile
dated 5/11/95
- N(BM) 6/14/95 Report of 2 deaths in a foreign
clinical study
- N(BM) 6/20/95 Additional data in response to item 2
of FDA facsimile dated 5/11/95
- N(BM) 6/29/95 Case report forms of patients
reported in correspondence dated 6/14/95
- N(BM) 7/17/95 Response to information requested in
teleconference with FDA dated 7/6/95
- C 8/8/95 Response to FDA facsimile dated
7/20/95
- BZ 8/11/95 Response to information requested in
FDA facsimile dated 8/4/95
- N BL, SU, BM 8/18/95 Draft physician package insert

labeling incorporating the pediatric data and Study Report of No. A 132 (RRCE92L2503)-Efficacy and safety in children and adolescents with asthma. The medical officer has completed the review of the draft physician package insert included in this correspondence as it refers to the tablet.

N (BM) 8/11/95 Case Report Forms and patient identifiers requested in FDA facsimile dated 8/1/95

Response to consult by Epidemiology on ketoconazole and hydroxyzine dated 6/23/95

C 9/12/95 Response to FDA facsimile dated 8/25/95.

Outline and Table of Contents of this review:

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- II. Reviewer's general comments and regulatory recommendations.

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Memo

From: Ana M. Saavedra-Delgado, M.D.

To: Marty Himmel, M.D.

Subject: Proposed amendment to the revised labeling for NDA
19835 drafted in the 9/21/95 "in-house" meeting

Date: September 27, 1995

Ana Saavedra-Delgado
9/27/95

*Noted.
in 9/28/95*

"Following cutaneous antigen challenge, the late phase recruitment of eosinophils, neutrophils and basophils, components of the allergic inflammatory response, is inhibited by Zyrtec."

The following change is proposed:

"In studies conducted for up to twelve hours following cutaneous antigen challenge, the late phase recruitment of eosinophils, neutrophils and basophils, is inhibited by Zyrtec."

The references for the sponsor's statement are attached. Only the summary for studies CP-18, CP19 and CP20 were readily available. Copies of the two referenced literature articles, #57 and #58 are attached. In addition, the reviewer references study 104, that was submitted in the 4/25/95 submission in vol 18.

The summary report of study CP-18 appears to be the same study described in reference #57: J Allergy Clin Immunol:83(5):905-912, 1989.

The two published articles by the Baltimore group use the same skin chamber technique. In both studies 20 mg of cetirizine was used; in #57 for 2 days and in #58 for 3 days and they both had placebo controls. In #57 the cell infiltration was studied for up to 8 hrs and in study #58 for up to 12 hours. Statistical significant reduction of eosinophil and neutrophil infiltration was achieved for the pooled results of hours 6-8 in study #57. At 8 hours there was significant reduction in neutrophil and eosinophil infiltration. The results in basophils followed the same trend but perhaps due to small numbers they were not statistically significant.

In study #58 the group extends the observation for up to 12 hours and other two antihistamines are studied. In this study the statistical significant changes on cell infiltration are observed at 10-12 hrs for eosinophils and basophils and 8-12 hours for neutrophils.

In study #58, wheal and flare were measured at hourly intervals for up to 12 hours and cetirizine significantly inhibited the immediate reaction to cutaneous antigen challenge (up to 3 hours) but did not alter the late phase cutaneous reactivity as measured by wheal and flare (4-12 hours).

Study 104 studied cetirizine 15 mg bid for 4.5 days in a cross-over design comparing it to prednisolone 20 mg for 4.5 days and placebo. The investigators attempted to use the skin window technique but was not effective. Skin biopsy at 6 and 24 hours were obtained. Biopsies were read blindly. No statistical significant effect was noted with cetirizine in terms of the number of eosinophils or neutrophils at 6 or 24 hours compared to placebo. Prednisolone significantly inhibited the number of eosinophils compared to placebo in the skin biopsies. Neutrophils were also reduced but the difference was not statistically significant.

In summary, the above results do support Zyrtec's inhibition of cellular infiltration at the skin following cutaneous antigen challenges of eosinophils, neutrophils and basophils in studies conducted up to 12 hours post antigen challenge. However, even though the cellular infiltration is inhibited, the cutaneous manifestation of late phase reactivity, i.e. wheal and flare, does not appear to be inhibited.

The elimination of the phrase "component of allergic inflammatory response" is proposed because even though these cell types indeed are component of the inflammatory response, for the reader, the statement could imply that cetirizine inhibits this response.

This study showed that cetirizine administered prophylactically significantly reduced the degree of allergic nasal reaction induced by specific allergen contact.

c. Effects on Mediator Release and Eosinophil Migration (CP-18 to CP-20)

CP-18

Study CP-18 evaluated the effect of cetirizine on mast cell mediator release and cellular migration during the cutaneous late phase. Ten atopic subjects who had been previously shown to have a cutaneous late phase response to ragweed extract were entered in the study. Subjects were given either cetirizine 20 mg or placebo once each morning for 3 consecutive days in a crossover design with a 7 day washout period between treatment periods. Heat/suction-induced blisters were created, aseptically unroofed and sterile chambers were placed over the unroofed blisters and taped in place. Ragweed extract was added into one chamber and an equal amount of Ringer's lactate and heparin was placed into the control chamber. Blister fluid from the chambers was removed hourly for 8 hours and the supernatant saved for measurement of histamine and prostaglandin D₂ (PGD₂). The cell pellet was resuspended and the cells were stained with a modified Wright-Giemsa stain and the total number were determined. A competitive radioimmunoassay was used to measure PGD₂ and a radioenzymatic assay was used to measure histamine concentrations. Each subject was skin tested with ragweed and the surface area of erythema was calculated at 2, 4, 6 and 8 hours.

Cetirizine significantly reduced the erythematous response to antigen challenge compared with placebo for at least 4 hours and the difference approached significance (p less than 0.06) at 6 hours. Histamine release peaked at hour 1 and fell thereafter until it reached control levels at 5 hours. Cetirizine did not significantly inhibit the release of histamine compared with placebo at any time point. In contrast, cetirizine significantly reduced the release of newly synthesized PGD₂ at every time point from 1 to 8 hours.

Cetirizine also had a significant effect on the infiltration of eosinophils into the skin chamber after antigen challenge. The increase in eosinophils in placebo-treated patients began at 6 hours and continued until the end of the experiment (8 hours). Cetirizine significantly decreased eosinophil infiltration at hours 6, 7 and 8 (by 65-83%) when increased numbers were seen in the placebo group. Neutrophils were significantly decreased at 8 hours and basophils were decreased but not significantly because of small numbers.

This study showed that cetirizine induced a significant reduction in both the inflammatory cell infiltrate (eosinophils) and PGD₂ production during the late phase in atopic patients.

CP-19

Study CP-19 evaluated the inhibitory effect of cetirizine on the migration of eosinophils and neutrophils in the skin induced by an antigen challenge in allergic subjects. A randomized, double-blind, pilot study measuring cutaneous and leukocyte

responses to skin test challenges was performed in eight healthy and eight grass-pollen allergic subjects. Responses to the skin test challenges without drug administration were assessed, followed one week later by a second set of challenges performed four hours after administration of a single oral dose of cetirizine 10 mg or placebo.

The agents used for the challenge were histamine, compound 48/80, methacholine and, in the allergic subjects, grass pollen. Twenty minutes after injection of the reagents, the diameters of skin wheals and erythemas were measured, after which epithelial layers at the injection sites were scraped away and the abraded area was rinsed with saline solution and covered for 24 hours with a coverslip. Following removal and staining of the coverslips, cells were counted by blinded, qualified investigators to a total of 400 cells per coverslip, and results were expressed in percentages of types of cells per total number.

The cutaneous reactions induced in the healthy subjects were inhibited by the test drug by 19 to 50% in the median diameters of skin wheals and by 47 to 100% in the median diameters of erythemas. Except for the methacholine-induced erythema, none of these inhibitions were statistically significant. In contrast, in the allergic subjects, cetirizine inhibited all reactions, including those of pollen-induced reactions, significantly better than placebo.

The skin tests induced no recruiting of eosinophils in the healthy subjects, and only a small recruitment of neutrophils was induced by compound 48/80 but not by the other two reagents. Administration of cetirizine brought no change in these migrations.

In the allergic subjects, eosinophils were recruited to some degree by compound 48/80 and histamine, and, to a considerable degree, by grass pollen. Treatment with cetirizine 10 mg significantly (p less than 0.05) inhibited the migration of eosinophils following the grass pollen challenge in the allergic patients, reducing the number observed by 60%. Histamine-induced migration was not affected, and that brought on by compound 48/80 was only slightly inhibited. Treatment with cetirizine had little effect on the migration of neutrophils or monocytes.

Results from the first part of the study led to a second study in which cutaneous and leukocyte responses to skin test challenges with and without prior administration of cetirizine were observed in 10 healthy and 10 grass-pollen allergic subjects. In this second study, methacholine was not a test agent and histamine was injected in three different amounts per site — 0.1, 1.0 and 10 mcg per 100 mcl. Cetirizine or placebo tablets were administered once a day for four days in a randomized, crossover fashion prior to the skin tests, which were performed four hours after the last dose. At least one week elapsed between the first nondrug skin tests and those following treatment. Cell counts were determined as described above.

Cutaneous reactions in the healthy subjects were inhibited by cetirizine by from 41 to 68% in skin wheal diameters and from 83 to 95% in erythema diameters. Similar inhibition was observed in the allergic patients' cutaneous reactions to test reagents and grass pollen following treatment.

In healthy subjects, none of the reagents except 48/80 produced recruitment of eosinophils and neutrophils. In atopic patients, cetirizine significantly inhibited the migration of eosinophils following 48/80 (-53%) and grass pollen challenge (-62%).

In conclusion, cetirizine produced an inhibitory effect on the migration of eosinophils induced by skin test challenges with compound 48/80 and grass pollen.

CP-20

Study CP-20 evaluated the effect of cetirizine on the release of mediators of allergy and on cellular migration during a cutaneous allergic challenge in pollen-sensitive subjects. This study consisted of three parts. In part one, four healthy male volunteers were given cetirizine 20 mg, and four hours later blood sampling was performed by conventional methods. A suction blister technique was performed 6.25 hours after cetirizine dosing and a second conventional blood sampling was obtained at this time. After a 7-day washout period, the subjects were given hydroxyzine 50 mg and the same series of blood sampling and suction blister procedures were performed. Drug concentrations in plasma and in blister fluid were measured and compared.

At 6.25 hours following administration of cetirizine 20 mg, cetirizine concentration in blister fluid (112 ng/ml) was about half that in plasma (246 ng/ml). Cetirizine levels at 8 hours following hydroxyzine 50 mg in blister fluid (99 ng/ml) and in plasma (188 ng/ml) were comparable to those found after cetirizine 20 mg. Hydroxyzine levels were much lower.

In part two, six suction blisters were created in two healthy volunteers. The tops of the blisters were excised, allowing placement of six 0.5 cm windows. Sterile migration chambers were glued on the cutaneous windows.

One ml of autologous serum containing six increasing concentrations of cetirizine (0, 0.1, 0.5, 1.0, 10 and 50 mcg/ml) was introduced into each of the chambers. The medium of each chamber was renewed with 1 ml fresh medium after 2, 6 and 8 hours, and was collected after 24 hours. Each collected medium was analyzed for inflammatory cells. Chambers were removed, Rebeck windows applied and percentage of inflammatory cells determined following Giemsa staining of the topical impression.

Cetirizine added locally in concentrations ranging from 0.1 to 10 mcg/ml had no effect on the migration of polymorphonuclear leukocytes induced by autologous serum. In one subject 50 mcg/ml cetirizine induced a decrease in such cellular migration, while in the other no change occurred. This study showed that recruitment of inflammatory cells was not modified by local addition of cetirizine up to the concentration of 50 mcg/ml.

In part three, six pollen-allergic patients were given cetirizine 10 mg and placebo once a day (at night) for 4 days in a randomized, double-blind, crossover study. Suction blisters were produced in each patient on day 3. On day 4, the blister fluid was taken and cetirizine levels were determined. The migration chambers were placed on the blisters on day 4 and histamine, compound 48/80 and pollen were added to the chamber. On day 5, 24 hours after cutaneous challenge (12 hours after last dose of study drug), the chambers were removed and a Rebeck window applied. Determination of inflammatory cells in the superficial dermis was accomplished hourly for 6 hours using the Rebeck window technique. Also on day 5, skin wheals and erythemas were induced, measured and compared.

Treatment with cetirizine 10 mg significantly (p less than 0.05) inhibited induced skin wheals from 55 to 76 percent of control values, and erythemas from 84 to 90 percent. Release of endogenous histamine was observed 30 minutes after adding pollen to the migration chambers. This increase was significantly, though moderately (-18 to -21%) inhibited by cetirizine 10 mg. There were no significant effects at 6 to 24 hours after challenge with pollen. The amount of prostaglandin D2 following challenge with 48/80, histamine or Hanks medium was markedly lower after drug administration at 30 minutes and 6 hours after challenge with mediators. Migration of eosinophils was significantly increased in a dose dependent manner following challenge with two different concentrations of pollen. Treatment with cetirizine significantly inhibited the recruitment of eosinophils following pollen challenge.

d. Effects on Central Nervous System (CP-21 to CP-29)

CP-21

Study CP-21 evaluated the effects of cetirizine on objective measures of daytime sleepiness and performance. Sixty healthy subjects (59 men, 1 woman) were randomly assigned to one of 5 parallel groups and 59 were efficacy evaluable. Subjects received a single oral dose of either cetirizine 5 (N=13), 10 (N=13) or 20 mg (N=10), hydroxyzine 25 mg (N=12), or placebo (N=11). Treatment was administered double-blind at 7:30 a.m. All subjects slept in the laboratory the night preceding the test. Multiple Sleep Latency Tests (MSLTs), in which subjects were given opportunities to fall asleep in bed in a light and sound-proof room while EEG and eye movements were recorded, were given every 2 hours throughout the day. A 30-minute vigilance test was given at 10:00 a.m. and 4:00 p.m. to test reaction time. Subjects also rated their feeling of impairment on a number of linear scales before each MSLT. All reported adverse experiences were recorded.

Cetirizine at doses of 5-20 mg did not produce any significant reduction in sleep latency compared with placebo in any of the objective or subjective measures of daytime alertness, whereas hydroxyzine 25 mg caused a significant increase in sleep latency as measured by MSLT and the vigilance test. In the MSLT, the primary objective measure of daytime alertness, hydroxyzine-treated subjects, at 2 and 4 hours post dose, were significantly sleepier than the placebo controls. In contrast, none of the cetirizine groups were significantly different than placebo in the MSLT. In the vigilance test, at 2.5 hours post dose, only hydroxyzine-treated subjects had significantly slower central vision reaction times than controls. Subjective self-ratings of impairment did not show significant effects attributable to active treatment.

Results of this study demonstrate that cetirizine, at doses of 5, 10 and 20 mg, did not produce objectively measured daytime sedation or performance impairment compared with placebo, whereas hydroxyzine 25 mg produced significantly diminished alertness in both these measures.

CP-22

Study CP-22 evaluated the relative antihistaminic and psychomotor effects of hydroxyzine and cetirizine. Twelve atopic male subjects received single doses of

Effect of cetirizine on mast cell-mediator release and cellular traffic during the cutaneous late-phase reaction

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A new H₁ antihistamine, cetirizine, was studied to determine its effects on mediators and cellular infiltration during the cutaneous late-phase response (LPR). Ten ragweed-allergic subjects, who had previously demonstrated a cutaneous LPR, were examined in a double-blind, crossover study. Either cetirizine, 20 mg, or placebo was administered orally once daily for 2 days before and the morning of placement of a skin chamber overlying an unroofed heat/suction-induced blister to which was added antigen or buffer. Skin test erythema was significantly reduced by cetirizine at 15 minutes, 2 hours, and 4 hours by 56%, 40%, and 39%, respectively (all, $p \leq 0.01$), but by 6 and at 8 hours, the cutaneous erythema was not significantly lessened. Histamine release was not altered by cetirizine treatment, but prostaglandin D₂ (PGD₂) production, which peaked at 3 to 5 hours, was clearly reduced by cetirizine treatment, being lower at all time points during the reaction; this was significant by analysis of variance ($p \leq 0.04$). The inhibition was most marked during the fifth hour of the reaction when there was a 50% suppression of the PGD₂ level by cetirizine (0.193 ng/ml to 0.075 ng/ml [$p \leq 0.03$]). The most dramatic effect of cetirizine was attenuation of the inflammatory cell migration into the chamber. Eosinophil infiltration was decreased by about 75% during hours 6, 7, and 8 ($p \leq 0.04$), whereas the number of neutrophils was reduced by the same magnitude at the same times ($p \leq 0.04$). Basophils appeared to enter the chamber together with the eosinophils and were decreased by 64% during hours 6 through 8, but not significantly due to small numbers. We conclude that cetirizine influences the pathogenesis of the LPR by causing a significant reduction in both the inflammatory cell infiltrate and PGD₂ production. These effects apparently are not related to its anti-H₁ activity. (J ALLERGY CLIN IMMUNOL 1989;83:905-12.)

Cetirizine, a new H₁ antagonist, is the major human metabolite of hydroxyzine, being formed by oxidation of the primary alcoholic side chain to a carboxylic acid moiety.¹ Hydroxyzine is widely and preferentially

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Abbreviations used

Ag:	Antigen
LPR:	Late-phase response
LTB ₄ :	Leukotriene B ₄
OCD:	Optimal challenge dose
PGD ₂ :	Prostaglandin D ₂
PNU:	Protein nitrogen unit
RW:	Ragweed
RLH:	Ringer's lactate with 250 µg/ml of heparin

used to treat skin disorders, allergic and inflammatory.² It has been demonstrated to be somewhat more effective than other H₁ antagonists in these conditions, although the mechanism of this increased efficacy has not been identified.³ Ting et al.⁴ reported that the parent antihistamine, hydroxyzine, inhibits the release of histamine from human skin mast cells in vivo, whereas Juhlin et al.⁵ reported that cetirizine signifi-

TABLE I. Individual skin test reactivity tabulated with the corresponding OCD and the final amount of antigen that was placed into the skin

Subject	OCD (PNU)	Skin test (wheal times erythema) (mm)	Challenge dose (PNU)
1	100	15 × 57	1000
2	100	18 × 66	1000
3	100	16 × 65	1000
4	100	15 × 40	1000
5	100	16 × 44	1000
6	100	14 × 62	1000
7	10	16 × 45	100
8	100	13 × 53	1000
9	100	22 × 62	1000
10	10	20 × 62	100

cantly decreases the wheal-and-flare reaction in patients with idiopathic and cold urticaria induced by several stimuli, including histamine and 48/80. More interesting was the observation by Fadel et al.⁶ that cetirizine blocks the migration of eosinophils onto a skin window 24 hours after Ag challenge, a phenomenon not explained by H₁ blockade.

To assess further whether cetirizine has activities other than histamine antagonism, we used a skin-chamber model to study the effects of cetirizine in a double-blinded Ag challenge study. The parameters observed were visible skin test responses, the appearance of preformed (histamine) and newly generated (PGD₂) mast cell mediators, and the appearance of eosinophils and neutrophils over time after Ag challenge. We observed that cetirizine had effects apparently unrelated to its histamine antagonism. These included inhibition of the production of the cyclooxygenase product, PGD₂, and a decrease in the number of inflammatory cells that attend the late-phase reaction.

MATERIAL AND METHODS

Ten atopic subjects (six male and four female subjects), 18 to 45 years of age (median age, 29), were studied. They gave written informed consent and previously had demonstrated a cutaneous LPR to RW extract. Intradermal skin tests with RW extract (saline diluent with 0.03% human albumin, Hollister-Stier Laboratories, Spokane, Wash.) in concentrations ranging from 0.1 PNU/ml to 1000 PNU/ml were used to define the OCD as the concentration of Ag required to produce a 4+ cutaneous reaction, i.e., a wheal with a diameter >10 mm with pseudopods or >15 mm without pseudopods, and having >45 mm of erythema (Table I). Cutaneous erythema was also measured at 15

minutes, and 2, 4, 6, and 8 hours. At the time of the study, all subjects were out of the pollen season that caused their symptoms.

Study design

Subjects received either 20 mg of cetirizine or placebo each morning for 3 consecutive days in a randomized, cross-over design. There was a 7-day washout period between the initial treatment and the crossover. On the second day of treatment, a blister was created on the volar forearm by placing a hollow plate heated to 40° C over the precleaned skin. Continuous suction (60 mm Hg) was applied for 45 to 60 minutes until a complete 5 mm blister was formed. All blisters were formed 12 hours before skin-chamber placement to allow any inflammatory mediators related to trauma to return to baseline.

Skin-chamber collections

On the morning of the third dose of study medication, the blisters formed 12 hours previously were aseptically unroofed. Sterile aluminum chambers, with entry and exit ports, were placed over the unroofed blister and taped in place. A cutaneous adhesive (Skin-Bond, Largo, Fla.) was used to secure an adequate seal with the skin. Five hundred microliters of RW extract in RLH, representing 10 times the OCD, were placed into the chamber, and an equal amount of RLH alone was placed into the control chamber. The chamber contents were removed hourly for 8 hours and replaced with 500 µl of RLH. The chamber fluid from each sample was spun at 1000 rpm in microcentrifuge tubes for 2 minutes, and the supernatant was saved for measurement of PGD₂ and histamine. The pellet was resuspended in 500 µl of RLH and gently agitated, after which 10 µl was placed on a Neubauer hemocytometer (American Optical, Buffalo, N. Y.) for counting.

Cell counts

Cell counts were done on at least 100 nucleated cells in nine large squares. The cell suspension was then placed in a Cytospin centrifuge (Shandon Southern Instruments, Inc., Sewichley, Pa.) and spun at 600 rpm for 6 minutes. Paired slides were stained with Diff-Quick (American Scientific Products, McGraw Park, Ill.), a modified Wright-Giemsa stain, and 0.5% alcian blue (pH, 1.0) for 60 minutes. After rinsing with distilled water, slides were counter stained with 0.1% safranin in 1% acetic acid. For Wright-Giemsa stained cells, 200 to 300 cells were counted. For alcian blue-stained cells, either the total number of cells on the slide or 1000 cells were counted.⁷ All cell counts reported represent the net influx of cells into the Ag-challenged chamber. The absolute number of cells in the control chamber was subtracted from the number of cells in the Ag-challenged chamber for each respective time point that was examined.

Measurement of mediators

For measurement of PGD₂, 200 µl of blister fluid was precipitated immediately after collection in 1600 µl of high-

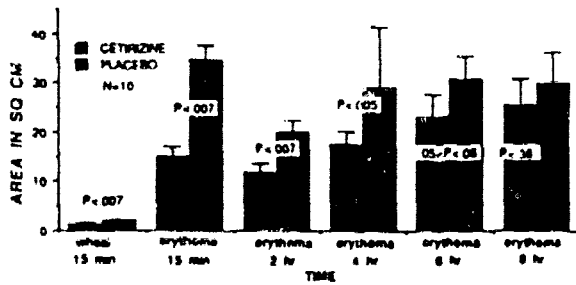


FIG. 1. Skin test response to 0.02 ml of RW Ag at the doses equal to the previously determined OCD. The results are expressed as the mean area in square centimeters ($\pm$ SE).

performance liquid chromatography-grade ethyl alcohol. The tubes were centrifuged at 5000 rpm for 5 minutes, and the supernatants that contained the prostanoids were transferred to separate tubes to be evaporated in an evaporating centrifuge for 3 hours. The specimens were then stored at -70° C. The specimens from each subject at the cetirizine and placebo visits were assayed for PGD₂ in parallel. A competitive radioimmunoassay with a sensitivity of 40 pg/ml, as described previously, was used for PGD₂ measurements.¹⁴

Raw blister fluid and the hourly chamber collections for histamine assay were frozen immediately after removal of the cells and stored at -70° C. The histamine levels from the subjects at the drug and placebo visits were also assayed in parallel with a previously described radioenzymatic assay with a sensitivity of 0.10 ng/ml. This radioenzymatic assay is based on the conversion of histamine to [³H]-methylhistamine in the presence of histamine-N-methyltransferase and [³H]-S-adenosyl-L-methionine.¹⁶

As with the cell counts, all values reported for both histamine and PGD₂ represent the mediator production with the control value being subtracted from the respective Ag for each of the time points.

Skin testing

Simultaneous with the introduction of RW Ag into the skin chamber, each subject was skin tested with 0.02 ml of the RW concentration that had previously been determined to cause a +4 reaction followed by a cutaneous LPR. The surface area of erythema was calculated at 2, 4, 6, and 8 hours with a composite diameter derived by averaging the long and short axis of cutaneous erythema. The opposite arm was consistently used for placing both skin tests and introducing Ag into the chamber during the subsequent visit to avoid interference induced by a local refractoriness.

Statistical analysis

Nonparametric analysis was used for comparison of drug versus placebo parameters, since they did not necessarily follow a Gaussian distribution. The Wilcoxon signed-rank test was applied between the paired visits with the Statview program (Brainpower, Inc., Calebasas, Calif.). A z value

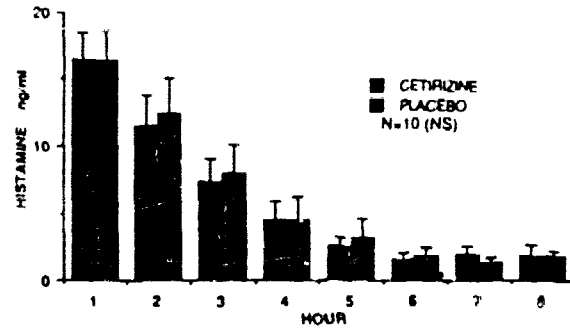


FIG. 2. Hourly histamine levels in skin chamber fluids after initial placement of 10 times the OCD of RW Ag in the chambers for 60 minutes. The results are expressed as mean nanograms per milliliter ($\pm$ SE).

was determined and the two-tailed probability was obtained from a table of probabilities.

RESULTS

The erythema was significantly less in patients treated with cetirizine at 15 minutes and for at least 4 hours thereafter, although the magnitude of the difference between placebo- and cetirizine-treated patients decreased from 60% to <40% during this time (Fig. 1). The wheal was also inhibited during the acute reaction by about 30%. The induration at later times was difficult to quantify and was not measured. Our subjective impression, however, was that the induration was decreased by the antihistamine with a time course similar to that observed with respect to erythema.

The time course of histamine release observed during the 8 hours after Ag challenge was similar to that described previously and did not differ whether the patients were receiving placebo or drug (Fig. 2).¹⁴ In five of the study subjects, enough raw blister fluid could be collected to be measured for histamine with the average being 1.74 ng/ml (SE $\pm$ 0.58), representing a 12-hour accumulation. The highest histamine levels were found during the first hour; i.e., about 16 ng/ml in both groups. The histamine levels fell thereafter, and by 5 hours, levels were not significantly above control levels. The control values for histamine ranged from 0.33 ng/ml during the first hour to 1.27 ng/ml at 8 hours.

Although the H₁ antagonist did not affect the production of the preformed mediator, it had a clear effect on the generation of a newly synthesized product, PGD₂. In six of the 10 patients studied, cetirizine dramatically decreased the PGD₂ levels at virtually every time point (Fig. 3, A-C), whereas in four subjects, the drug appeared to have no effect (Fig. 3, D).

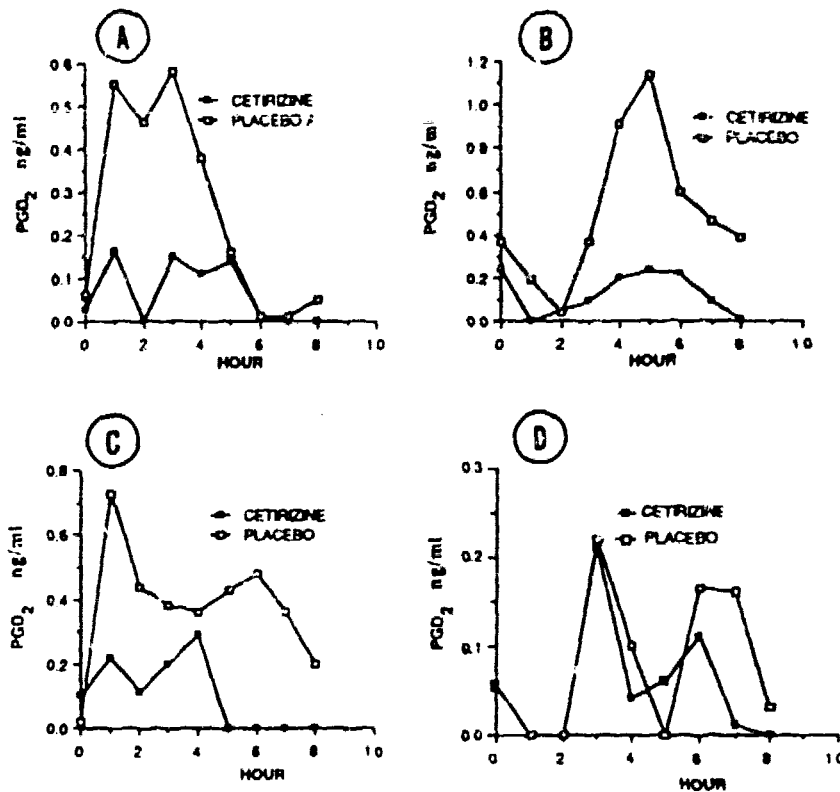


FIG. 3. A-C, Individual PGD₂ data from four representative patients challenged with RW Ag. The results demonstrate attenuation of PGD₂ generation by cetirizine that occurred in 60% of subjects. D. The remaining 40% of the subjects demonstrated no inhibition of PGD₂ by the drug. Note that all subjects maintained the same pattern of release in response to the Ag, whether or not they received cetirizine.

The patterns of PGD₂ generation, unique for each individual patient, were duplicated on both cetirizine-treatment and placebo-treatment days, although they were much lower (in six of 10 cases) with the drug. There was no tendency for histamine release to be less while patients were receiving the drug in those patients in whom the PGD₂ generation was blunted.

Averaging the PGD₂ data, suppression of PGD₂ generation by cetirizine is noted (Fig. 4). The level of this prostaglandin in chamber fluids was reduced at every time point from 1 to 8 hours, which, by analysis of variance, is significant ($p \leq 0.04$). The control PGD₂ values, with no Ag stimulation, ranged from 0.07 ng/ml at baseline to a high of 0.17 ng/ml during the second hour. As mentioned previously, all PGD₂ values presented represent the control values subtracted from the corresponding Ag-stimulation chamber. When the data from each individual time point are examined, the PGD₂ levels are significantly lower in the second, fourth, and fifth hours during cetirizine treatment because of the marked interindividual var-

iation. When the overall pattern is observed, it appears that the effect of cetirizine is to markedly blunt both the magnitude and duration of PGD₂ production. Thus, in the presence of cetirizine, the level of PGD₂ at 5 hours is clearly lower than that observed at the peak of the reaction at 3 hours, whereas in placebo-treated individuals, the third to the fifth hours are essentially the same and a decrease in PGD₂ levels is not observed until 6 hours.

Cetirizine also changed the infiltration of inflammatory cells into the skin chamber after Ag challenge. In the control (placebo-treated) individuals, eosinophil numbers began to increase at 6 hours when there were approximately 300,000 eosinophils per milliliter, and this continued until the end of the experiment, at 8 hours, when there were more than a million eosinophils per milliliter. Cetirizine pretreatment decreased eosinophil infiltration by 80% ($p \leq 0.04$) during the 3-hour period when increased numbers were observed in the control patients (Fig. 5, A). When single hourly measurements were observed there was a statistically

significant decrease of eosinophil numbers only during the eighth hour ($p \leq 0.03$), again because of the marked interindividual variation.

The effect of cetirizine on neutrophil infiltration was similar. Significant accumulation of neutrophils occurred by 5 hours when there was not a difference between the two groups (Fig. 5, B). However, during hours 6, 7, and 8, the cetirizine-treated individuals had less than half the number of neutrophils, and at 8 hours, there was a 75% reduction. When the pooled data are observed for hours 6, 7, and 8, there is a significant decrease in neutrophil infiltration ($p \leq 0.05$), although because of the marked variation from patient to patient, this became significant in each individual hour only at the eighth hour ($p \leq 0.02$).

Basophil numbers were lower than numbers of the other two cell types. The pattern, however, appears to be the same with the basophil numbers being lower at hours 6, 7, and 8 when the individuals were treated with cetirizine (Fig. 5, C). By the eighth hour, there were only one-fourth as many basophils in the treated individuals as in the control individuals. However, because of the low numbers, this decrease did not reach statistical significance.

DISCUSSION

Antihistamines were introduced about 50 years ago and, since that time, have been in widespread use for diseases accompanied by the real or supposed release of histamine.^{12, 13} Although there is no question that these drugs are quite specific at inhibiting the effects of histamine *in vitro*, their mechanism of action in man is not clear, but it is assumed that their effects are due to antagonism of H_1 receptors.¹⁴⁻¹⁶ Based on the tissue concentrations of antihistamines used clinically and on the affinity of histamine and its antagonists for the histamine receptor, there is reason to believe that receptor blockade may not be their only mechanism of action. It has been speculated that locally, *in vivo* concentrations of histamine may reach high micromolar levels. Some years ago we carried out a study in primates in which we induced a wheal-and-flare reaction with either *Ascaris* Ag or histamine and then attempted to block these reactions with either antihistamines or drugs that block histamine release (theophylline and β -adrenergic agonists).¹⁷ The antihistamine blocked the response to injected histamine but not the Ag-induced wheal-and-flare reaction, whereas the antirelease drugs had the reverse effect, i.e., blocked the Ag-induced skin reactions but did not block the response to histamine. Clinically, the efficacy of antihistamines in pruritic diseases and in allergic rhinitis is clear, even though their mechanism

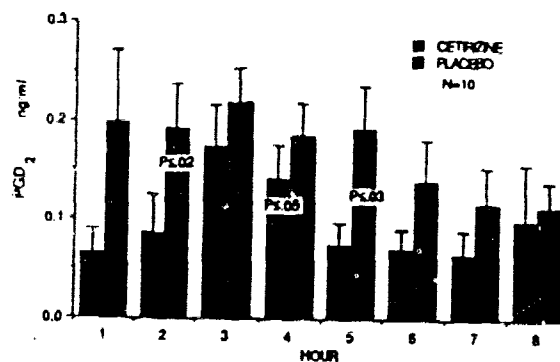


FIG. 4. Hourly PGD₂ production in response to 10 times the OCD of RW Ag in the skin chamber for 60 minutes. The results are expressed as mean nanograms per milliliter ($\pm$ SE).

of action is not. For example, while we were studying the antiallergic effects of the antihistamine, chlorpheniramine, we used as controls both placebo and phenobarbital.¹⁸ Both drugs were clinically more effective than placebo, but phenobarbital was less sedative than the antihistamine. Given these observations, it appears fair to conclude that the mechanism of action of antihistamines *in vivo* in man is not clear and that further studies on this subject are needed.

That antihistamines have effects in addition to histamine antagonism has been appreciated since 1960 when Mota and DaSilva¹⁹ demonstrated that certain classes of antihistamines at high concentrations were histamine releasers, whereas the same drugs at lower concentrations decreased Ag-induced mediator release in certain animal models. Fifteen years later, we repeated these studies using human basophils and found that most classes of antihistamines would inhibit release at 0.1 to 1 mmol/L concentrations, with the phenothiazine antihistamines being about tenfold more active.²⁰ Although these concentrations are not usually obtained clinically, we have found that topically applied phenothiazine-like antihistamines inhibit nasal mast cell-mediator release *in vivo* in man.^{41, 22} In this context, Ting et al.⁴ demonstrated that hydroxyzine, the parent compound of cetirizine, decreased histamine release in a skin chamber. Using a rat model, Lemanske et al.²³ demonstrated that diphenhydramine decreased both the immediate and the cutaneous LPR to anti-IgE and further demonstrated that this effect was even greater if combined with an H_1 antihistamine. Smith et al.²⁴ examined the effect of chlorpheniramine on the immediate and cutaneous LPR in human volunteers. They were unable to demonstrate an inhibition of the cutaneous LPR with an H_1 antihistamine alone, but when both an H_1 and an

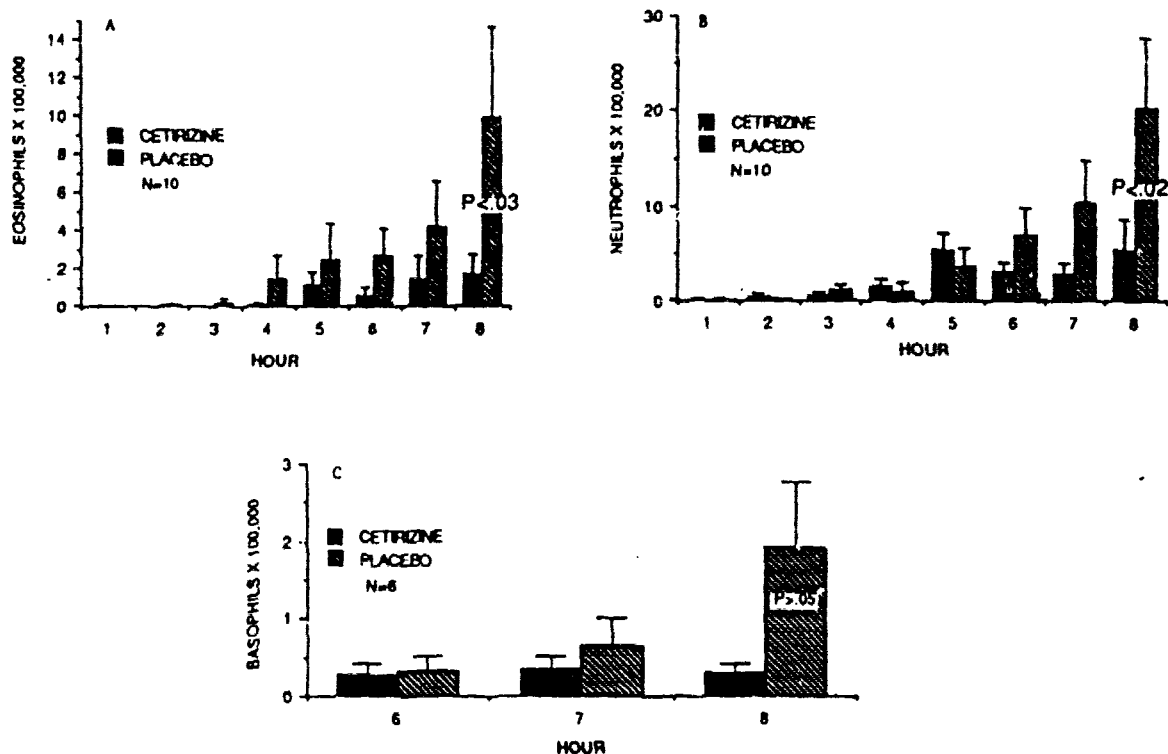


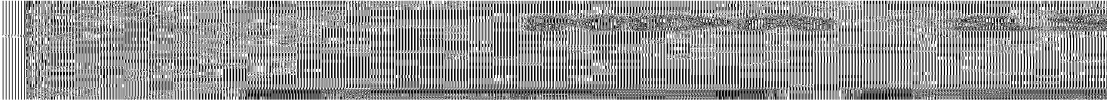
FIG. 5. A, Absolute numbers of eosinophils in the skin chamber in response to Ag challenge expressed as mean ($\pm$ SE). B, Absolute number of neutrophils in the skin chamber after Ag challenge expressed as mean ($\pm$ SE). C, Absolute number of basophils in the skin chamber expressed as mean ($\pm$ SE).

H₂ were combined, they were able to demonstrate a decrease in the LPR. Ketotifen has also been demonstrated to have a slight suppressive effect on the cutaneous LPR not found with clemastine.²³ It is worth noting that cetirizine has the same effects as other antihistamines in vitro, inhibiting histamine release from peripheral blood basophils, albeit at rather high concentrations. It is as effective in inhibiting histamine release in human skin mast cells as the phenothiazine class of antihistamines (unpublished data).

How can the observations presented in this article be explained? The first effect of cetirizine, to decrease both the immediate skin reaction and the erythema that occurs during the first several hours after Ag challenge, is not different from what has been demonstrated with multiple other antihistamines.^{26, 27} This may represent H₁ receptor antagonism. By contrast, although we did not reproduce the observations of Ting et al.⁶ regarding inhibition of histamine release by hydroxyzine, we did demonstrate that cetirizine blocks the release of PGD₂. Although there are other possibilities, it remains likely that the PGD₂ produced in this situation is of mast cell origin and that cetirizine may be acting to prevent release of a mediator that is synthesized after the allergic stimulus is applied.²⁸⁻³⁰

It would not be unexpected to find inhibition of a product of arachidonic acid metabolism without the inhibition of histamine release, since several drugs have been demonstrated to be more effective in altering arachidonic acid metabolism than affecting histamine release.³¹ We may, in this experimental protocol, simply have been at a dose range in which the first effect was observed without the latter.

The other effects of cetirizine are more unusual. It causes inhibition of both eosinophil and neutrophil infiltration during the late-phase reaction in the skin. This inhibition of the influx of inflammatory cells into the Ag-challenged skin chamber corroborates the work by Fadel et al.⁶ using a modified Rebeck skin-window technique. Our experiments suggest that with larger numbers and a longer period of study, a decreased infiltration of basophils might also be demonstrated. In attempting to analyze this effect of cetirizine, we are hampered by a lack of knowledge concerning the mechanisms that promote and direct inflammatory cells to the site of an allergic reaction. In many IgE-mediated allergic reactions, there can be a 5% to 10% local eosinophil infiltration when there is a <1% peripheral eosinophilia. The eosinophils are clearly being selectively attracted to the site of Ag



challenge, but our knowledge of the mechanisms that control this phenomenon is incomplete. Although there are many chemical substances that cause eosinophil chemotaxis, the question of whether there is a selective eosinophil chemotactic substance is controversial, but the eosinophil chemotactic factor of anaphylaxis tetrapeptide (a family of acidic peptides with molecular weights ranging from 360 to 1000) described several years ago appears to be inactive.³²⁻³⁵ Other factors including platelet-activating factor, LTB₄, and monohydroxyeicosatetraenoic acids have been demonstrated to be chemotactic for eosinophils, but they all lack selectivity.³⁶⁻³⁸ Therefore, the mechanism of selective eosinophil tissue accumulation at the site of allergic reactions is not fully understood, and we do not yet have an adequate model to examine this aspect of the activity of cetirizine. Given the clear-cut in vivo effects of cetirizine, it may indeed be possible to use this drug to study many aspects of the complex processes that lead to inflammatory cell infiltration, including cell margination, endothelial cell adherence, chemokinesis, and chemotaxis itself. It may well be that a drug that blocks inflammatory cell infiltration in vivo will provide an insight into more basic pathogenetic mechanisms.

Thus, further studies with cetirizine are indicated. Whether the effects that are observed with this H₁ antagonist are characteristic only of this particular class of antihistamine or pertain to antihistamines in general remains to be determined.

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Effect of H₁ Receptor Blockade on the Early and Late Response to Cutaneous Allergen Challenge^{1,2}

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ABSTRACT

We investigated whether cutaneous antigen-induced inflammatory cell infiltration and mediator release were modified by H₁ receptor antagonists. Three chemically unrelated antihistamines (cetirizine, promethazine and chlorpheniramine) were tested in three groups of allergic subjects in a double-blind, crossover design. Chamber fluids were collected for 12 hr and histamine release, prostaglandin D₂ production and cellular infiltration were quantified. Cetirizine significantly decreased late leukocyte migration into antigen-challenged chambers: eosinophils by 68% ($P < .04$), basophils by 64% ($P < .04$) and neutrophils by 72% ($P < .04$), whereas mononuclear cells were not significantly affected. No alteration in the numbers of peripheral blood leukocytes or eosinophils occurred while on cetirizine treatment,

suggesting that the decrease in inflammatory cells during the late phase reaction in the skin is not secondary to alterations in the peripheral leukocyte pool. In contrast, neither promethazine nor chlorpheniramine induced any significant alteration in inflammatory cell infiltration. All three antihistamines caused significant inhibition of the immediate reaction to antigen without any significant alteration in late phase reaction cutaneous reactivity. None of the three antihistamines caused any significant alteration in histamine or prostaglandin D₂ levels. Thus, cetirizine may be an antihistamine uniquely capable of downregulating the late phase reaction inflammatory cell milieu without altering either early or late mediator production. The mechanisms involved and the clinical relevance of these findings remain to be explored.

Classical H₁ receptor antagonists have been used as competitive pharmacologic inhibitors of the effects of histamine on tissues and cells which possess the appropriate receptors. Even at low concentrations, these antihistamines act as antagonists to locally released histamine, and thereby decrease vascular permeability, relax smooth muscle and decrease the pruritus caused by histamine (Simons, 1989). Recent evidence, however, suggests that some of the newer, non-sedating antihistamines may have effects which cannot be explained solely on the basis of H₁ receptor blockade. Several of these drugs have the effect of inhibiting the release of histamine and leukotrienes *in vitro* and *in vivo* at pharmacologic concentrations. Certain classical antihistamines also had such activity, but only at concentrations higher than those considered clinically desirable. (Togias *et al.*, 1986; Simmet and Luck, 1989; Temple and McCluskey, 1988). The development of moderately lipophobic antihista-

mines, which effectively block the peripheral H₁ receptors without crossing the blood-brain barrier, has also allowed relatively large doses of medication without the soporific side effects typical of classical antihistamines (Mann *et al.*, 1989). A reinvestigation of the use of H₁ blocking drugs in the treatment of asthma demonstrated that terfenadine, azelastine and cetirizine have modest bronchodilatory effects (Holgate and Finnerty, 1989; Beutra *et al.*, 1989; Rafferty and Holgate, 1987; Brik *et al.*, 1987). With recognition of the importance of the late cellular events in allergic disease, interest has been generated in antihistamines that might attenuate the infiltration and activation of inflammatory cells during the LPR (Rafferty and Holgate, 1989a; Busse *et al.*, 1989).

Our group has recently shown that cetirizine, a relatively non-sedating carboxylic acid metabolite of hydroxyzine, decreased the migration of both neutrophils and eosinophils into antigen-challenged chambers affixed to the skin during an 8-hr study (Charlesworth *et al.*, 1989a). This study confirmed the results of Fadel *et al.* (1987), who found that cetirizine inhibited the migration of eosinophils onto skin windows 24 hr after an antigen challenge. Subsequent studies using the skin chamber model to study the LPR to antigen demonstrated that 12 hr of

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ABBREVIATIONS: LPR, late phase reaction(s); H₁, histamine type 1 receptor; PGD₂, prostaglandin D₂; OCD, optimal challenge dose; RIA, radioimmunoassay; WBC, white blood cell; PAF, platelet activating factor; LTC₄, leukotriene C₄; RLH, Ringer's lactate buffer containing 250 µg/ml heparin; IL, interleukin.

observation were necessary to evaluate fully the late increase of histamine and the infiltration of eosinophils, neutrophils and basophils (Charlesworth *et al.*, 1989b).

We undertook to confirm the changes in inflammatory cell infiltration caused by cetirizine during the LPR over the more appropriate time frame of 12 hr. We also asked if the effects of cetirizine are characteristic of H₁ antihistamines in general or were specific for certain drugs and not for others. We investigated cetirizine, promethazine and chlorpheniramine pretreatment in allergic individuals by monitoring cellular infiltration and measuring histamine and PGD₂ over 12 hr in skin blister chambers challenged with an allergen.

Materials and Methods

Thirty adult atopic subjects were entered into a double-blind crossover study to examine the following antihistamines: cetirizine, promethazine and chlorpheniramine. All subjects gave written informed consent. Each subject had a documented cutaneous LPR when challenged via intradermal skin test to ragweed extract (saline diluent with 0.03% human albumin, Hollister-Stier Laboratories, Spokane, WA). Concentrations ranging from 0.1 to 1000 protein nitrogen U/ml were used to define the OCD as the lowest concentration of antigen required to produce a 4+ cutaneous reaction (i.e., a wheal with a diameter >10 mm with pseudopods or >15 mm without pseudopods) and having >45 mm of erythema. Cutaneous erythema was also measured at 15 min and then hourly for the duration of each 12 hr experiment.

Study design. Three different groups, each containing 10 atopic adult subjects, were entered into a double-blind crossover study in which they received either placebo or an antihistamine (cetirizine 20 mg/day, promethazine (25 mg) four times per day or chlorpheniramine (4 mg) four times per day for 3 consecutive days). There was a 7-day washout period between the initial treatment and the crossover. On the 2nd day of the treatment, a blister was created on the volar aspect of each forearm by placing a hollow plate heated to 40°C over the preselected skin. Continuous suction (80 mm Hg) was applied for 45 to 60 min until a complete 5-mm blister was formed. All blisters were induced 12 hr before removing the epidermis and challenging the denuded dermis to compensate for the release of inflammatory mediators (PGD₂ and LTC₄) related to the trauma of blister induction and to allow these levels to return to base-line.

Although the placement of the heat/suction-induced blister 12 hr before the antigen challenge reduces base-line nonspecific production of arachidonic acid metabolites (Charlesworth *et al.*, 1989b), it is possible that the early blister induction may contribute to nonspecific influx of neutrophilic leukocytes. For this reason, the results are reported as net cellular influx with the absolute cells from the control site being subtracted from the antigen challenged site.

Skin testing. Simultaneous with ragweed antigen challenge of the denuded dermis, each subject was skin tested with 0.02 ml of ragweed at the concentration that had previously been determined to cause a 4+ reaction followed by a cutaneous LPR. The skin test was placed on the upper arm, which was being challenged simultaneously with antigen challenge of the denuded dermis on the forearm. The surface area of the LPR was calculated using a composite diameter derived by averaging the long and short axes of the cutaneous erythema and edema.

Skin chamber collections. Seventy-two hr after receiving the first dose of study medication (cetirizine, promethazine or chlorpheniramine), the blisters were aseptically unroofed. Sterile aluminum chambers with entry and exit ports were placed over the unroofed blister and taped in place. A cutaneous adhesive (Skin-Bond, Largo, FL) was used to secure an adequate seal with the skin. Five hundred μ l of ragweed extract, representing 10 $\times$ the OCD, were placed into the test chamber for 60 min. In the opposite arm, an equal amount of RLH was placed into the control chamber for 60 min. Equal concentrations of heparin were present in both antigen and control chambers, as fibrin clots will otherwise form over the denuded dermis. Hourly for 12 hr,

the contents of each skin chamber were aspirated with a tuberculin syringe and the volume replaced with 500 μ l of RLH. The blister fluid from each sample was centrifuged at 1000 rpm in microcentrifuge tubes for 2 min and the supernatant was reserved for measurement of PGD₂ and histamine. The pellet was resuspended in 500 μ l of RLH and gently agitated. Ten μ l of the suspension were placed onto the surface of a hemocytometer (Neubauer; American Optical, Buffalo, NY) for cell counting. For each sample, at least 100 nucleated cells were counted in nine large squares. The remaining cell suspension was then centrifuged (Cytospin; Shandon Southern Instruments, Inc., Sewickley, PA) at 600 rpm for 8 min. Paired slides from each sample were stained with 1) DIFF-QUIK (a modified Wright-Giemsa stain, American Scientific Products, McGraw Park, IL) and 2) 0.5% alcian blue (pH, 1.0) for 60 min. After rinsing with distilled water, the alcian blue-stained cells were counter-stained with 0.1% safranin in 1% acetic acid. A total of 200 to 300 Wright-Giemsa-stained cells were counted. For the alcian blue-stained cells, 1000 cells were counted, or the total number of cells on the slide if the total was less than 1000 cells (Gilbert and Ornstein, 1975).

Measurement of mediators. For measurement of PGD₂, 200 μ l of blister fluid, precipitated in 1.6 ml of high-performance liquid chromatography grade ethyl alcohol, were centrifuged at 5000 rpm for 5 min. The prostanoid-containing supernatants (stored at -70°C until assayed) were transferred to separate tubes and placed in an evaporating centrifuge for 3 hr. A competitive RIA with a sensitivity of 40 pg/ml, described previously, was used for PGD₂ measurements (Schulman *et al.*, 1981). The identity of the prostanoid measured by the RIA was confirmed by negative ion gas chromatographic mass spectrophotometry (Hubbard *et al.*, 1986). Blister fluid for the histamine assay was frozen immediately after collection and stored at -70°C. The radioenzymatic assay used for histamine has a sensitivity of 0.05 ng/ml (Brown *et al.*, 1982). The assay is based on the conversion of histamine to [³H]methylhistamine in the presence of histamine-N-methyltransferase and [³H]S-adenosyl-L-methionine.

Statistical analysis. Nonparametric analysis was used, as there is no evidence that the inflammatory cell influx or mediator release necessarily follow a Gaussian distribution. The Wilcoxon signed-rank test was applied using a commercial statistics program (Statview). A Z value was determined and the two-tailed probability was obtained from a table of probabilities.

Results

All three antihistamines significantly suppressed the histamine-induced immediate wheal and flare response to intracutaneous skin testing with the previously determined OCD, as illustrated in figure 1. Table 1 reports the percent suppression of the antigen-induced flare at 15 min with the antihistamines studied, reflecting the actual extent of H₁ receptor blockade. Skin test suppression extended to the 3rd hr with cetirizine and to the 2nd hr with promethazine and chlorpheniramine. Although cetirizine showed greater suppression, there was no statistical difference in the suppression of the immediate reaction using a one-way analysis of variance for the three groups (0.05 < P < .1). The dosages selected in the current study reflect dosages which are customarily used in clinical practice, and were not necessarily selected for equal H₁ receptor blockade. All three antihistamines showed some suppression of the prolonged cutaneous erythema and induration which follows the initial wheal and flare reaction and which typically peaks at hours 8 to 12 (termed the LPR); over hours 6 to 12, cetirizine reduced the response by 38 $\pm$ 6%, whereas with promethazine, the reduction was 10 $\pm$ 10%; and with chlorpheniramine, the decrease was 21 $\pm$ 12%. However, this inhibition of late inflammation did not reach statistical significance with any single drug.

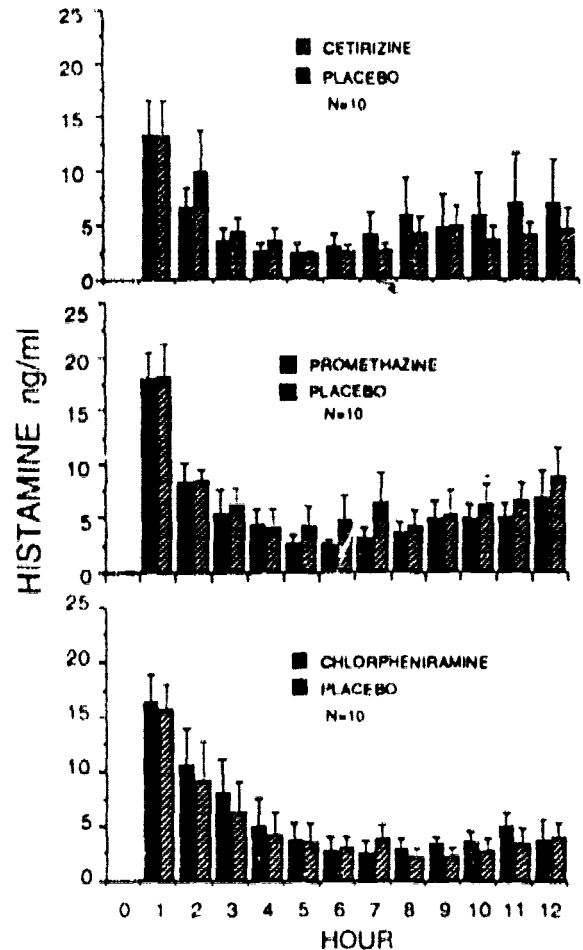
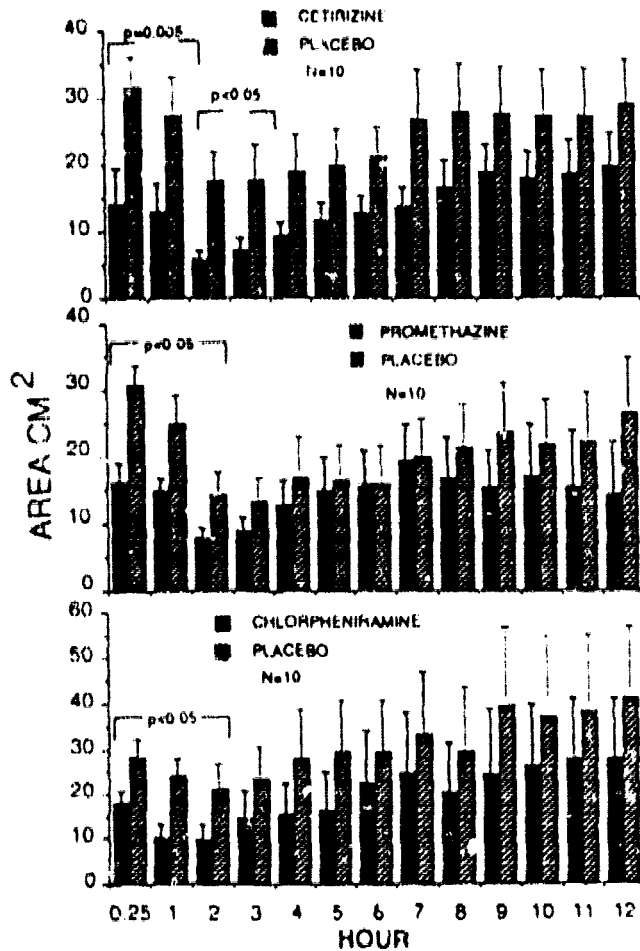


Fig. 1. Skin test reactions, measured in square centimeters, for subjects treated with each of the three antihistamines studied (cetirizine, promethazine and chlorpheniramine). All three antihistamines significantly suppressed the immediate wheal and flare reaction, but none had any significant effect on the LPR.

Fig. 2. Histamine released into the skin chambers measured hourly for 12 consecutive hr. None of the three antihistamines (cetirizine, promethazine or chlorpheniramine) showed any suppression of histamine release either immediately or during the LPR.

TABLE 1

Suppression of the immediate flare diameter at 15 min in each antihistamine study group

both mean and median values are presented, in addition to the S.D. and S.E.M. There was no statistically significant difference between the three groups ($P < 1$) using one-way analysis of variance.

	Skin Test Suppression at 15 min		
	Cetirizine	Promethazine	Chlorpheniramine
Mean (%)	60.11	48.85	33.90
S.D. (%)	28.6	28.79	17.87
S.E.M. (%)	9.045	9.105	5.65
Median (%)	61.79	49.61	37.05

The late phase increase in histamine release into the skin chamber during the last four hours of the study was in a pattern similar to that previously described. None of the three antihistamines showed any suppression of histamine release either immediately after antigen challenge or during the LPR (fig. 2). The chlorpheniramine group had less total release of histamine during the LPR. This reflects individual variation within the separate groups, not a difference in skin reactivity between the three groups (fig. 1).

PGD₂ production in the skin follows a different pattern than is seen after antigen challenge of the nose or lungs. It peaks much later, at 2 to 3 hr after antigen, and then falls to

insignificant levels by 5 or 6 hr. There is no late increase, as was seen with histamine. None of the antihistamines affected PGD₂ production, and there were no significant differences between the three antihistamine-treated groups (fig. 3). In our previous study, we examined the effect of cetirizine over an 8-hr time period and found that 6 of 10 subjects showed a decrease in PGD₂ through the 8th hr. It was anticipated that we might see a similar trend with the 12-hr cetirizine study, but this did not occur. When the pattern of PGD₂ production for each individual patient was examined (data not presented), the pattern of PGD₂ release during the cetirizine and placebo days was preserved in each patient and the amount of prostanoid released was statistically similar in both the cetirizine and the placebo groups. Overall, the cetirizine test group displayed a somewhat blunted pattern of PGD₂ production when compared to the promethazine and chlorpheniramine groups, but without significant differences.

The most significant effect observed was the influence of cetirizine on the pattern of inflammatory cell migration into the antigen-challenged site. Of the three antihistamines, only cetirizine decreased the net leukocyte influx into the skin chambers for hours 3 through 12 ($P < .003$). Figure 4A illustrates the observed 68% suppression of eosinophil infiltration for hours 10 through 12 ($P < .04$). Neither promethazine (fig.

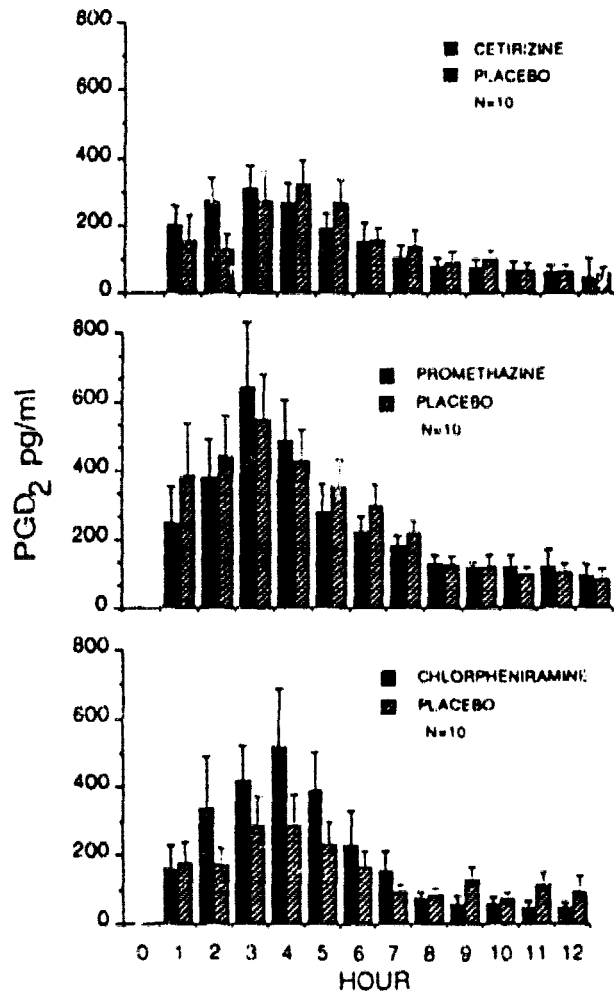


Fig. 3. PGD₂ production showed no significant differences between the three antihistamine treatment groups (cetirizine, promethazine or chlorpheniramine).

4B) nor chlorpheniramine (fig. 4C) showed any effect on late phase eosinophil migration into the skin chambers. The effects of the three antihistamines on basophils are shown in figure 5. Cetirizine pretreatment suppressed the appearance of basophils during hours 10 through 12 ($P < .04-.01$), whereas promethazine and chlorpheniramine had no effect. The effects of these three antihistamines on neutrophil migration are shown in figure 6. Suppression by cetirizine was also observed, beginning at hour 8 and continuing through hour 12 (all P values $< .05$). Again, neither promethazine nor chlorpheniramine reduced the appearance of neutrophils. Although there was a trend toward decreased mononuclear cell infiltration with cetirizine pretreatment, this did not reach statistical significance. Likewise, neither promethazine nor chlorpheniramine had any significant effect on mononuclear cell infiltration except for hour 12 when there was suppression with promethazine ($P < .03$, data not shown).

Because others have shown decreased cutaneous eosinophil migration, we wanted to determine whether cetirizine had any effect on either the peripheral blood leukocyte count or on the absolute eosinophil count. The decrease in eosinophil infiltration during the LPR caused by corticosteroids is attended by a marked decrease in blood eosinophil numbers, which may explain, in part, the effect. In the cetirizine study group, total

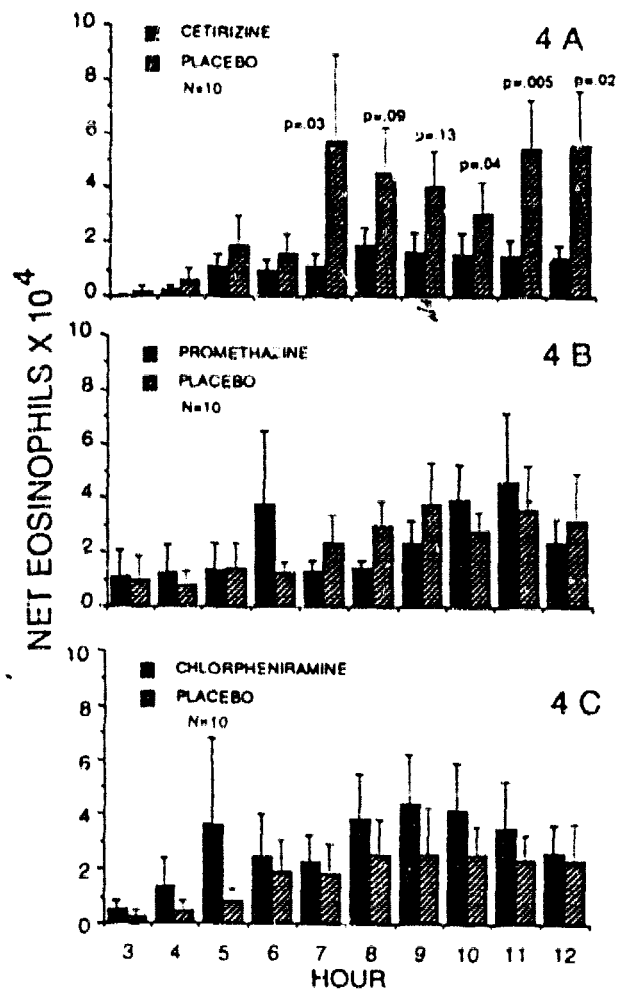


Fig. 4. Hourly eosinophil migration into skin chambers after cetirizine (4A), promethazine (4B) and chlorpheniramine treatment (4C). Cetirizine caused significant suppression of eosinophil infiltration for hours 10 through 12. Neither promethazine or chlorpheniramine had any effect on late phase eosinophil infiltration.

WBC counts and absolute eosinophil counts were obtained before antigen challenge and again at 8 hr after removal of antigen from the skin chambers. During both placebo and drug treatments, the cetirizine group had comparable WBC counts ($5.4 \pm 1.3 \times 10^3/\text{mm}^3$ and $5.7 \pm 1.5 \times 10^3/\text{mm}^3$, respectively). Likewise, there was no significant difference in the total eosinophil counts while on placebo or cetirizine, with 171 and 211 eosinophils/ mm^3 , respectively.

Discussion

The past decade has witnessed a focusing of research on the inflammatory components of the LPR to allergen. Allergen provocation of the lower airways results in a late bronchoconstrictor response and an increase in nonspecific airway responsiveness (Barnes, 1985). Naclerio and his colleagues have shown that after antigen challenge in the nose, two distinct phases of histamine release can be identified. Within minutes of the challenge histamine, PGD₂ and tryptase is released by mast cells, and hours later, a second wave of histamine release is associated with the arrival of basophils, which have entered into the tissues along with eosinophils and neutrophils (Naclerio *et al.*, 1985; Batcom *et al.*, 1988). Using a skin chamber

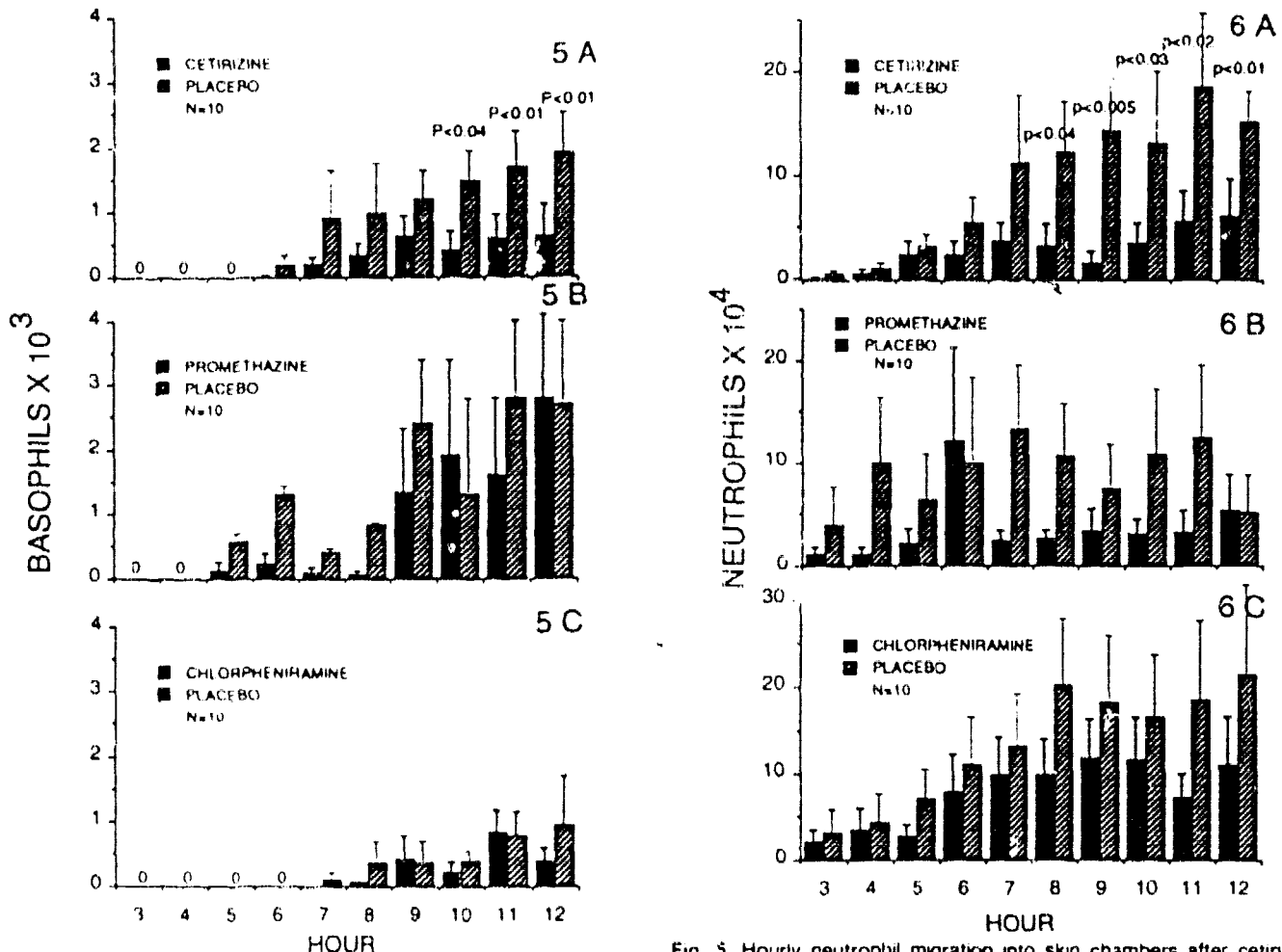


Fig. 5. Hourly basophil migration into skin chambers after cetirizine (5A), promethazine (5B) and chlorpheniramine (5C). Cetirizine caused significant suppression of basophil infiltration for hours 10 through 12. Neither promethazine nor chlorpheniramine had any effect on late phase basophil infiltration.

model, we have recently confirmed the presence of a biphasic release of histamine in the skin after antigen challenge, similar to that which has been observed in the airways (Charlesworth *et al.*, 1989b). Histologic and cytologic examinations have shown that the LPR in the lung, nose and skin is characterized by a polymorphous infiltrate consisting of eosinophils, basophils and, to a more variable extent, neutrophils and mononuclear cells (Dunnill, 1960; Metzger *et al.*, 1986; Liu *et al.*, 1990; Guo *et al.*, 1990). Late phase infiltration of inflammatory cells leads to the generation and release of multiple mediators which interact in a complex manner, culminating in the pathophysiologic responses observed in these organs. Clearly, the events which occur during the LPR have important clinical implications, and therapeutic modulation of this aspect of the allergic reaction would be expected to alter disease morbidity significantly.

Using Rebeck skin windows, Fadel *et al.* (1987) presented data suggesting that cetirizine, a new H_1 antihistamine chemically related to hydroxyzine, reduces the migration of eosinophils onto glass coverslips at 24 hr. A year later, Leprevost *et al.* (1988) presented data suggesting that cetirizine decreased the PAF-induced and FMLP-induced chemotaxis of eosino-

Fig. 5. Hourly neutrophil migration into skin chambers after cetirizine (6A), promethazine (6B) and chlorpheniramine (6C). Cetirizine caused significant suppression of neutrophil infiltration for hours 8 through 12. Neither promethazine nor chlorpheniramine had any effect on neutrophil influx.

phils *in vitro*. Michel *et al.* (1988) used a skin chamber model to show that cetirizine decreased the immediate release of histamine and PAF, in addition to decreasing eosinophil migration onto glass coverslips. As none of the above studies examined the kinetics of changes in either cells or mediators after cetirizine pretreatment, we recently carried out an 8-hr chamber study examining the effect of cetirizine on both mediators and inflammatory cells (Charlesworth *et al.*, 1989a). We were not able to demonstrate any effect by cetirizine on the immediate release of histamine. This is distinct from the finding of Ting *et al.* (1985), who showed a decrease in the immediate release of histamine as a result of hydroxyzine, the parent compound of cetirizine, and from the findings of Michel *et al.* (1988) cited above. We were, however, able to confirm a decrease in eosinophil migration into the skin chambers during the 7th and 8th hr after antigen challenge. Our findings with cetirizine suggest that there may be hitherto unsuspected aspects of the pharmacology of compounds selected as H_1 blocking agents. Most H_1 blockers have anticholinergic effects, some have antiserotonin effects and some are useful as antidepressants.

Recently, other antihistamines have been reported to display unique anti-allergic properties. As noted, azelastine has been

own to inhibit mast cell histamine release triggered by both antigen and nonantigenic stimuli in addition to having modest vasodilation actions (McTavish and Sorokin, 1989). Rafferty (199b) further showed that azelastine had an inhibitory effect on both the early and the late bronchoconstrictor responses to inhaled antigen challenge, although it did not seem to have any significant inhibitory effect on the early increase in plasma histamine. Togias *et al.* (1986, 1989), using an *in vivo* nasal model, showed that terfenadine significantly reduced the immediate release of histamine, similar to their results with topically applied azatadine. Other investigators have shown that terfenadine inhibits histamine release from human basophils and LTC₄ production by eosinophils (Nabe *et al.*, 1989). These findings suggest that H₁ antihistamines possess anti-inflammatory properties unrelated to histamine antagonism which might alter the late inflammatory events of allergic disease.

In the present study, we extended our previous skin chamber studies of cetirizine to 12 hr in order to address better this drug's effect on the cutaneous LPR. Because antihistamines other than cetirizine have been shown to have antirelease and anti-inflammatory effects, we also investigated the effects of two other well-studied drugs promethazine and chlorpheniramine. These compounds were chosen because of previous work showing that *in vitro* promethazine, at concentrations of 0.1 to 1.0 mM, inhibited antigen-induced histamine release from peripheral blood basophils (Lichtenstein and Gillette, 1975). In contrast to promethazine, chlorpheniramine showed no tendency to affect basophil histamine release at any concentration. In this study, as in our previous work, we were unable to confirm the findings of others showing a suppression of the immediate release of histamine with cetirizine (Michel *et al.*, 1988). Nor did the other antihistamines have such an effect. Although we cannot explain this discrepancy, our data are in keeping with the *in vitro* results with this drug, in which concentrations many orders of magnitude higher than those obtained *in vivo* are required to inhibit mediator release. In the present study, we were unable to confirm our previous speculation that cetirizine might suppress PGD₂ production in a subset of allergic patients (Charlesworth *et al.*, 1989a). Although the overall production of PGD₂ in the presence of cetirizine appeared to be less than that noted with either promethazine or chlorpheniramine, the results were not statistically significant.

These results confirm previous observations of others and ourselves that cetirizine blocks the influx of eosinophils into the skin many hours after antigen administration, and extend these findings in several ways. First, detailed kinetics indicate that the suppression begins at 6 to 7 hr and extends until at least 12 hr, when the experiments were stopped. Second, it is not only the eosinophils that are affected, but all granulocytes, because neutrophil and basophil infiltration also were affected. These anti-inflammatory effects of cetirizine may be unrelated to histamine antagonism. Although the H₁ blockade was not perfectly matched for the three antihistamines, the suppression of the immediate wheal and flare by cetirizine and promethazine was similar and was not significantly different at 60 and 30%, respectively, and this suggests similarity in H₁ blockade. Besides this, the two drugs appeared to have different effects on the movement of cells, particularly eosinophils and basophils, to the fluid above antigen-challenged skin blister sites. The skin chamber findings probably reflect events in the dermis

accurately, because we have shown that they correlate well with biopsy findings (Charlesworth *et al.*, 1989b).

It is interesting to compare these results with the effects of corticosteroids, which selectively block eosinophil and basophil infiltration into the skin and decrease the swelling and erythema of the LPR (Charlesworth *et al.*, 1991). Because of the important anti-inflammatory effects of the steroids in human disease (Schleimer, 1985), the similar effect of the antihistamines may be clinically relevant. The effects of 60 mg of prednisone daily for 3 days before antigen challenge differ from those of cetirizine in several ways. Steroids have minimal effects on neutrophils. They inhibit the eosinophil and basophil infiltration 100%, not the <60% seen with cetirizine, and they completely block the clinical phase of the LPR. Cetirizine seemed to have a similar effect on the LPR, but it was not statistically significant. We suspect that greater numbers of patients or more sophisticated and precise monitoring of the skin response would show a partial, significant effect which correlates with the partial suppression of eosinophils and basophils. Thermographic analysis might be appropriate.

Another difference between steroids and cetirizine, which can only be noted parenthetically at this time, refers to toxic side effects: Those of steroids are well known, but based on the safety record of the parent compound, cetirizine should have essentially no side effects.

Little is known about the mechanisms by which these drugs decrease inflammatory cell infiltration. Steroids cause a blood eosinopenia and down-regulate cellular adherence (Altman *et al.*, 1981). In light of recent data on adhesion molecules on granulocytes and endothelial cells (Bevilacqua *et al.*, 1987; Bochner *et al.*, 1988; Hakanson *et al.*, 1990; Henocq and Vargaftig, 1988), the effect of cetirizine on these molecules is of interest. In particular, the recent findings demonstrating that very late antigen-4 expressed on eosinophils and basophils, but not neutrophils, binds to vascular cell adhesion molecule-1 on endothelial cells (Walsh *et al.*, 1991; Bochner *et al.*, 1991) raises the exciting possibility that drugs such as cetirizine might reduce eosinophil/basophil influx by affecting the function or expression of these adherence molecules. The recent evidence that mast cell activation leads to the delayed appearance of proinflammatory cytokines (*i.e.*, IL-3, IL-4 and IL-5) that can up-regulate these adhesion molecules makes this an even greater area of interest (Plaut *et al.*, 1989). This drug has been shown in one laboratory to block eosinophil chemotaxis *in vitro* (Leprevost *et al.*, 1988), and the reported effects of cetirizine on PAF generation may be relevant (Michel *et al.*, 1988; Smith *et al.*, 1988; Page, 1988).

Although cetirizine appeared to inhibit inflammatory cell infiltration, it is important to realize that it was not developed with this activity in mind. Development based on cetirizine's structure, but focusing on anti-inflammatory effects, might be rewarding clinically.

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Send reprint requests to: Lawrence M. Lichtenstein, M.D., Ph.D., Johns Hopkins Asthma and Allergy Center, 5501 Hopkins Bayview Circle, Baltimore, MD 21224.

SEP 27 1995

Ana M. Saavedra-Delgado, M.D.

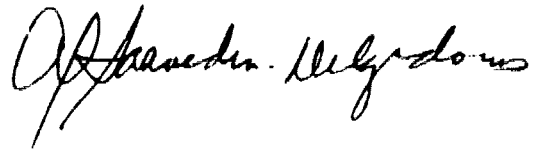
September 27, 1995

Medical Officer Reviewer attachment to the Pulmonary Drug Product Draft Labeling dated September 21, 1995, for NDA 19835:

The medical reviewer has reviewed the changes made to the proposed 4/25/95 labeling for NDA 19,835 in the document: Revised Labeling, dated 9/21/95. The changes made to the NDA 19835 proposed label document are an accurate representation of the discussion that took place in the 9/21/95 "in-house meeting".

The medical reviewer's memo dated 9/27/95, represents a new proposed change to the labeling that was not considered at the 9/21/95 "in house" meeting.

The medical reviewer will include in the medical officer review of the sponsor's response to the 2/21/95 approvable letter, a discussion of the reviewer's proposed changes to the labeling that were overruled in the discussions at the 9/21/95 "in house meeting".



10
5. send NDA 19 835
HFD-155/Div. Files
HFD-155/ K. Lee
HFD-155/ E. Schumaker
HFD-155/A. Saavedra-Delgado
HFD-155/M. Himmel

Interoffice Memorandum

Medical Officer Review

To: Dr. Marty Himmel

NDA: 19385

Documents Reviewed:

DSI reports # 2703, 2707, 2764, 2770, 2801, 2917, and 2925,

Review completed: May 12, 1994

From Medical Officer Reviewer: Ana M. Saavedra-Delgado, M.D.

Seasonal Allergic Rhinitis

DSI report #2801 FAR-1

Investigator: Jerome Miller, M.D. 84-N-0049
59 patients

Letter to Investigator: "We find no major departures from FDA regulations or commonly accepted drug investigation practices. The problems that were observed were due to the lack of documentation that all subjects signed a consent form and the lack of documentation regarding the return to the sponsor of all unused study medication."

Inspector's report:

Data audit report: "FDA copies of CRFs agreed with the investigator's copies. The laboratory values in the CRFs were seen to agree with those values which were legible in the FDA copies. While the reviewed clinic charts did not have a great deal of study information, that which there was did not conflict with the CRFs."

Subject characteristics: "I did not see actual specific skin tests results. I asked Dr. Miller if the skin tests were of the kind that were read in 12 hours, 24 hour, etc. He replied that the tests were the kind whose results you could be observed within a few minutes."

Laboratory tests: "The skin testing was performed in the investigator's facilities at intake according to Dr. Miller. He said that this was a simple test with observable results in a few

A. Saavedra-Delgado
May 12, 1994
M. Himmel
5/12/94

minutes."

MOR comments: It is standard practice to have the skin test results in the patient's record if they are done. Review of exhibit #4 (copy enclosed) 8/24, indicates pt #5 tested- : this could be interpreted as negative, or done. At the end of the investigator's note on 8/31, it appears to say "tested". This would be the end of the study for this patient and if tested meant that skin tests were done, then it should not have been done again on 8/31 since the protocol did not call for it. The investigator did not provide any other source data to compare to CRFs.

Overall the report indicates very poor record keeping by the investigator and from the data included I cannot say that skin tests were done.

DSI Report #2917 SAR-1

Investigator: Elwood Buchman, M.D. 84-N-0060
49 patients

Letter to Investigator: "we find no significant departures from FDA regulations or commonly accepted drug investigation practices. However, in reviewing the consent form, we note in the second paragraph on page 3 the subjects are informed that they will be paid a specified amount for completion of the study and if the subjects drop out of the study they will not be paid."

Inspector: "This inspection and data audit covered the comparison of subject information, review of study consent forms, review and comparison of raw data, clinical chemistry, hematology, urine analysis, subject medical and allergy history and other patient status records.

The study was carried out according to the written protocol with no protocol deviations found. All abnormal laboratory values were returned to normal per protocol required monitoring. One adverse reaction was mild and transitory as patient #39 (see exhibit #9). No deaths or significant reactions were found."

MOR comments: I could not find a statement where the inspector would specify in the report whether there was accurate reporting of data from the source documents to the CRFs. However, from the included report of adverse event, it appears that the investigator's reporting was

adequate.

The fact that patients' payments were not prorated, may have in fact influenced patients to complete the study and therefore influence the study results in terms of efficacy and safety. It could have decreased the number of patients that would have otherwise discontinued the study for lack of efficacy and/or for mild to moderate adverse effects.

Perennial Allergic Rhinitis

DSI Report #2770

PAR-1

Investigator: Bernard Berman, M.D. 84-N-0065
35 patients

Letter to Investigator: "we find no significant departures from FDA regulations or commonly accepted drug investigation practices. We note, however, that the consent form signed by the subjects does not specifically identify whom the subjects may contact with questions relating the subjects' right."

Inspector: "Review of all subject case report forms found that written informed consent was obtained in all cases."

"Review of patient records for subjects 12, 16, 21, and 28 found that these case histories did not indicate that any of the audited subjects had participated in the drug trial. Also, in some cases, office records ended a year or more prior to the subjects participation in the study."

"One of the associate investigator listed on the FDA-1572, Gary A. Cohen, M.D., had actually participated in the study as subject #9. This was done under the supervision of Stanly Sakowitz, M.D., another investigator associated with the study. It was also disclosed that Dr. Gary Cohen had supervised at least 3 family members in the study as subjects 1, 3, and 21."

MOR comments: Although it appears that the investigator found inadequate case histories as source documents and what appears is an inappropriate inclusion of an investigator as a subject in the study with the additional inclusion of family members as subjects, the letter to the investigator does not mention these. It is my impression that this practice may have introduced biased in this center, and that this should have been communicated to us.

The inspector does not reach a conclusion on how accurate was the information transfer from the source documents to the CRFs. The material provided for review does not include copies of source labs or patient's records.

Chronic Idiopathic Urticaria

DSI Report # 2764 URT-1

Investigator: Richard F. Lockey, M.D. 85-N-0039
34 patients

Letter to Investigator: "we find no significant departures from FDA regulations or commonly accepted drug investigation practices. We note, however, that the consent form signed by the subjects does not inform the subjects whom to contact with questions relating the subjects' right... In addition, we note in section 4 of the consent form a statement that cetirizine is clinically effective in controlling symptoms of urticaria. The purpose of this study is to determine the effectiveness as well as the safety of cetirizine and this statement is misleading to the study subjects and should not have been included in the consent form."

Inspector: "The data audit showed only minor discrepancies. ... Attached to assignments were case report forms of six patients. These case report forms were compared to the study center copies and no discrepancies were found. The study center patient files had laboratory reports for all reported tests for chemistry, hematology, and urines. Also present were report sheets for skin testing. In general, files were complete and well organized. Discrepancies observed during the data audit were:

1. Patient 07 I.D> Skin Testing on 5/5/86 showed on the case report form (Exhibit 5, page 1) as a 2+ reaction to the histamine control and no reaction to the diluent control. These figures were reversed on the source document (Exhibit 5, page 2). Ms Baird-Warren said she felt the case report form had to be the correct results.
2. Patient 07 case report form for a 5/27/86 urinalysis (Exhibit 5, page 3) had two results reversed when compared to the laboratory report (Exhibit 4, page 4).

3. There was no source report form for Patient 07 I.D. Skin Testing done 6/9/86 as reported on the case report form for that date (Exhibit 5, page 5).

The discrepancies were discussed with Ms. Baird-Warren. No FDA-483 was issued."

MOR comments: It should also be noted that on the u/a source document and the CRF also differ on the reported number of casts/LPF. In the CRF (Exhibit 5) is noted as neg and in the source document (Exhibit 4) as occ. It appears that if the only discrepancies found in the data audit were those reported, they were indeed minor. However, it should be emphasized that when these are found they should be reported as such to us, so that we could decide its clinical significance in terms of the study.

DSI Report # 2925 Uncontrolled study

Investigator: Don Q. Mitchell, M.D. 86-N-0043

Letter to Investigator: "we find no significant departures from FDA regulations or commonly accepted drug investigation practices; however the consent form does not specifically states whom the subject should contact to answer pertinent questions about the subject's rights..."

Inspector: " I was provided with case report files for eight subjects and each of these were audited and all data in the subjects medical history files correspond with that in the case reports. It was determined that the raw data of the physicians observations is recorded directly on the case report format the time of the observation. Laboratory results were transposed from the lab report to the case report forms accurately. Errors were lined thru, initialed, and dated."

MOR: This study is not a pivotal study. Examples of raw data were not included in the inspector's report.

Pruritus

DSI Report # 2925 PRU-1

Investigator: James T, Gourzis, M.D. 85-N-0135

Letter to Investigator: "we find no significant departures from FDA regulations or commonly accepted drug investigation practices."

Inspector: "I compared the case reports of four patients against raw data. This consisted of screening checklist, clinical notes, progress notes, chemistry, hematology and EKG. Personal history notes and chest X rays with interpretations were also audited. No discrepancies were found. "

MOR: Pruritus is not an indication for this drug at the present time. Examples of raw data were not included in the inspector's report.

DSI Report # 2703 PRU-2

Investigator: Tom Russel, M.D. 86-N-0202

Letter to Investigator: "we find a departure from FDA regulations or commonly accepted drug investigation practices. The departure involved a failure to submit to the IRB the information sheet supplied to the prospective study subjects. Although the consent form states that a stipend will be paid for participating and completing the study, it does not include the amount to be paid. Only the information sheet contains this information and included a proviso that only subjects who complete the study will be paid... The information sheet characterized the drug as safe and effective, claims inconsistent with the purpose of the study as stated in the consent form... you do not identify whom the subjects may contact for questions relating to subject's rights..."

Inspector: Laboratory tests: " A comparison of these raw data results was made against results on the case report forms for the eight patients whose case reports were provided with the HFD-344 assignment. No discrepancies were found."

Raw data files: no discrepancies were noted when the copies of case report for the eight patients were compared with the CRF provided by the sponsor.

MOR: Pruritus is not an indication for this drug at the present time. Examples of raw data were not included in the inspector's report. The fact that patients' payments were not prorated, may have in fact influenced patients to complete the study, and therefore influence the study results in terms of efficacy and safety. When the included example of patient's raw data (exhibit 21) was compared to the CRF (exhibit 22) no discrepancies were found.

General MOR review comments:

Only 4/7 of the reviewed DSI inspection reports, consider studies that are pivotal for the drug's indications. From these four reports, the two for the seasonal allergic rhinitis indication (SAR-1) are one week studies. From the review of the DSI reports, these two centers inspected had considerable deficiencies from the medical reviewer standpoint. The review of the DSI report #2801, for Jerome Miller, M.D. 84-N-0049, suggests very poor record keeping and questions whether skin tests were done or not and as well as their results. From the review of DSI Report #2917, for Elwood Buchman, M.D. 84-N-0060, the fact that patients' payments were not prorated, may have in fact influenced patients to complete the study and therefore influence the study results in terms of efficacy and safety.

Only one center was inspected for the perennial allergic rhinitis indication. The review of the DSI Report #2770, for Bernard Berman, M.D. 84-N-0065, questions the data integrity and the judgement of the principal investigator to allow the inclusion of one of the investigators and family members as subjects. It also questions the objectivity of the investigator (study subject) in terms of the study conduct.

In terms of the allergic rhinitis indications the MOR review of the DSI reports show considerable deficiencies in terms of data integrity, and questions the possibility of asking for the inspection of additional centers from SAR and PAR pivotal studies, before drug approval.

Only one pivotal study center was inspected for the chronic idiopathic urticaria indication, DSI Report # 2764 for Richard F. Lockey, M.D. 85-N-0039. I agree with the inspector that if the only discrepancies found were the ones reported, they are indeed minor.

In general examples of raw data were not included in these reports. If discrepancies are found by the inspectors in the clinical record (hx, exam, labs, tests, etc) we should be made aware of them and copies of these should be included in their report, so that we could decide its clinical significance in terms of the study review.

100000
FEB 27 1994

Medical Officer Review

NDA 19835

Drug: Cetirizine tablets

Sponsor: Pfizer

Correspondence:

SU 1/30/92 Final Safety Update
SU 3/12/93 Response to request for additional
safety information of 1/28/93
AM 9/28/93 Study Results 90CK16-0497
AM 9/30/93 Study Results 92CK16-0603
BM 9/30/93 Study Results 92CK16-0604
AM 10/8/93 Integrated clinical safety assessment
of the above three studies
BM 10/29/93 Further analysis of above three
studies in response to our fax of 10/23/93
BM 11/19/93 Further analysis of the above three
studies in response to our fax of 11/08/93
NC 11/24/93 Response to our 11/23/93 fax
BM 1/20/94 Further analysis of above three
studies and response to questions from our
teleconference on 11/23/93 and fax of 11/24/93
NC 1/24/94 english translation of medical
literature

In-House Meetings: November 2, 1993, February 2, 1994
February 15, 1994

Subject: Electrocardiographic effects of: 20 and 60 mg of
cetirizine in adult males; 20 mg cetirizine- 400 mg
ketoconazole interaction and 20 mg cetirizine-500 mg
erythromycin interaction in adult males.

Medical Officer Reviewer: Ana M. Saavedra-Delgado, M.D.

Date: February 23, 1994

A. Saavedra-Delgado MD
Feb/23/1994

The purpose of this review is to integrate the information that we have received on the subject of electrocardiographic effects of cetirizine since the submission of the first study report of 9/28/93, incorporate our understanding of these effects prior to this time and include our analyses and requests since that time. The review of the studies will be limited to the evaluation of the electrocardiographic effects and in particular to the QT_c interval in terms of safety. The safety review of the remaining safety data based on a cursory review of the summary reports of these three studies show no new safety concerns.

01/23/94

Cetirizine and QT_c Prolongation**Table of Contents****Part I****A. Prior to the Advisory Committee Meeting**

1. Summary report of no effect up to 60 mg/day in healthy volunteers
2. Retrospective analysis of EKG data from 2 SAR studies in 161 patients- % of patients with QT_c prolongation, no different from placebo.
3. Cardiac toxicity update
 - a. Hydroxyzine and torsades
4. Similarity of structure to cardiac output rhythm drug Considered - but not fully explored

B. Post Advisory Committee Meeting

1. Submission of the study reports 90CK16-0497, 92CK16-0604 and 92CK-0604 (9/28/93 and 9/30/93):
2. Related structure to cetirizine-cardiac output rhythm drugs
3. PK of cetirizine vs hydroxyzine
4. Hydroxyzine - Reported Cardiac Interactions
 - a. Literature reports
 - b. Epidemiology Consult
 - c. Sponsor's database search- response (1/20/94)

d. Preclinical data on hydroxyzine's electrocardiographic effects

5. Preclinical data on cetirizine's electrocardiographic effects

6. In vitro I_h channel data for hydroxyzine cetirizine and ketoconazole

7. Cetirizine's metabolism - what we know

8. Ketoconazole effects on QT_c prolongation

Part II

A. Study summaries

1. Study 90CK16-0497

2. Study 92CK16-0604

3 Study 92CK16-0603

B. Number of subjects with prolongations in QT_c >10%

C. Number of events of prolongations in QT_c >10%

D. Individual patients data for QT_c prolongation and plasma cetirizine in the drug interaction studies, collected by the MOR, using the data from the original study submissions.

Part III

A. Requests to Sponsor following the submissions of the above three studies:

1. October 26, 1993

2. November 8, 1993

3. November 23, 1993

Part IV

A. MOR Summary of the Sponsor Response to our requests

1. Study 90CK16-497

2. Study 92CK16-0603

3. Study 92CK16-0604

B. MOR conclusions on the Sponsor's response to our requests for further analysis of the electrocardiographic effects of cetirizine in 90CK16-0497, 92CK16-0603, and 92CK16-0604, following their original submission.

C. MOR overall conclusions and recommendations

Part V

A. Appendix 1 - Tables and Figures

B. Appendix 2 - Copies of literature reports

A. Prior to Advisory Committee Meeting - April 1993

1. Summary report of no effect up to 60 mg/day in healthy volunteers

Reference is made to the Final Safety Update (1/30/92) vol. 1., p 2.42, where the results of this study are summarized and to the April 1993 Advisory Committee Meeting, Executive Summary p.88 (see Appendix 1, item 1). The results were also published in abstract form in JACI January of 1993, and they showed, that in a double blind cross-over study in 24 normal volunteers to evaluate the electrocardiographic effects of cetirizine, after doses of 20 and 60 mg of cetirizine, for seven days, there was no change in QT_c as compared to placebo.

MOR: At the time of the Advisory Committee meeting we had not received the study report of this study. In our review for the Advisory Committee Meeting based on the results presented in the above references we accepted the Sponsor's conclusions on this study without further questioning the results or its analysis.

2. Retrospective analysis of EKG data from 2 SAR studies in 161 patients- % of patients with QT_c prolongation, no different from placebo.

Reference is made to our request for further safety information of 1/28/93, when we requested that the Sponsor submit a final update on the effects of cetirizine on the heart, to include the # subjects or patients with a QT_c prolonged >5%, >10%, spontaneous reports of palpitations and syncope, and to give all reports of overdosage and describe symptoms. In the 3/12/93 response, reference is made to Table 18C (Appendix 1, item 2). This table summarizes the data available at the time on patients with prolonged QT_c.

According to the Sponsor, only two cetirizine efficacy studies (SAR-8, SAR/LOR) collected ECGs at baseline and at the end of treatment. SAR-8 (protocol L-0148) was a one week comparative trial with cetirizine 10 mg qd and terfenadine 60 mg bid. SAR/LOR (protocol C-001) was a placebo controlled trial comparing cetirizine 10 mg qd and loratadine 10 mg qd given for two weeks. These trials were not specifically design to critically assess treatment effects on ECGs. The incidence of patients with QT_c prolonged by >5 to 10% and >10% is

pooled across the two studies. The results show that the incidence of cetirizine patients with prolonged QT_c >10% is less than patients given placebo, loratidine, and terfenadine. These results were presented at the Advisory Committee Meeting of April 1993.

At the time of this review we realized that there could be other studies (safety, foreign efficacy, other indications) for which this information could be available. This was discussed in the 2/15/94 meeting. A request for this information will be made to the Sponsor.

3. Cardiac toxicity update

Hydroxyzine and torsades

1 death - overdose

50 y/o female, 31,300 mg Atarax tabs, deep coma by 3 hours. To hospital within 24 hours: ventricular extrasystoles, ventricular tachycardia, torsades de pointes and ventricular fibrillation. Patient developed a severe respiratory distress syndrome and probably septic shock. Patient died on the fifth day.

1 death - IM 100mg in patient receiving terfenadine

48 y/o female patient, that had received 120 mg of terfenadine for at least 2 days with symptoms of malaise with dyspnea and tachycardia. ECG was normal in the hospital according fire brigades. On morning of event patient again developed dyspnea with thoracic discomfort; ECG was again normal. A few minutes after injection of Atarax (100 mg), torsades de pointes developed. Patient died despite resuscitation attempts.

MOR: Reference is made to the Final Safety Update (1/30/92) vol. 1., p 2.44 where these cases were described. At the time of the safety review for the Advisory Committee Meeting these cases were considered by the reviewer, but were given a low weight in terms of their relevance to the possible effects of cetirizine to QT_c in view of two negative reports of no electrocardiographic effect after receiving cetirizine 60 mg/day for 7 days, and no difference from placebo in the available data, from the two SAR studies.

On April 22, 1993, 4 days prior to the Advisory Committee meeting we received the C10MS report of a 73 y/o female that had developed increased QT interval and torsades after receiving 10 mg of cetirizine for 13 days prior to the development of torsades.

This patient had a history of heart disease with a supraventricular arrhythmia, hypertension, chronic asthmatic bronchitis and urticaria. She was treated with disopyramide, nicardipine, captopril, aminophylline, lorazepam, in addition to cetirizine. For symptoms of fever and viral illness, she was also started on lysinesprin, paracetamol and josamycin, 2 days prior to the event. The report mentions the documentation of a normal QT interval prior to treatment with disopyramide and prolongation of the QT interval post-disopyramide.

A letter interpreting the submission from Dr. Raymond Woosley accompanies this report.

MOR: At the time of the review of this report, we concurred with Dr. Woosley's conclusions on this case, that the torsades in this patient, was most likely due to disopyramide, perhaps precipitated by hypokalemia.

4. Similarity of structure to cardiac output rhythm drug Considered - but not fully explored:

MOR: A structure search had been done for structures, similarly related to cetirizine. This search picked up a couple of drug structures that were described as cardiac output rhythm drugs. At the time our concern and the focus of our review was to try to see if we could identify a structure similarity with compounds capable of inducing an immunologic reaction, in an effort to try to explain some rare hematologic-immunologic adverse reactions that had been reported, by cross-sensitization to other drugs, previously used by the patient. In these searches prior to the April Advisory Committee, meeting we identified the possibility of the piperazine ring as a possible common chemical structure, and we tried to explore this issue. The results of these searches and communications with the Sponsor did not result in positive findings in terms of the immunologic issues that we were initially concerned about.

B. Post Advisory Committee Meeting

1. Submission of the study reports 90CK16-0497, 92CK16-0604 and 92CK-0604 (9/28/93 and 9/30/93):

Cetirizine's effect on QTc prolongation:

Study 90CK 16-0497: (-) study summary

A Multiple Dose Crossover Study to Determine Electrocardiographic Effects of Cetirizine in Normal Volunteers. (20 and 60 mg cetirizine)

Population: 24 males 20 to 37 years of age, 23 white, 1 black; 2 subjects on placebo were dropped due to increases in LFTs, 1 discontinued study due to personal reasons

Design: third party blinded, multiple dose, placebo-controlled, crossover study, wash-out 5 days

Day 1 and 2 placebo
 Days 3-9 placebo or
 cetirizine 20 mg or
 cetirizine 60 mg

ECG recording on days 1, 2, 3, 5 and 9: 15 min prior and 1, 2, 4, and 6 hours post dose

Plasma cetirizine on day 9, prior to dosing and at 1, 2, 4, 6, 12, 24, 36 and 48 hrs post dose.

Study 92CK16-0604: (-) study summary

A Multiple Dose Study to Determine the Interaction of Cetirizine and Erythromycin in Young Adult Males. (20 mg cetirizine and 500 mg erythromycin)

Population: 16 males ages 22-40, 9 hispanics, 7 white; 13 completed the study

Design: Randomized, multiple dose, open (cardiologist-blinded), two way cross-over with a 20 day wash-out period.

Regimen 1 day 1: placebo QD
 days 2-6: 20 mg cetirizine QD
 Days 7-16: 500 mg erythromycin Q8h and 20 mg cetirizine QD

Regimen 2 day 1: placebo QD
 days 2-6: 500 mg erythromycin Q8h
 days 7-16: 500 mg erythromycin Q8h and 20 mg cetirizine QD

ECG on days 1 and 6: predosing and 2, 4, 6, 10, and 16 hrs post-dose

ECG on days 2, 7, and 12 pre dose, 2 and 24 hrs post dose

ECG on day 16: predosing and 2, 4, 6, 10, 16, 24, 30, 36, and 48 hrs post-dose

ECG on day 12: pre-dose 2, 4, 6, 8, 10 and 16 hrs post dose (in the second period)

Blood samples for plasma cetirizine and erythromycin levels: prior to dosing and at 2, 4, 6, 8, 10 and 16 hrs post dose on days 6 and 16 plus at 24, 30, 36 and 48 hrs post dose on day 16.

Subject #4 wide complex tachyarrhythmia of 150 bpm for 5 sec while sleeping. Twenty four hr Holter monitor, the following day recorded isolated PVCs, 25 days later on the study Holter showed multiple PVCs but were other wise within normal limits. Repeat Holter on February 1993, within normal limits.

Study 92CK16-0603: (+) study summary

A Multiple Dose Study to Determine the Interaction of Cetirizine with Ketoconazole in Young Healthy Males. (20 mg cetirizine and 400 mg ketoconazole)

mean prolongation of QT_c:

8.16 msec for cetirizine

8.32 msec for ketoconazole

Sponsor: results on QT_c prolongation are not clinically significant

Population: 16 male subjects 22-40 yrs of age, 12 hispanics, 2 black, 2 white; one subject discontinued study due to positive baseline drug screen.

Design: Randomized, multiple dose, open (cardiologist-blinded), two way cross-over with a 20 day wash-out period.

Regimen 1	day 1:	placebo QD
	days 2-6:	400 mg ketoconazole QD
	Days 7-16	400 mg ketoconazole QD and 20 mg cetirizine QD
Regimen 2	day 1:	placebo QD
	days 2-6:	placebo
	days 7-16:	20 mg cetirizine QD

During phase I:

ECG on days 1 and 6: predosing and 2, 4, 6, 8, 12 and 14 hrs post-dose
 ECG on days 2, 7, and 12 pre dose, 2 and 24 hrs post dose
 ECG on day 16: predosing and 2, 4, 6, 8, 10, 12, 14, 16, 24, 30, 36, and 48 hrs post-dose
 ECG on day 12: pre-dose 2, 4, 6, 8, 10 and 16 hrs post dose (in the second period)

During phase II:

ECG as above but with the addition of recordings at 4, 6, 8, and 12 hrs on days 7 and 12.

Blood samples for plasma cetirizine and ketoconazole levels: prior to dosing and at 2, 4, 6, 8, 12 and 14 hrs post dose on days 6 and 16 plus at 24, 30, 36 and 48 hrs post dose on day 16.

MOR: Upon initial review of the positive results presented in the Sponsor's summary for the report of the interaction study with ketoconazole, we considered that the positive results appeared to be of the same magnitude as were those initially found to be positive for terfenadine.

We first began a review of the available in-house information that could clarify whether the effect of QT_c prolongation, seen in this interaction study was one that had been previously identified in drugs with related drug structures, and in antihistamines with related chemical structures, i.e. hydroxyzine, meclizine, and cyclizine.

2. Related structure to cetirizine-cardiac output rhythm drugs

3. PK of cetirizine vs hydroxyzine

Cetirizine is the principal human metabolite of

hydroxyzine; a single 50 mg oral dose of Hydroxyzine produces plasma level exposure (AUC) of cetirizine equivalent to approximately a 20 mg dose of cetirizine. (Executive Summary 4/93, p. 12). It has been found that approximately 40% of an oral dose of hydroxyzine is recoverable in the urine as a metabolite, cetirizine, in which the terminal hydroxyl group has been oxidized to a carboxyl group. (Executive Summary 4/93, p. 4)

After a single 10 mg oral dose of cetirizine, a C_{max} of 250-350 ng/ml is reached at a T_{max} of about one hour. The plasma elimination half-life of cetirizine is 7 to 9 hours. The principal route of excretion is renal, with about 60% of the dose excreted unchanged in the urine. The total body clearance of the drug is about 60 ml/min. No major metabolite consisting of $\geq 10\%$ of the dose has been identified. (Executive Summary 4/93, p. 12) A metabolite, PO26 (produced by oxidative dealkylation of the terminal carboxymethyl group), has been identified in the plasma, urine and feces in animals and humans following chronic treatment. (Executive Summary 4/93, p. 11)

NOR: The PK data on cetirizine is based mostly in male patients (102 males and 6 females 6-12 years of age), as per Biopharm report at the 2/2/94 in-house meeting. An adequate PK characterization in females is needed*.

As discussed in the 2/2/94 meeting and reiterated in 2/15/94 provisional decision meeting, the recommendation is to request a dose escalation study with the top dose to be decided with the pharmacologists input. In this study women would be included and their PK studied.

*Makkar RR, Fromm BS, et al. Female Gender as a Risk Factor for Torsades de Pointes Associated with Cardiovascular Drugs. JAMA, 270:2590-2597, 1993 (Appendix 2, item 1)

4. Hydroxyzine - Reported Cardiac Interactions -

a. Literature Reports:

If the potential for cetirizine to induce prolongation of the QT_c is a real phenomenon, as suggested by the positive effects in the interaction studies with ketoconazole, then the search for those reports had to start with case reports of hydroxyzine treated patients.

We are only aware of one anecdotal report:

Hollister, L.E. Hydroxyzine Hydrochloride: Possible Adverse Cardiac Interactions. Psychopharmacology Communications, 1 (1), 61-65, 1975. Copy of article in Appendix 2, item 2).

100 mg tid and qid in psychiatric patients

Hydroxyzine : sedative, antihistaminic, anticholinergic, and quinidine like-effects

Anecdotal report of 27 elderly psychotic patients studied in 1958 using maximal daily doses of 300 mg over a 9 week period.

At that time the drug was promoted as an anti arrhythmic drug.

Electrocardiographic changes were mild except for alterations of T-waves which showed definite changes in 9 patients.

"Usually T-wave changes were observed in leads 1, 2, AVL and V_{3,4}. In each case the T wave changes was lowered in amplitude and tended to be broader and flatter in contour. In several cases the broadening and flattening of the T wave was rather striking, producing a somewhat notched appearance of this wave. The QT interval was usually somewhat prolonged as well. In one case U waves became quite prominent, along with the change in configuration of T waves.

"The report of this study was never published because of its generally unfavorable tone, but was submitted to the company sponsoring the drug."

- The EKG observations were almost precisely the same as had been subsequently reported for thioridazine (Mellaril).

Appendix 2, item 2, Sponsor's Fig 1 is of an EKG a patient on 400 mg hydroxyzine for 28 days that show marked attenuation of cardiac repolarization.

"cardiologists associate it with increased propensity to cardiac death"

" When drug-induced, this EKG abnormality is most often associated with drugs having a combination of quinidine-like, anticholinergic and adrenergic effects"

Increased risk of aggravating these EKG changes:

polypharmacy in: psychiatric patients
 the elderly
 the cardiac patient
 alcoholics with cardiomyopathy

MOR: The above article was included by the Sponsor in the Jan 1992 Final Safety Update. The records or ECGs of the nine patients cited in article were unavailable, both from Pfizer or from the author (personal telephone conversation).

The author, Dr. Hollister, is a well known psychopharmacologist, that was professor at Stanford and is now living in Texas.

The study suggests that at the concentrations of 300 to 400 mg/day of hydroxyzine, and as per Dr. Hollister given on a dose of 100 mg tid to qid, can produce changes in cardiac repolarization. In addition, it also suggests a potential group of patients that could have problems with potential cardiac effects due to drug interactions; polypharmacy in: psychiatric patients the elderly, the cardiac patient, alcoholics with cardiomyopathy. Of note, however, is the fact that the magnitude of ECG prolongation was not reported and that many of these subjects may have also been receiving other concomitant medications, some of which may be cardioactive, in their own right.

In an attempt to try to understand the claims of hydroxyzine as an antiarrhythmic drug at the time of the above report we also searched the literature. Considering that the following may be a rather incomplete sampling of this literature, due to the fact that there is no electronic database for the 50's and early 60's, this summary is included to show a number of cases where a clinically significant electrocardiographic effect has been reported in hydroxyzine treated patients within the recommended therapeutic dose range at the time, although because the studies were not randomized or controlled one cannot attribute these effects to hydroxyzine.

Hydroxyzine

Literature Review

Copy of original reports can be found in Appendix 2, item 3)

Studies	Design	Route/Dose	Patients	Results
Burrel (1958)	open	IV (50- 100mg) IM (25-50) PO (10-50 QID)	50	30 to NSR 6- dec cardiac rate or extrasysto les 14- no effect
King (1959)	open	PO (50 BID to QID)	2	2 parox tach to NSR
Salmons (1960)	open	IV 50 mg PO (50 TID - QID)	10	3 SPVT to NSR 1 Parox Tach to NSR 6 no effect
Tolusan (1960)	open	IV 50 mgx3 maintained PO	10	3 PSVT to NSR 1 Atrial fib to NSR 1 Parox ventric tach to NSR
Ziffer (1960)	open	IV (25-75 mg) IM (50-100 mg) PO (10-25 TID to QID)	13	10 no effect 1 + effect 1 partial+ effect 1 adverse effect (NSR to atrial fib in a pt with acute MI)

Weil (1960)	open	IV 75 mg	12	1 temp + effect (nodal rhythm to NSR)
Keiffer (1962)	controlled placebo single dose	PO 1-2 mg/lb	45 (2mo to 15 yrs) pts with congenital heart disease pre- catheteriza tion	No effect except for a dec in # of (>3) premature nodal contractio ns
Andersen (1966)	open	IV (0.015, 0.3, 1.5 mg/kg)	8 normal volunteers	dec heart rate dec cardiac output inc peripheral resistance
Lauria (1968)	controlled	IV (0.75-1 mg/lb)	14 normal volunteers	2/10 (+) rapid tilt test with sympt. hypo- tension

SPVT: supraventricular tachycardia
 PSVT paroxysmal ventricular tachycardia
 NSR normal sinus rhythm
 Parox tach paroxysmal tachycardia- not specified whether
 atrial or ventricular

b. Epidemiology consult

i. piperazine structure search

Epidemiology was consulted to search and identify pertinent reports on antihistamines with a piperazine structure (search strategy and classification as in Appendix 1, item 3) from their database; presented at

the 11/2/93 in-house meeting, by Ms. Anastasia Nasis. From these, (Appendix 1, item 4), the Sponsor was asked to provide all medical records on case 937778.

Case 937778: This 78 y/o female patient was on procainamide for 3 yrs; started on oral Vistaril as a sleep aid. In 3 days presented to the ER and was diagnosed to have torsades. Vistaril was discontinued, and the event resolved. Vistaril was restarted with recurrence of arrhythmias. Vistaril was discontinued and the patient recovered with no sequela.

MOR: We have not yet received the medical records for this patient, from the Sponsor. However, the Sponsor submitted by fax a follow up to the initial report, Appendix 1, item 5), however it is still not clear from this report and from telephone communications with the initial reporter whether the patient was receiving procainamide when the Vistaril was restarted.

c. Sponsor's database search- response (1/20/94)

Case Reports of patients treated with hydroxyzine and meclizine that can relate to prolongation of QT from the Sponsor's response dated (1/20/94).

Database:

-early alert database regardless of severity and all spontaneous and all serious adverse effects during clinical trials after 1989

-non US after 1/84 and US after 1/86 based on drug severity

Rationale for validity of this database:

-adverse event reporting is more complete in recent years than 30 yrs ago

- increased attention to antihistamines and cardiac arrhythmias in recent years has stimulated reporting

Sponsor's Conclusions:

No indication that serious arrhythmias occur at normal therapeutic doses in otherwise healthy patients.

Hydroxyzine: 12 cases all spontaneous reports. Eight female, four male; 7 female patients, 20-50 y/o.

Of these:

R2P991: 31,300 mg, intentional overdose: coma respiratory arrest, anoxia, cyanosis, convulsions, arrhythmias, torsades.

R11S492: 39 y/o female, 100 mg hydroxyzine and 120 mg/day terfenadine for dental procedure. Extreme somnolence, 3 days later: syncope, 4 days post dose: circulatory collapse torsades. Rechallenge with terfenadine-wide QT.

R9300233: 78 y/o female on procainamide received hydroxyzine for 3 days as sleeping aid, dose?, pt. develops torsades. Hydroxyzine d/c, arrhythmia resolved; syncopal symptoms recur with reintroduction of hydroxyzine. Was the pt. on procainamide when rechallenged with hydroxyzine? -patient recovered

R7S192: 100 mg of hydroxyzine given IM to a 48 y/o female that had received terfenadine (120 mg/day). Pt. developed ventricular arrhythmia, ? torsades, ECGs provided by Sponsor. Patient died.

Meclizine: 6 cases; 4 female (8-80 y/o), 2 male

Med Watch

9390909

80 y/o female that was taking meclizine and had increased the dose to 6-8 tabs/day- torsades. She had heart failure and liver disease. QTU 480 after meclizine was stopped, QTU=>600 during ECGs torsades. Meclizine levels at the time, 660 ng/ml. Reporting physician comments: these levels can be seen in ambulatory patients; liver disease and CHF of severity seen in ambulatory patients.

MOR: In three patients receiving concomitant medication that can prolong the QT interval, torsades des pointes was apparently precipitated by the addition of hydroxyzine at recommended doses. The complete medical records of patients 9300233 and R-7S192 were requested.

A case report in an elderly patient taking meclizine (chemically related antihistamine to cetirizine) at above the recommended dose develops torsades.

d. Preclinical data on hydroxyzine's electrocardiographic effects

MOR: A summary of available English translated literature was presented by Dr. Joe Sun in the 2/2/94 "in-house" meeting. The summary of these reports will be part of a separate review by Dr. Sun. However, from the presented data of 4 articles from the 1950's to 1960's:

Hydroxyzine can prolong the QT interval in the Dog at doses of 3 mg/kg i.v. (although the degree of prolongation is not reported in the literature), and that in the cat's auricle it can prolong the refractory period (100% at 53 micromolar). A decrease amplitude (28-89%, 117-234 micromolar) in an isolated cat auricle model to 7-31% (125-500 micrograms) in an isolated cat heart model. In the isolated cat auricle model the frequency of contraction was decreased to 11-19% using hydroxyzine at 117-234 micromolar concentration.

This preclinical data appear to support the clinical findings in the literature at the time.

5. Preclinical data on cetirizine's electrocardiographic effects

MOR: A summary of these findings was presented by Dr. Joe Sun in the 2/2/94 "in-house" meeting. The summary of these reports and their relation to human drug exposure and safety will be part of a separate review by Dr. Sun.

Cetirizine can induce electrocardiographic effects in the anesthetized dog (lowering ST, conduction block (14.7 mg/kg iv) and increase in T wave (148 mg/kg i.d.)).

6. In vitro I_k channel data for cetirizine, hydroxyzine and ketoconazole

Not available from Sponsor.

MOR: However, from Marion Merrel Dow, (Submission provided by Dr. Michael Sevka), the effect of several antihistamines and other drugs (including cetirizine and hydroxyzine) on membrane ion currents and action potential duration in ventricular myocytes is reported (Appendix 1, item 6), Marion Merrel Dow Table 2 and Table 9. The number under the I_{k1} and I_k columns represent % control current amplitude. I_{k1} = inward rectifying K^+ current and I_k = delayed rectifier K^+ current.

From Table 2

	(mM)	I_{k1}	I_k
hydroxyzine	1	84+/-7	75+/-24
	10	71+/-27	60+/-14
cetirizine	1	---	93+/-3
	10	98+/-3	71+/-5
ketoconazole	1	89+/-12	91
	10	92+/-2	48+/-2

From Table 9

	(mM)	I_{k1}	I_k
terfenadine	.01	99+/-2	100
	.1	95+/-2	100
	1.0	86+/-4	98+/-2
	10	75+/-12	0

MOR: In our 11/2/93 in-house meeting, Dr. Joe Sun compared the concentrations tested in the above set of experiments to the usual plasma levels of cetirizine. It was concluded that cetirizine had to be tested at higher concentrations for the above experimental design.

7. Cetirizine metabolism -what we know

Cetirizine's major elimination pathway is renal - approximately 60% of the daily dose is excreted unchanged in the urine. About 20% of the compound is metabolized and less than 4% as the human metabolite, PO26. PO26 is a product of oxidative dealkylation of

the terminal carboxymethyl group, that according to the Sponsor's report has minimal antihistaminic activity (H-1), but that in mice can influence general behavior at lower doses (2-4 times lower) than cetirizine. According to the only clinical PK study that we are aware of, CPK-12 (p2. 75 and 2. 85 in the Item 2 part VI Human Pharmacokinetic and Bioavailability Summary) after a single dose, at 30 hrs, increasing proportions of the metabolite were found (maximally 5 ngeq/ml at 30 hrs).

Results of consult to Dr. Jerry Collins for metabolic studies-2/7/94

It was not considered that metabolic studies would be helpful to elucidate the mechanism of the drug's action at this time or in explaining the different outcomes between the ketoconazole study and the dose escalating study (in-house meeting 2/15/94). (Appendix 2, item 4)

MOR: As discussed in the 2/2/94 meeting and reiterated in 2/15/94 provisional decision meeting, the recommendation is to request a dose escalation study with the top dose to be decided with the pharmacologists input. In this study women would be included and their PK studied.

8. Ketoconazole effects on QT_c prolongation

L.A. Paserchia, J. Hewett, R.L. Woosley. Effects of Ketoconazole on QT_c. Abstract submitted to the American Society for Clinical Pharmacology and Therapeutics.

Six healthy volunteers (1F, 5M) were given placebo q12h (days 1-3), then Ketoconazole 200 mg q 12h (days 4-8). Multiple EKGs on days 3 and 8, Ketoconazole produced a significant increase in mean QT_c (402.1 msec to 407.6 msec) [p<0.02].

"This results suggests that ketoconazole contributes to QT_c prolongation in the ketoconazole-terfenadine interaction."

MOR: This appears to be the first report in the literature (Peter Honig 2/2/94 -in-house meeting) that supports the findings that ketoconazole can prolong the QT_c in normal volunteers and it is suggested that this effect may contribute to QT_c prolongation in the ketoconazole-terfenadine interaction. The magnitude of the mean prolongation of QT_c in this study is of 5.5

usec. The magnitude of this prolongation is of about the same magnitude as that observed with cetirizina.

Part II

A. Study Summaries:

1. Study 90CK 16-0497: (-) study summary

A Multiple Dose Crossover Study to Determine Electrocardiographic Effects of Cetirizine in Normal Volunteers. (20 and 60 mg cetirizine)

Population: 24 males 20 to 37 years of age, 23 white, 1 black; 2 subjects on placebo were dropped due to increases in LFTs, 1 discontinued study due to personal reasons

Design: third party blinded, multiple dose, placebo-controlled, crossover study, wash-out 5 days

Day 1 and 2 placebo
Days 3-9 placebo or
cetirizine 20 mg or
cetirizine 60 mg

ECG recording on days 1, 2, 3, 5 and 9: 15 min prior and 1, 2, 4, and 6 hours post dose

Plasma cetirizine on day 9, prior to dosing and at 1, 2, 4, 6, 12, 24, 36 and 48 hrs post dose.

2. Study 92CK16-0604: (-) study summary

A Multiple Dose Study to Determine the Interaction of Cetirizine and Erythromycin in Young Adult Males. (20 mg cetirizine and 500 mg erythromycin)

Population: 16 males ages 22-40, 9 hispanics, 7 white; 13 completed the study

Design: Randomized, multiple dose, open (cardiologist-blinded), two way cross-over with a 20 day wash-out period.

Regimen 1 day 1: placebo QD
days 2-6: 20 mg cetirizine QD
Days 7-16: 500 mg erythromycin Q8h and 20 mg cetirizine QD

Regimen 2 day 1: placebo QD
days 2-6: 500 mg erythromycin Q8h
days 7-16: 500 mg erythromycin Q8h and 20 mg cetirizine QD

ECG on days 1 and 6: predosing and 2, 4, 6, 10, and 16 hrs post-dose

ECG on days 2, 7, and 12 pre dose, 2 and 24 hrs post dose

ECG on day 16: predosing and 2, 4, 6, 10, 16, 24, 30, 36, and 48 hrs post-dose

ECG on day 12: pre-dose 2, 4, 6, 8, 10 and 16 hrs post dose (in the second period)

Blood samples for plasma cetirizine and erythromycin levels: prior to dosing and at 2, 4, 6, 8, 10 and 16 hrs post dose on days 5 and 16 plus at 24, 30, 36 and 48 hrs post dose on day 16.

Subject #4 wide complex tachyarrhythmia of 150 bpm for 5 sec while sleeping. Twenty four hr Holter monitor, the following day recorded isolated PVCs, 25 days later on the study Holter showed multiple PVCs but were other wise within normal limits. Repeat Holter on February 1993, within normal limits.

3. Study 92CK16-0603: (+) study summary

A Multiple Dose Study to Determine the Interaction of Cetirizine with Ketoconazole in Young Healthy Males. (20 mg cetirizine and 400 mg ketoconazole)

mean prolongation of QT_c:

8.16 msec for cetirizine

8.32 msec for ketoconazole

Cetirizine produces overall mean prolongation of QT_c of 8.16 msec (p=0.001). Ketoconazole produces an overall mean prolongation in QT_c of 8.32 (p=0.028). The Sponsor estimates that based on these findings, the effect of combination treatment on Hodges QT_c to be additive, 16.48 msec.

Sponsor: results on QT_c prolongation are not clinically significant

Population: 16 male subjects 22-40 yrs of age, 12 hispanics, 2 black, 2 white; one subject discontinued study due to positive baseline drug screen.

Design: Randomized, multiple dose, open (cardiologist-blinded), two way cross-over with a 20 day wash-out period.

Regimen 1	day 1:	placebo QD
	days 2-6:	400 mg ketoconazole QD
	Days 7-16	400 mg ketoconazole QD and 20 mg cetirizine QD
Regimen 2	day 1:	placebo QD
	days 2-6:	placebo
	days 7-16:	20 mg cetirizine QD

During phase I:

ECG on days 1 and 6: predosing and 2, 4, 6, 8, 12 and 14 hrs post-dose

ECG on days 2, 7, and 12 pre dose, 2 and 24 hrs post dose

ECG on day 16: predosing and 2, 4, 6, 8, 10, 12, 14, 16, 24, 30, 36, and 48 hrs post-dose

ECG on day 12: pre-dose 2, 4, 6, 8, 10 and 16 hrs post dose (in the second period)

During phase II:

ECG as above but with the addition of recordings at 4, 6, 8, and 12 hrs on days 7 and 12.

Blood samples for plasma cetirizine and ketoconazole levels: prior to dosing and at 2, 4, 6, 8, 12 and 14 hrs post dose on days 6 and 16 plus at 24, 30, 36 and 48 hrs post dose on day 16.

B. Number of subjects with prolongations in $QT_c > 10\%$

90CK 16-0497*: Bazett's $QT_c > 10\%$

placebo 6

20 mg cet 4

60 mg cet 6

92CK16-0604*: Hodges $QT_c > 10\%$

cetirizine -

erythromycin 2

comb follow
cetirizine 2

comb follow
erythromycin 4

92CK16-0603* Hodges $QT_c > 10\%$

placebo -

20 mg cet 2

ketoconazole 1

combination 5

* each subject counted once regardless of the number of occurrences

C. Number of events of prolongations in $QT_c > 10\%$

90CK 16-0497: Bazett's $QT_c > 10\%$

placebo	8
20 mg cet	8
60 mg cet	11

90CK16-0497: Hodges $QT_c > 10\%$

placebo	11
20 mg cet	0
60 mg cet	3

92CK16-0604: Hodges $QT_c > 10\%$

cetirizine	-
erythromycin	2
comb follow cetirizine	3
comb follow erythromycin	4

92CK16-0603 Hodges $QT_c > 10\%$

placebo	-
20 mg cet	3
ketoconazole	2
combination	18

MOR: The above tables referring to the # of subjects with a $> 10\%$ increase in QT_c and # of events where

subjects QT_c was prolonged $>10\%$, are derived from the Sponsor's Tables 4 (# subjects) for each one of the study reports in vol 1 and Table 5 (# events) for each one of the study reports in vol 1. (Appendix 1 item 7).

The calculations using the Hodges method for study 90CK16-049, not only reflect a change in the methodology used for calculating QT_c , but also respond to a request from our part, to calculate this data regarding baseline, in a similar way to the other two studies. Refer to Request to Sponsor dated November 8, 1993. This topic will be covered later, in the review of the Sponsor's response to these analyses.

D. Individual patients data for QT_c prolongation and plasma cetirizine in the drug interaction studies, collected by the MOR, using the data from the original study submissions. The events are the QT_c prolongations $>10\%$ as defined by the Sponsor. The individual data was collected for 5 of the patients in study 92CK12-0603 and for 2 of the 4 patients of Study 92CK12-0604 that are summarized in the previous tables.

Protocol 92CK16-0603

A Multiple Dose Study to Determine the Interaction of Cetirizine with Ketoconazole in Young Healthy Males.

H= hispanic W= white

Subject #2 (H)

Number of events= 4, during ketoconazole combination-Phase 2
 on day 12: 4 and 6 hours post dose
 on day 16: 4 h post dose
 on day 17 :24 h post dose

Cetirizine plasma levels:

Phase 1

cetirizine	Day 7 hour 2	481.0
alone	12 2	186.5
	16 2	232.0

Phase 2

cetirizine after	Day 7 hour 2	-
keto	12 2	356.0
	16 2	544.5

Subject #5 (H)

Number of events= 3, during ketoconazole combination-Phase 2

on day 12: 4 and 12 hours post dose
on day 16: 16 h post dose

Cetirizine plasma levels:

Phase 1			
cetirizine	Day 7	hour 2	254.5
alone	12	2	562.0
	16	2	655.0
Phase 2			
cetirizine after	Day 7	hour 2	-
keto	12	2	584.5
	16	2	658.5

Subject #7 (H)

Number of events= 4, during ketoconazole combination-Phase 1
on day 16: 2, 4, 8, and 12 hours post dose

Cetirizine plasma levels:

Phase 1			
cetirizine after	Day 7	hour 2	456.0
keto	12	2	561.0
	16	2	351.5
		4	498.7
Phase 2			
cetirizine	Day 7	hour 2	-
alone	12	2	524.5
	16	2	498.7

Subject #14 (H)

Number of events= 5, during ketoconazole combination-Phase 2
on day 12: 0, and 2 hours post dose
on day 16: 0, 2 and 4 h post dose

Cetirizine plasma levels:

Phase 1			
cetirizine	Day 7	hour 2	448.0
alone	12	2	499.5
	16	2	438.5
		4	438.5
Phase 2			
cetirizine after	Day 7	hour 2	-
keto	12	2	358.5
	16	2	443.5

Subject #6 (W)

Number of events= 2, during cetirizine alone-Phase 2

on day 12; 0, and 24 hours post dose

Cetirizine plasma levels:

Phase 1

cetirizine after	Day 7	hour 2	424.5
keto	12	2	213.0
	16	2	306.0
		4	428.5

Phase 2

cetirizine	Day 7	hour 2	-
alone	12	2	463.5
	16	2	317.0

Protocol 92CK16-0604:

Subject # 10 (W)- Phase 2

The event was recorded 4 hours post dose on day 16 on the combination after the erythromycin, corresponds to an absolute value of QT, Hodges of 425 and to a QT, Bazzet of 445.

Cetirizine plasma levels:

Phase 1

Cetirizine alone	Day 2	hour 2	369.0
	6	2	338.5
	7	2	417.5

After cetirizine combination

Day 12	hour 2	358.5
16	2	417.0

Phase 2

After erytho combination

Day 7	hour 2	-
12	2	430.0
16	2	421.0

Subject #15- (W) phase 2

The 2 events recorded at 6 and 16 hours post dose on day 16 on the combination after cetirizine, corresponds to an absolute value of QT, Bazzet 449 and 445 respectively.

Cetirizine plasma levels:

Phase 1

After erytho combination

Day 7	hour 2	418.5
12	2	448.5
16	2	431.5

Phase 2			
Cetirizine alone	Day 2	hour 2	785.0
	6	2	440.5
	7	2	-
After cetirizine combination	Day 12	2	438.5
	16	2	413.5

MOR conclusions from review of the individual patient data on QT_c prolongation:

The number of events of >10% QT_c prolongation is increased in 4/16 (25%) (subjects # 2, 5, 7, and 14) healthy volunteers that received the combination of cetirizine-ketoconazole, as compared to when these subjects were on cetirizine, ketoconazole or placebo alone, as can be seen in the Sponsor's Table 5 (Appendix 1, item 7). The individual data on these patients was included in the above section. Although there are occasional patients in which a relative increase in plasma cetirizine concentration are seen at the time of these events, it is not a consistent finding.

Part III**A. Requests to Sponsor following the submissions of the above three studies:****1. October 26, 1993**

1. Please calculate changes in QT_c interval for study 90CK16-0497 similarly to those in the drug interaction studies. For the k hour value on the treatment on phase c for a subject's 2 day average of placebo at k hours in that phase. (There are two days of placebo here as opposed to only one day in the drug interaction studies). Then do an analysis of variance on:

- a) AUC under QT_c on day 9
- b) the 2 hour changes in the QT_c interval for Day 9
- c) on the daily average (hour 1, 2, 4, and 6 only, do not include hour -0.25 value in the daily average) on day 9 changes in QT_c .
- d) $QT_{c \max}$

2. Please do ANOVA on $QT_{c \max}$ for the two interaction studies, 92CK16-0604 and 92CK16-0603.

3. Please do ANOVA on AUC under QT_c interval for the two interaction studies, 92CK16-0604 and 92CK16-0603.

4. For the above three studies please do Pearson's correlation coefficients with cetirizine/metabolite concentrations.

2. November 8, 1993

1. Please perform the following analyses for study 90CK16-0497:

A. An analyses of variance on:

1. QT_c AUC for hours 0-6 and 0-24 on day 9 (assuming steady state, the -0.25 hour value of day 9 can be used as the 24 hour value for day 9) compared to the mean QT_c AUC of days 1 and 2 for hours 0-6 and 0-24 for each treatment arm.
2. QT_c AUC for hours 0-6 and 0-24 on Day 9 (assuming steady state, the -0.25 hour value of day 9 can be used as the 24 hour value for

day 9) compared between the three arms (placebo, 20 and 60 mg cetirizine). Please do analyses to check for sequence effects in the cross-over model.

B. Use plasma cetirizine levels on days 7, 8, and 9 to demonstrate steady state.

C. Mean number of ECGs for hours 0-6 and 0-24 on day 9 with a > 10% increase in QT_c from the mean of the predose ECGs on Days 1 and 2 v.s. the mean number of ECGs with a > 10% increase in QT_c for hours 0-6 and 0-24 on Days 1 and 2, for each treatment arm.

D. Mean number of ECGs for hours 0-6 and 0-24 on day 9 with a > 10% increase in QT_c from the mean of the predose ECGs on Days 1 and 2 compared between the three treatment arms.

E. Please submit copies (high quality) of all the above ECGs with QT_c increase of >10% as well as those baseline ECGs on Day 1 and 2, for review.

F. Please submit absolute numbers, in table form, for $QT_{c, \max}$ for hours 0-24 on Day 1, Day 2 and Day 9 (assuming steady state, the -0.25 hour value of day 9 can be used as the 24 hour value for day 9) for each treatment arm. Do analysis of variance for the three days within each treatment arm; please check for sequence effect.

G. Please submit PC SAS dataset of patient data to our Biometrics Division.

2. Please do appropriate analyses to correlate plasma cetirizine clearance with $QT_{c, \max}$ for the three studies: 90CK16-0497, 92CK16-0604 and 92CK16-0603. To calculate $QT_{c, \max}$ for study 90CK16-0497, please use the same procedure as was described in 1F above.

3. Please submit all data, from all sources that could relate to prolongation of QT by: hydroxyzine, meclizine or cyclizine.

4. Please submit all study reports, records, and ECGs from the 1958 study on hydroxyzine in psychotic patients by Dr. Hollister cited in the Hollister L.E. Hydroxyzine hydrochloride: Possible Adverse Cardiac Interactions. Psychopharm Commun 1:61-65, 1975.

5. All metabolites of cetirizine should be identified and characterized using appropriate in vitro or in vivo techniques. The pharmacodynamics of these metabolites should be evaluated. In addition, the metabolites of hydroxyzine other than cetirizine should also be identified and characterized.

6. The effects of cetirizine and its metabolites on cardiac repolarization, including ion currents and action potentials should be evaluated. The data on I_K , I_{K1} , I_{Ca} , I_{Na} can be expressed in terms of IC_{50} and $\%$ control current amplitude, data on amplitude of AP, dv/dt , and duration AP.

3. November 23, 1993

1. Please compare all possible demographic parameters between the three studies, 90CK16-0497, 92CK16-0603, and 92CK16-0604, that could explain the different outcome observed in study 92CK16-0603 on QT_c prolongation by cetirizine versus the other two trials.

2. Please explain the switch from negative to positive and the change in magnitude in the correlation coefficients for cetirizine clearance when the drug is administered by itself vs combination (see Table 4B). Does this indicate a pharmacodynamic interaction of cetirizine with ketoconazole or effects of a cetirizine metabolite?

3. Please explain the different correlation coefficients for cetirizine clearance when the drug is administered by itself vs combination, based on Table 4C.

4. Please submit the medical records of the 48 y/o female patient reported in 15 day report identified with a manufacturer control No. as R-7S192, submission date January 20, 1992.

5. Please submit any information which you may have regarding cases (worldwide) of torsades de pointes, QT_c prolongation or ventricular arrhythmias in subjects receiving hydroxyzine.

Part IV

A. MOR Summary of the Sponsor Response to our requests:

1. Study 90CK16-497 Cetirizine 20 mg, cetirizine 60 mg and placebo

Day 9

QT_cAUC

-

There are no significant differences between treatment groups. Refer to Table 1 from the October 29, 1993 Sponsor's response. (Appendix 1, item 8)

2 Hr QT_cAUC

-

There are no significant differences between treatment groups. Refer to Table 1 from the October 29, 1993 Sponsor's response. (Appendix 1, item 8)

QT_c max

decrease in cet 20

There are significant differences between treatment groups. The decrease in the the QT_cmax for the 20 mg cetirizine group is significantly different from the placebo and the 60 mg cetirizine groups. Refer to Table 1 from the October 29, 1993 Sponsor's response. (Appendix 1, item 8)

Mean change QT_cAUC 24h within treatment groups

vs. Day 1 + 2

(-)?

The change from baseline in QT_c AUC 24 h within treatment groups are depicted in Table 1.A.1 from the November 19, 1993 Sponsor's response. (Appendix 1, item 9). However, it is not clear to this reviewer that a statistical analysis comparing the within treatment groups differences vs baseline are included in the Sponsor's 11/19/93 response, Table 1.A.2 (Appendix 1, item 10)

Mean change QT_cAUC 24h between treatment groups

vs. Day 1 + 2:

cetirizine 60 is 2x>placebo and 9x>cet 20

The changes from baseline in QT_c AUC 24 h between treatment groups are depicted in Table 1.A.1 from the November 19, 1993 Sponsor's response. (Appendix 1, item 9). The reported mean changes are 71.1 +/- 166.29, 21.1 +/- 254.08 and 185.3 +/- 263.38 for placebo, 20 mg cetirizine and 60 mg cetirizine respectively. The statistical analysis comparing the changes between treatment groups are included in the Sponsor's 11/19/93 response, Table 1.A.2 (Appendix 1, item 10). The p value for this comparison is 0.078, showing a trend to a significant difference.

Mean # ECG with >10% increase QT_c within groups ?
 Mean # ECG with >10% increase QT_c between groups ?

We asked the Sponsor for the mean number of ECGs for hours 0-6 and 0-24 on day 9 with a > 10% increase in QT_c from the mean of the predose ECGs on Days 1 and 2 v.s. the mean number of ECGs with a > 10% increase in QT_c for hours 0-6 and 0-24 on Days 1 and 2, for each treatment arm; the between treatment group comparison was also requested.

In the Sponsor's response of 11/19/93, summarized in Table 1.C.1. (Appendix 1, item 11) the Sponsor reports the incidence of greater than 10% increase in QT_c from mean dose on placebo Days 1 and 2. For each subject and treatment the control QT_c was defined as the mean of the pre-dose (hour 0) QT_c on placebo run in days 1 and 2. The percentage out of 5 QT_c 's (at hour 0, 1, 2, 4, and 6) on day 9 which were greater than the control QT_c by more than 10% was determined. The baseline incidence of greater than 10% increase over control QT_c was similarly defined as the percentage out of ten QT_c 's on placebo run in days 1 and 2. The incidence on day 9 was compared to the corresponding baseline incidence, and for each treatment the number of subjects was counted for which the day 9 incidence was less than, equal to or greater than the baseline incidence. The listing of specific occurrences is listed in the Sponsor's Table 1.C.2. (Appendix 1, item 12)

Seventeen out of 21 subjects had no occurrences of a greater than 10% increase over control QT_c on any treatment.

Two subjects had incidence of 2/5 (subject #16) and 1/5 (subject #19) respectively on day 9 after

cetirizine 60 mg dosing, but no occurrences on corresponding baseline.

Eleven events occurred in one subject (subject #20) during the placebo treatment phase only, with no occurrences after cetirizine 20 or 60 mg dosing. Another subject (subject # 5) had one occurrence on placebo run -in day 1 but no events on day 9 of the cetirizine 60 treatment phase.

Cetirizine steady state levels were achieved on Day 8, i.e. by the sixth dose. (Days 1 and 2 were placebo run-in days)

Pearson correlation coefficient of $QT_{c\max}$ (-)
vs cetirizine clearance -last day
of treatment

The $QT_{c\max}$ was not significantly correlated with plasma cetirizine clearance for either dose. For cetirizine 20 mg it was 0.366 ($p=0.102$) and for 60 mg cetirizine it was 0.181 ($p=0.434$).

2. Study 92CK16-603, Interaction of Cetirizine with Ketoconazole in Young Healthy Males. (20 mg cetirizine and 400 mg ketoconazole)

Change QT_{cAUC} 0-24 Day 16 + Cet + Keto +Comb

Refer to Table 3A in the October 29, 1993 Sponsor's response (Appendix 1, item 13). The estimated overall cetirizine effect is 189.20 msec ($p=0.001$). The estimated overall ketoconazole effect is 211.60 msec ($p=0.021$). The p values for the pairwise comparison of the components and combination are $p=0.005$ for combination versus cetirizine and $P=0.009$ for combination versus ketoconazole.

Change $QT_{c\max}$ Day 16 + Cet + Keto +Comb

Refer to Table 2A in the October 29, 1993 Sponsor's response (Appendix 1, item 14). The estimated overall cetirizine effect is 6.77 msec ($p=0.001$). The estimated overall ketoconazole effect is 9.57 msec ($p=0.021$). The p values for the pairwise comparison of the components and

combination are $p=0.003$ for combination versus cetirizine and $P=0.020$ for combination versus ketoconazole.

Correlations:

	Cet	Comb	Keto	Comb
Mean Change QT_{cmax}				
vs. Drug C_{max}	-	-	-	-
vs. Drug clearance	+	-	-	-
Max Change QT_{cmax}				
vs. Drug C_{max}	-	-	-	-
vs. Drug clearance	-	-	-	-

The correlations of average change and maximum change from baseline Hodges QT_c with drug C_{max} and clearance were not statistically significant with the exception of correlation of the mean average change in QT_{cmax} from baseline and cetirizine clearance. For an $N=16$, it was -0.545 ($p=0.036$). Refer to the Sponsor's Table 4B from the October 29, 1993 submission (Appendix 1, item 15).

QT_{cmax} on last day of treatment-Pearson

vs. Drug clearance	-	-	-	-

Upon further requests to the Sponsor in our fax dated Nov. 8, 1993, the Sponsor response of 11/19/93, does not show a significant correlation at day 16 of QT_c and drug clearance. Refer to Table 2 of the 11/19/93 submission (Appendix 1, item 16).

It is difficult to ascertain the significance of the only positive significant correlation for cetirizine clearance on the mean QT_{cmax} . The Sponsor does not consider that this positive correlation could be due to drug interaction, since no significant effects were obtained with the drug combination. In addition, since no significant effects were obtained with the drug

combination on changes in QT_c , it was considered that this would imply a lack of interaction of cetirizine metabolites with ketoconazole.

PK interaction between cetirizine and ketoconazole

The study report does not show a significant pharmacokinetic interaction between cetirizine and ketoconazole. Tables 8, 9 and 10 of the Study report (9/30/93 submission). (Appendix 1, item 17).

3. Study 92CK16-604, Interaction of Cetirizine and Erythromycin in Young Adult Males. (20 mg cetirizine and 500 mg erythromycin stearate). C1 is the combination of cetirizine and erythromycin following cetirizine and C2 is the combination of cetirizine and erythromycin following erythromycin treatment.

Change QT_c AUC 0-24	Day 16	*- Cet - Eryt	-C1 -C2
Change QT_c max	Day 16	- Cet - Eryt	-C1 -C2*

Cetirizine by itself decreases QT_c AUC, the estimated effects for cetirizine alone taking into consideration the results on Day 6 and Day 16 are not statistically significant. Refer to Table 3B, Sponsor's 10/29/93 (Appendix 1, item 18).

Since in this study there was no placebo treatment period, the significance of the effects cannot be tested under the null hypothesis. The Sponsor's Table 2B 10/29/93 (Appendix 1, item 19), includes the mean values of the maximum change from baseline for when the drug was administered alone or in combination. The most pronounced changes are for the drug combination after receiving erythromycin for 5 days. However, this value (21.69 msec) is no different from when erythromycin is administered alone (21.62 msec).

Correlations

C1 is the combination of cetirizine and erythromycin following cetirizine and C2 is the combination of cetirizine and erythromycin following erythromycin treatment.

	Cet	C1	C2	Eryth	C1	C2
Mean Change QT_{cmax}						
vs. Drug C_{max}	-	-	-	-	-	-
vs. Drug clearance	-	-	(+)	-	-	-
Max Change QT_{cmax}						
vs. Drug C_{max}	-	-	-	-	-	-
vs. Drug clearance	-	-	(+)	-	-	-

For the above correlations refer to the Sponsor's Table 4C from the 10/29/93 submission (Appendix 1, item 20). The significant or nearly significant correlations occur only after the combination following the erythromycin treatment (C2). No significant correlations were found between changes in QT_c and drug clearance for cetirizine alone, erythromycin alone or either drug in combination following cetirizine alone.

The Sponsor's considers this finding to be anomalous in nature due to the lack of reproducibility within the study design (cross-over), when the combination was given following cetirizine (C1), and to the lack of effect on QT_c prolongation by ceterizine alone or in combination with erythromycin.

QT_{cmax} (Pearson) for the last day of treatment

vs. Drug clearance - - - - -

When this correlation is used there no statistical significant findings for any of the treatments. Refer to Table 2 from the 11/19/93 submission (Appendix 1, item 16).

B. MOR conclusions on the Sponsor's response to our requests for further analysis of the electrocardiographic effects of cetirizine in 90CK16-0497, 92CK16-0603, and 92CK16-0604, following their original submission.

Cetirizine has positive and potentially clinically significant effects on QT_c prolongation whose risks in terms of safety have not been adequately characterized for the intended population.

1. In the cetirizine-ketoconazole interaction study, 92CK16-0603, cetirizine has a positive statistically significant effect on QT_c prolongation. Cetirizine produces overall mean prolongation of QT_c of 8.16 msec ($p=0.001$). Ketoconazole produces an overall mean prolongation in QT_c of 8.32 ($p=0.028$). The Sponsor estimates that based on these findings, the effect of combination treatment on Hodges QT_c to be additive, 16.48 msec. In addition, in this study for both cetirizine and ketoconazole alone and in combination, statistically significant changes in QT_cAUC 0-24h and change in $QT_{c, max}$, were also observed.
2. There is no evidence of a statistically significant PK interaction between cetirizine and ketoconazole.
3. Plasma cetirizine concentrations, including C_{max} , have not been correlated with the electrocardiographic findings in any of the above three studies.
4. It is difficult to ascertain the significance of the only positive significant correlation for cetirizine clearance on prolongation of the mean $QT_{c, max}$, in study 92CK16-0603; mean average change in $QT_{c, max}$ from baseline and cetirizine clearance. For an $N=16$, it was -0.545 ($p=0.036$). Refer to the Sponsor's Table 4B from the October 29, 1993 submission (Appendix 1, item 15). When a Pearson correlation was calculated for the last day of drug treatment the positive effect is no longer seen. The Sponsor does not consider that the initially observed positive correlation could be due to drug interaction, since no significant effects were obtained with the drug combination; at this time we agree.
5. Drugs with chemical structures related to cetirizine can significantly prolong clinically the QT interval and produce torsades.
6. An anecdotal literature report suggests that hydroxyzine has direct cardiac effects on

repolarization.

7. The literature reports of the 1950s and 1960s on hydroxyzine as an antiarrhythmic do not agree on the nature or reproducibility of its antiarrhythmic properties, however a good number of individual cases are reported where it appears that an electrocardiographic effect can be observed.

8. There is one case report of torsades with hydroxyzine overdose.

9. There are three case reports of patients given recommended doses of hydroxyzine along with the concomitant use of medication that can prolong the QT_c interval in whom torsades was precipitated by the addition of hydroxyzine.

10. We do not have in-vitro channel data on cetirizine from the Sponsor. The in-vitro ion channel data on cetirizine (obtained from a separate submission) is not conclusive at the concentrations tested for the experimental model used, higher concentrations are needed.

11. The reproducibility of the positive effects of ketoconazole on QT_c prolongation and the validity of the conclusions drawn from just this study were questioned in the 11/2/93 in-house meeting. Subsequently, in an abstract (submitted for publication by Dr. Woosley's group) a mean positive effect of ketoconazole on QT_c prolongation was observed in 6 normal volunteers of about the same or less magnitude (5.5 msec) than that observed in Study 92CK16-0603. This lead the authors to suggest that in fact this could be a meaningful clinical effect and that it could contribute to the cardiac effects in the ketoconazole-terfenadine interaction.

12. In view of the absence of an adequate characterization of PK in women in this NDA and the reported higher incidence of torsades in women, the recommended dose escalation study to study cetirizine electrocardiographic effects should include women.

13. The summary data that we have available on studies with ECGs done before and the end or during treatment may not be complete, since the apparent data base for this search was the efficacy studies. This needs to be confirmed and the request for a search and report that would cover all studies needs to be made.

Recommended Regulatory Action

Non-Approval of NDA 19835, based on the above safety concern, as per the decision made during the Division in-house meetings (2/2/94 and 2/15/94).

The following comments should be included in the clinical section of the non-approvable letter:

1. A dose escalation study, including both males and females, to steady state for daily doses up to ___ (as per pharmacology input -Dr. J Sun) should be performed. This study should include pharmacokinetic and ECG pharmacodynamic assessments at regular intervals throughout the trial and repeated at appropriate points during the dosing interval.

2. A summary of the population variability of cetirizine metabolism should be provided. This should include presentations of histograms by dose of cetirizine, C_{max} and AUC after single and multiple (steady-state) dosing.

3. A tabulation of the number of ECGs performed in all clinical trials of cetirizine (not just efficacy trials), for all formulations, should be provided. Based on these ECGs the maximum change in QT_c from baseline should be compared between cetirizine and placebo and by dose of cetirizine. All ECGs in which there is a 10% or greater prolongation in QT_c should be evaluated by a cardiologist for changes in T-U wave morphology. The data for single and multiple dose trials should be evaluated separately and the analysis should include assessments of age, gender, and duration of treatment related effects. In addition to evaluating the mean and percent change from baseline, the data should describe the range of the QT_c prolongation seen. An analysis should also be performed comparing active treatment to placebo with regards to subjects with <10% in QT_c from baseline, 10-15%, 15-20% and >20% increase over baseline. Because of possible diurnal effects on QT_c , the analysis should include a description of how the ECGs included in the analysis compare with regard to the time they were collected. If serum drug concentration are available, an analysis of change in QT_c by drug level should be performed. Dispersion of QT_c intervals across precordial leads should also be examined.

4. Please submit the complete medical records for the adverse event reports with MFR numbers 9300233 and R-

7S192.

5. Please submit information regarding the premature withdrawal of subject #19, in study 42.

Group Leader's Addendum:

1 year studies in the dog support the safety of cetirizine up to 55x the C_{max} of a 20mg dose in humans and 200x the AUC of the same dose. The monkey 1 year studies support the safety of 3x the human C_{max} and 12x the AUC. The only adverse events seen in animals, particularly the dog, at lower concentrations are salivation and vomiting; the latter can easily be monitored in humans. The reason for the lower C_{max} in the monkeys is that there are no data at higher drug levels at which ECG's were also measured. There is data supporting the safety of 40x C_{max} in monkeys without ECG assessments. The clinical data (as well as preclinical data) indicate linear PK, at least to 60mg in humans. Based on the preclinical data and the evidence of linear PK it would be acceptable for the upper dose in the dose escalation trial to be 10x the upper clinical dose (200mg per day). In the study the sponsor should monitor the PK data at each dose level to ensure that they are within 55x the C_{max} and 200x the AUC of 20mg before proceeding to the next dose. m Hummel 2/24/94

Review

Addendum to Medical Officer Review

NDA-19835

Drug: Cetirizine tablets

Sponsor: Pfizer

Date: February 15, 1994

Medical Officer Reviewer: Ana M. Saavedra-Delgado, M.D.

Subject: Sponsor's submissions reviewed by Dr. Ana M. Saavedra-Delgado for the document titled "Safety Summary", dated April 19, 1993. [See review dated 2-23-94 in file]

Al Saavedra-Delgado MD
Feb 15, 1994

q Beaulieu
2/16/94

June 30, 1988 - Original NDA submission:

- vol 84 - integrated safety summary
- vol 83 - adverse effects of other antihistamines used in the NDA studies
- vol 82 - study reports of 32 and 33
- volumes 109-119 - case reports of discontinued patients due to adverse effects and case reports of serious events

December 18, 1991 - Canadian package insert

January 30, 1992 - Final Safety Update

30 vol
q Beaulieu
2/16/94

March 26, 1992 - Addendum to Safety Update

March 12, 1993 - Addendum to Safety Update - Response to our requests of 1/28/93

April 1993 - Sponsor's Executive Summary for the Advisory Committee Meeting on Cetirizine - (A copy of this document is included as Attachment 1 in this Addendum)

cc:

NDA 19835

HFD-155/Div Files

HFD-155/Ledet/Burke/Himmel/Saavedra-Delgado



Memorandum

Date April 20, 1993

From Executive Secretary
Pulmonary-Allergy Drugs Advisory Committee

Subject Additional FDA Medical Officer Safety Background on Reactine
(cetirizine HCL) Sponsored by Pfizer, Inc.

To Committee Members and Consultants

Enclosed you will find:

1. Dr. Saavedro-Delgado's, Pulmonary Medical Officer, FDA, comments on Pfizer's safety summary (which can be referred to on pages 84-126 of the Executive Summary for Reactine, black binder sent 4/6/93.)
2. Division information related to approval of Claritin, long acting antihistamine (Schering). This drug was formally approved on 4/12/93 and the material is for your general reference and not related to our April 26, 1993, meeting.

Leander B. Madoo

Leander Madoo
301/443-5455

NDA 19835
Cetirizine Tablets/capsules
To: Advisory Committee
Through: Greg Burke, M.D.
From: Ana M. Saavedra-Delgado, M.D.
Date: April 19, 1993

DRAFT

Ana Saavedra-Delgado

Safety Summary

For this Advisory Committee Meeting I have chosen to comment on the Sponsor's safety summary that is found on pages 84-126 of the Executive Summary for Reactine, dated April 1993.

These comments have been based on the review of: integrated summary of safety of the original submission (1988), epidemiology review of WHO database Oct 1992, review of the submitted CRFs regarding discontinued patients due to adverse events, serious experiences and deaths, safety updates, Sponsor's response to our questions (3/12/93), and Executive Summary (April 1993).

A. Extent of Exposure:

A total of 3810 patients were treated with cetirizine in all U.S. studies and 3085 in all controlled U.S. studies. A distribution of this last group of patients within the safety evaluable database can be seen in the Sponsor's Figure 1 from the March 12, 1993 submission. Also from this same submission, the total safety evaluable population in controlled trials for all allergic rhinitis studies is seen in Fig. 2.

A total of 2790 patients were treated with cetirizine in allergic rhinitis studies (SAR/PAR) or 75% of all cetirizine treated patients (Table Q2.A, 3/12/93 submission). In the controlled studies, 2321 or 73% were studied for allergic rhinitis. This in turn translates into 1020 patients treated with cetirizine for other indications or 27% of all cetirizine treated patients.

The extent of exposure as a function of time in all U.S. clinical studies and in controlled studies per indication is seen in Table Q3.A and Figures 3A-3D (3/12/93 submission). A majority of all cetirizine treated patients in all studies (64%) received treatment for 4 weeks or less (34% up to 2 weeks; 30% >2-4 weeks). The percent of patient receiving cetirizine as a function of time was: 17% -6weeks, 7% -12weeks, 2% -6 months, and 5% >6months.

B. Adverse Events:

From the 2513 adults that received cetirizine in placebo controlled studies, 42.8% reported adverse experiences. The

frequency for placebo treated patients (1501) was 36.6%.

It is important to note that in practically all studies conducted in the U.S. the record of adverse experiences that is reported by the Sponsor comes from the report of the patients to the investigators and not from the daily records of patients in their dairy cards. This method could have underestimate the frequency of these events.

At the time of the original submission (1988) for all controlled studies, the frequency of adverse events was 46.8% (641/1364) for cetirizine treated patients and 39.3% (323/821) for placebo treated patients. (vol.84, Table 4). When cetirizine was studied against specific active controls the frequency of patients with adverse experiences reached a maximum of 45.3% (PAR-3) when it was compared with diphenhydramine and a minimum of 42.3% when it was compared to chlorpheniramine (SAR-2, PAR-2). Overall, the frequency of adverse experiences in cetirizine treated patients remained within a narrow range.

In the placebo treated patients the maximum was seen when it was compared to hydroxyzine (URT-2) (54.2%) and the minimum of 35.2% when it was studied against terfenadine (SAR-4, SAR-5).

In these studies, in terms of the frequency of adverse reactions, cetirizine rated better than chlorpheniramine, diphenhydramine and hydroxyzine but worse than terfenadine. In general the observed rate of adverse experiences for cetirizine was within the range of what was observed for placebo and other active controls.

In terms of the specific adverse events as compared to placebo reported by 2% or more of adult patients, somnolence and fatigue stand out.

In the original submission of 1988, somnolence was reported by 18% of cetirizine treated patients (vol 84, Table 3) and by 8% of placebo treated patients and fatigue was 6% and 3% respectively. Cetirizine had a lower incidence of somnolence than chlorpheniramine, hydroxyzine and diphenhydramine but it produced more somnolence than terfenadine.

If the population of patients that participated in placebo-controlled fixed dose SAR/PAR allergic rhinitis studies is considered, 274/843 or 13.7% of cetirizine treated patients and 66/419 or 5.9% of placebo treated patients reported somnolence and 5.8 and 3.1 % respectively reported fatigue. See Table Q.4 3/12/93. It can also be observed in this table that there is an increase in the incidence of somnolence as the dose of cetirizine increases.

Although the overall reported incidence of adverse events in the elderly population is comparable to the adults age 12-64 years,

the total number of adult patients >65 years that received ceterizine and that also participated in placebo-controlled U.S. studies was only 148 or 5.9% of the total adult population (148/2513).

In terms of the pediatric population it is important to remember that in this data base no patient was treated for more than 6 weeks and that the total population that received cetirizine was 323 or 8.5% of the total population that received cetirizine (323/3810). In this context, the percent rate of adverse events may have been underestimated.

Women constituted 53% of the adult patients that received cetirizine in placebo controlled studies. In women, the frequency of adverse events was higher than in males and the five more frequently reported adverse events were also reported more frequently in women than in men. In Tables 6A and 6B (Executive Summary-April 1993) if we take the % of patients reporting severe somnolence for men it is 11% (22/194) and 15% (8/52) for cetirizine and placebo treated patients respectively. For women severe somnolence is reported in 17% (33/194) and 10% (5/48) in cetirizine and placebo treated patients respectively. The Sponsor does not offer an explanation for this observation. The relationship between weight and gender and adverse events was not presented.

In Tables 8A and 8B (Executive Summary-April 1993) the incidence of the most common adverse events in adults receiving cetirizine and placebo by duration of therapy are displayed. For both cetirizine and placebo treated patients the incidence of adverse events (somnolence included) reported up to 8 wks of therapy is reduced by half after the first two weeks. Although this may be a reflection of tolerance to the drug it is also observed in the placebo treated patients, however the incidence of somnolence in patients that are treated with cetirizine is twice of what it is observed in placebo treated patients in the 2-8 week interval.

A listing of all patients discontinued due to adverse events in controlled studies by indication was submitted on 3/12/93, (See Table Q.7). The reported adverse events by these patients were included. Approximately 80% of cetirizine treated patients discontinued due to adverse events did so in the first two weeks of treatment.

The incidence of adverse events reported in cetirizine treated patients is less than that reported by patients receiving first-generation antihistamines but it is more than that reported for second generation antihistamines such as terfenadine, in SAR/PAR allergic rhinitis studies. Please see Table Q.4 (3/12/93).

The observed incidence of reported adverse events to the investigators by the patients participating in long terms studies decreases in the later part of the studies; LTT-1 is given as an

example. This study was an open 26 week study, where 199 patients participated. Patients were evaluated at study visits: at baseline, weeks 1, 2, 4, 8, 12, 16, 20 and 26. The greatest reduction in the incidence of adverse events is seen between 4-8 weeks of treatment. However in the placebo controlled studies in the same time interval a decline in the incidence of adverse events reported by placebo treated patients was also seen. Please see Table 8B.

A short summary of the clinical history of most of the enclosed serious foreign reports is found in Table 98.B of the 3/12/93 submission. I have chosen to group some of these into categories that may have some clinical etiological significance only based on a suggestive clinical history and for the most part disregarding concomitant medications :

allergic -immunologic

skin: N00984, N00542, N00226
 necrotizing vasculitis:N00117
 angioedema:N00277, N00120, N00785

hematologic:

hemolytic anemia:N00982
 thrombocytopenia:N00912,N00785
 neutropenia:N00125
 agranulocytosis:N00114

anaphylaxis:N00546

Central Nervous System

hallucinations:N00909, N00479, N00126, N00121, N00122

interaction with antiepileptic therapy:N00875, N00127

seizure:N00276,N00127

vision:

temporary loss:9100891
 decreased:N00985
 diplopia:N00570

behavior:

confusion:N00115,N00717
 altered:N00116

Association with terfenadine and astemizole:

astemizole switch:N00717 dizziness, depersonalization,
 stupor
 terfenadine switch:N00590 extrasystole

terfenadine:N00535 severe hypotension

There were three open foreign studies for pruritus in which a total of 17 deaths were reported in the original submission (1988). Even though after reviewing the individual CRFs no death can be attributed to treatment with cetirizine it is important to note that in the first of these studies (n=32) where 13/17 deaths were reported, the investigator did not report any adverse event for a group of 32 patients that were treated with 10 mg of cetirizine for the entire duration of the study; many of these patients were elderly and senile.

C. Clinical Laboratory Data: All U.S. Clinical Trials:

According to Canadian labeling the incidence of transaminase elevations was 1.6% in the short term trials and 4.4% in the 6 month trials. (Sponsor's december 18, 1991 submission) In the safety update of January 1992 the experience in the U.S., with placebo controlled clinical trials was that the incidence of abnormal transaminase for results greater than or equal to two times the upper limit of normal was comparable for cetirizine and placebo. For cetirizine and placebo there were: SGOT 0.44% (9/2029) and 0.52%; SGPT 0.26% (5/1915) and 0.10% (6/1144).

When the WHO database was searched in October 1992 for hepatic adverse drug experiences associated with cetirizine there are 6 reports of hepatitis, 1 of jaundice, 2 SGPT increases and 2 SGOT increases. In the January 1992 Safety Update there were seven cases reported with hepatic experiences. The available clinical details of two of the cases were included in a safety report, the other 5 were from foreign spontaneous reports. According to this last submission, in the first two cases clinical details were minimal and did not allow for the exclusion of a reasonable possibility of a causal relationship to cetirizine. These cases have to be considered in context of an extensive foreign post-marketing experience.

Table Q.9 (3/12/93) provides a summary of the frequency with which SGOT increases in patients receiving cetirizine, placebo and the active controls used in all U.S. trials. The range for this frequency in cetirizine treated patients was 2.31 to 6.15%. In placebo treated patients the observed frequency was 1.61% and for the other active controls it was 1.43 to 4.62%.

Table Q.10 (3/12/93) displays the observed frequencies for the syrup form in patients age 6-11. This frequency was 3.77 to 6.78%

for cetirizine treated patients and 2.38% for patients that received placebo.

For the patients that had an elevation in their SGOT value we wanted to find out at what time interval of their treatment we would be able to observe the maximum increase in their SGOT. In Table Q11.C (3/12/93), for patients receiving cetirizine (combined) the frequency of values going from normal to high were observed to be in the about the same range (2.9-3.9%) up to 2 weeks, >2-4 weeks, >4-12 weeks and >12 weeks. In practice then, a maximum elevated SGOT could be observed at any time during treatment. For 10 mg of cetirizine, the most frequently used dose in these studies, there was an increase in the frequency of abnormal increases to maximum values in the second interval >2-4 wks.

For placebo treated patients, no apparent change was seen in the frequency during these time intervals and in this case the frequency of finding SGOT values going from normal to high was lower (1.3 to 1.8%). For terfenadine treated patients the frequency observed at >2-4 wks was the highest (9.1%). This frequency does not persist and goes back down to lower levels in the last interval. The low number of treated patients in the second interval may account for this high value.

In the case of the syrup Table Q.11D (3/12/93), there is an increase in the frequency of these values in the second interval >2-4 weeks (7%) for the all patients receiving cetirizine (combined). This is probably a reflection of what is seen in the 1.25 (16.7%) and 2.5 mg (7.1%) doses. It is important to note that at these last intervals for these doses, less than 20 patients were tested.

Table Q.15A (3/12/93) displays the frequency of SGOT values according to multiple of upper limit of normal by duration of therapy. Here too, values >1-2x normal were measured at higher frequency during the >2-4 interval for 10 mg of cetirizine, but were evenly distributed among the duration of therapy at time of maximum change up to 12 weeks, when all patients treated with cetirizine were considered. In the pediatric population changes in SGOT did not exceed 2x normal and there were seen with a higher frequency in the >2-4 week interval.

In women, although the frequency of values of SGOT going from normal to high do not appear to be different than those observed in the general population there seems to be an increase in the frequency of these abnormal values with an increase in dose, refer to Table Q.12A (3/12/93). For cetirizine doses 5, 10, 15, 20 the values observed were 1.17, 1.98, 4.55, and 4.71%. If this effect is real, i.e. not due to low population number, whether this effect is related to gender or to a lower body weight needs to be studied further.

The clinical significance of the increases in transaminases with cetirizine treatment is unknown. It also can be seen with other antihistamines such as terfenadine, even though in both cases the frequency appears to be higher than in placebo treated patients. There appears to be a normalization of these values towards normal as treatment continues as is seen in the open long term studies LTT-1).

D. Overdosage - refer to the Executive Summary

E. Drug Abuse - refer to the Executive Summary

F. Cardiovascular Safety:

In foreign spontaneous reports there have been three reported cases of hypotension, N00431, N00438, N00546 in women ages 12-35.

A search of WHO database (October 1992) found 2 cases of circulatory failure, 2 of hypotension, 2 of hypertension, 1 of bradycardia, 5 of palpitations and 1 of tachycardia.

The incidence of cardiac related adverse experiences from all controlled and uncontrolled studies is low and comparable to placebo treated patients (0.50% for cetirizine and 0.48% for placebo. (March 12, 1993)

There was a report of a case of torsades de pointes following the administration of hydroxyzine (100 mg IM) in a patient taking tefenadine.

Cetirizine has been studied in normal volunteers at doses of 60 mg without evidence of prolongation of the QT^c or QT interval.

Figure 1. Total Safety Evaluable Patients in All Controlled Clinical Trials

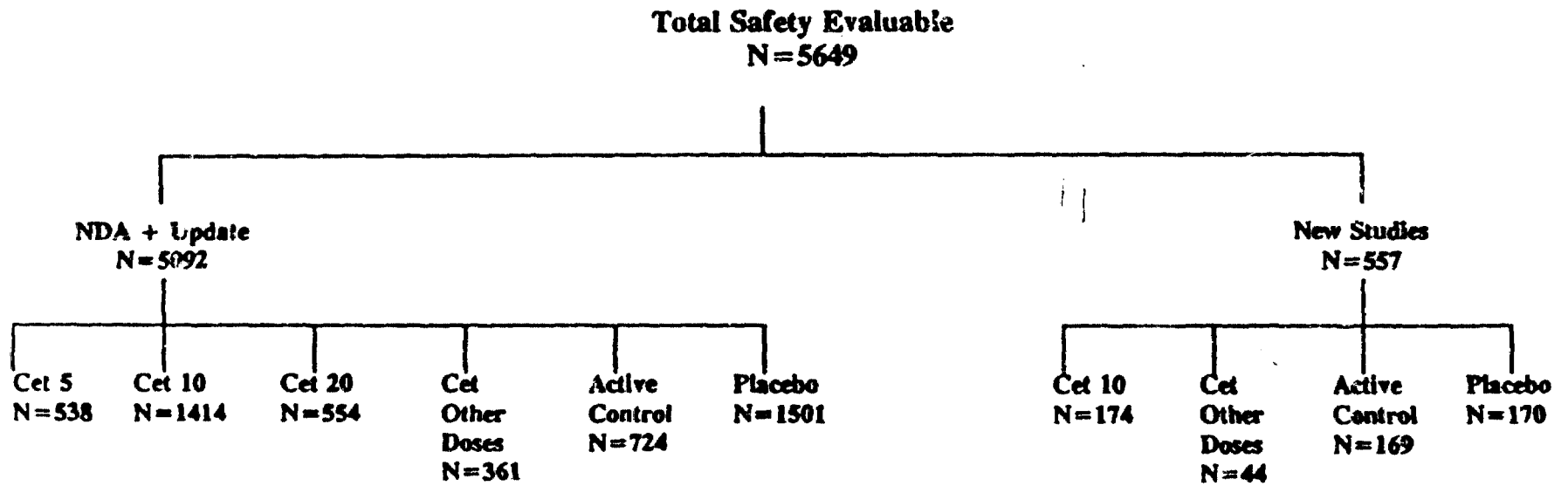


Figure 2. Total Safety Evaluable Patients in Controlled Clinical Trials - All Allergic Rhinitis Studies (SAR/PAR)

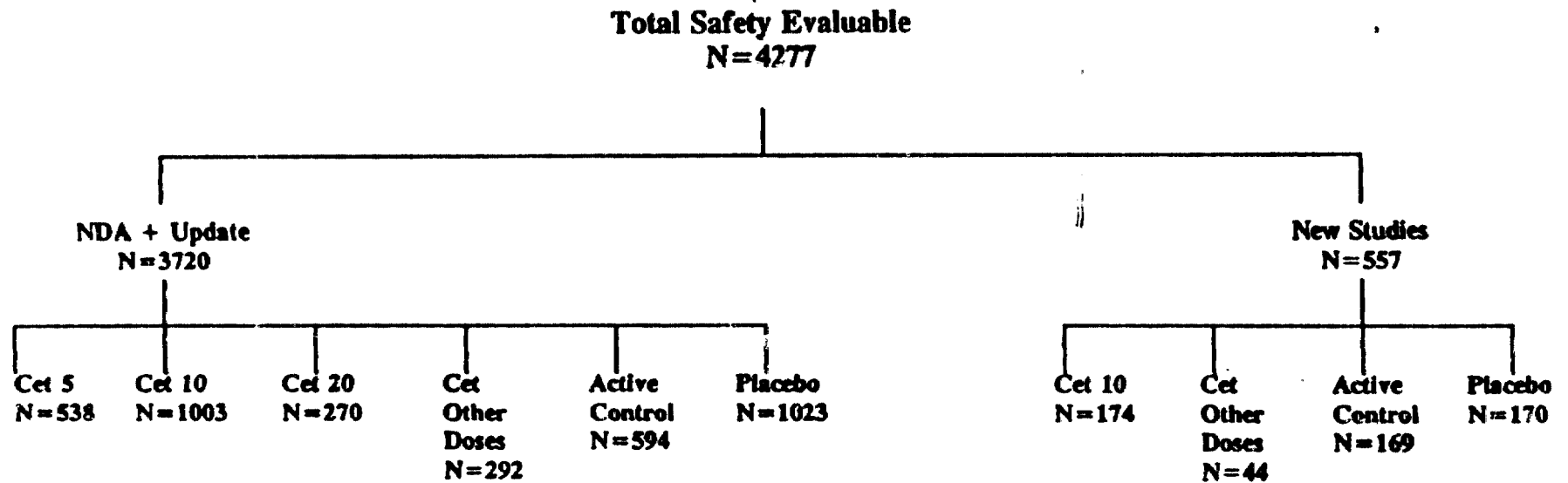


TABLE Q2.A: TOTAL SAFETY EVALUABLE PATIENTS IN ALL ALLERGIC RHINITIS (SEASONAL AND PERENNIAL) STUDIES

DPUG	DAILY DOSE	MDA-UPDATE STUDIES	NEW STUDIES	TOTAL
CETIRIZINE	1.25	79	0	79
CETIRIZINE	2.5	79	0	79
CETIRIZINE	5	530	0	530
CETIRIZINE	10	1003	174	1177
CETIRIZINE	15	59	0	59
CETIRIZINE	20	270	0	270
CETIRIZINE	YTR. #	243	345	588

CETIRIZINE	COMBINED	2271	519	2790

ACTIVE CONTROLLED		594	169	763
PLACENO		1025	170	1195

TOTAL		3000	850	4746

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TABLE 3A: DURATION OF THERAPY - ALL STUDIES *

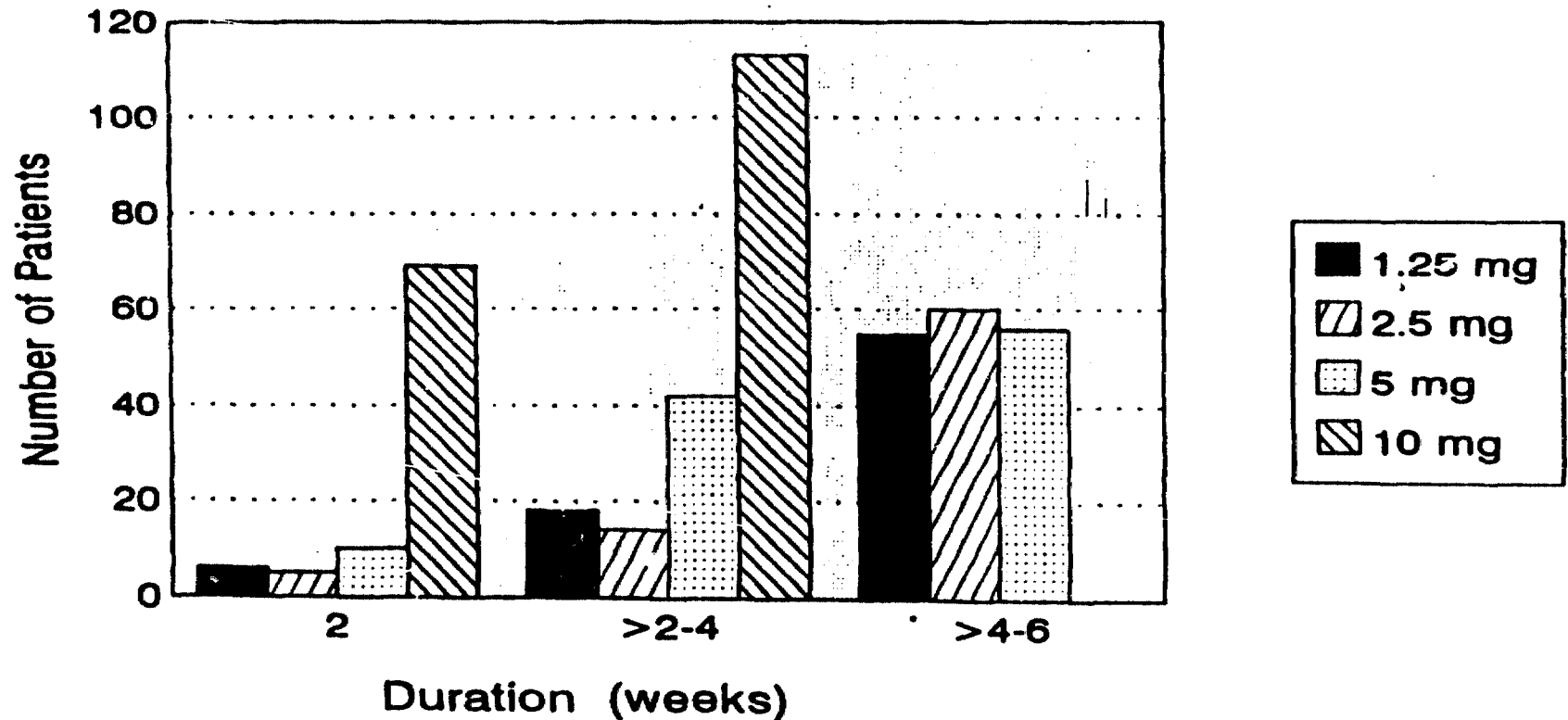
TREATMENT/DOSE FORMULATION	INDICATION	UP TO 2 WKS	>2 - 4 WKS	>4 - 6 WKS	>6 - 8 WKS	>8 - 12 WKS	>12-24 WKS	>24 WKS
CET. 1.25 SYRUP	SAR/PAR	6	18	55	0	0	0	0
CET. 2.5 SYRUP	SAR/PAR	5	14	60	0	0	0	0
CET. 5 SYRUP	SAR/PAR	10	42	56	0	0	0	0
CET. 5 TABLET/CAPS.	SAR/PAR	122	91	68	70	79	0	0
CET. 10 SYRUP	SAR/PAR	69	113	0	0	0	0	0
CET. 10 TABLET/CAPS.	SAR/PAR	301	364	135	115	86	0	0
	ALLERGIC SKIN	160	154	56	0	0	0	0
	ASTHMA	3	15	23	0	0	0	0
CET. 15 TABLET/CAPS.	SAR/PAR	4	6	6	43	0	0	0
CET. 20 TABLET/CAPS.	SAR/PAR	112	46	33	20	59	0	0
	ALLERGIC SKIN	153	46	43	1	0	0	0
	ASTHMA	2	12	27	0	0	0	0
CET. TITR. TABLET/CAPS.	SAR/PAR	200	120	31	0	9	56	151
	ALLERGIC SKIN	155	100	50	0	0	3	36
PLACEBO SYRUP	SAR/PAR	54	58	50	0	0	0	0
PLACEBO TABLET/CAPS.	SAR/PAR	241	316	237	140	69	0	0
	ALLERGIC SKIN	197	150	62	0	0	0	0
	ASTHMA	5	9	27	5	0	0	0
ACTIVE CON. SYRUP	SAR/PAR	13	50	3	0	0	0	0
ACTIVE CON. TABLET/CAPS.	SAR/PAR	196	243	166	57	10	30	0
	ALLERGIC SKIN	27	41	61	1	0	0	0

* DATA NOT AVAILABLE FOR 5 PATIENTS IN REACT-1 AND 13 PATIENTS IN REACT-2.

FIGURE 3A: CONTROLLED CLINICAL TRIALS

DURATION OF THERAPY: Pediatric

Syrup: Cetirizine 1.25, 2.5, 5 and 10 mg



patient treated for over 6 weeks

FIGURE 3B: CONTROLLED CLINICAL TRIALS

DURATION OF THERAPY: SAR/PAR

Tabs/cap: Cetirizine 5, 10, 15 and 20 mg

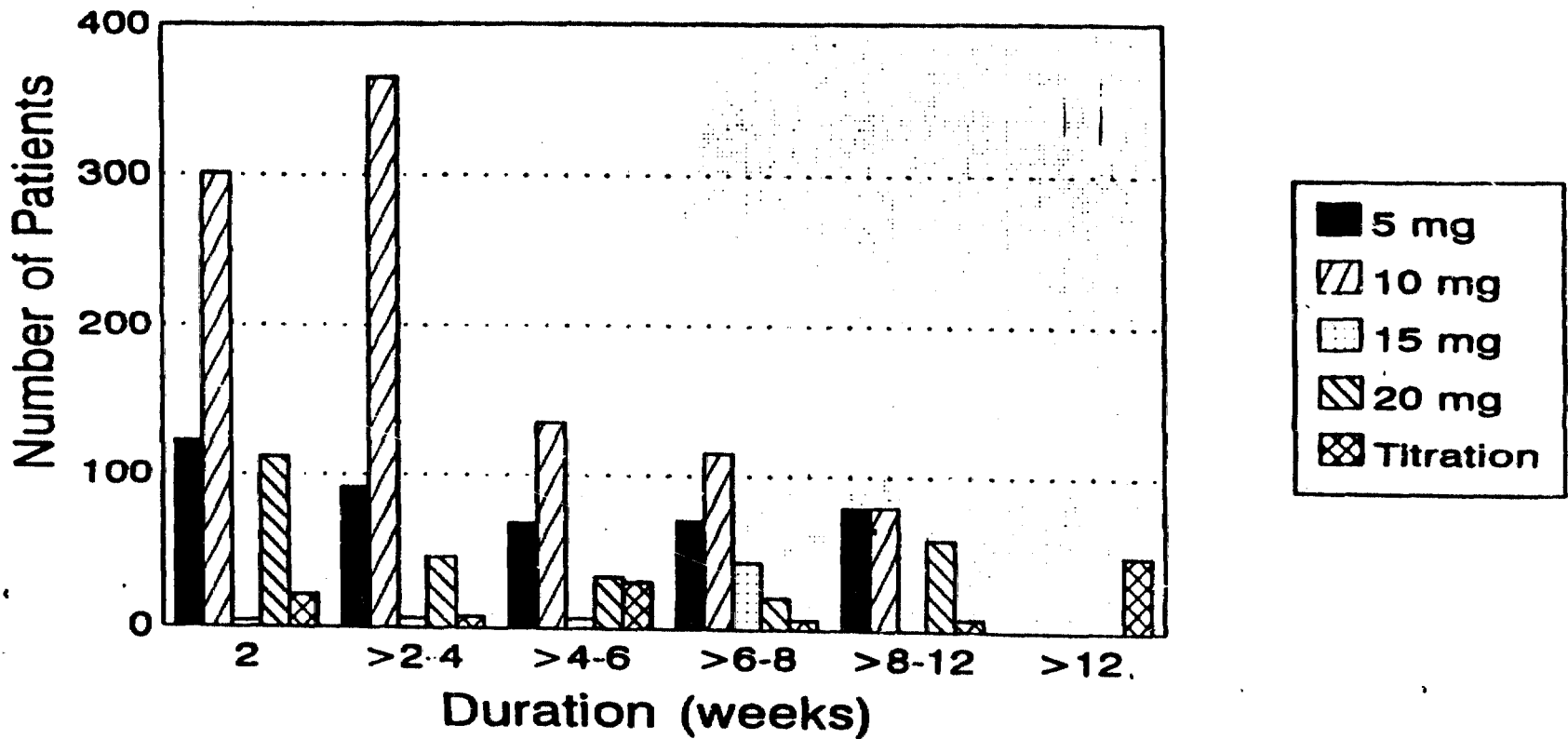


FIGURE 3C: CONTROLLED CLINICAL TRIALS

DURATION OF THERAPY: Allergic Skin

Tabs/caps: Cetirizine Titration, 10, 20 mg

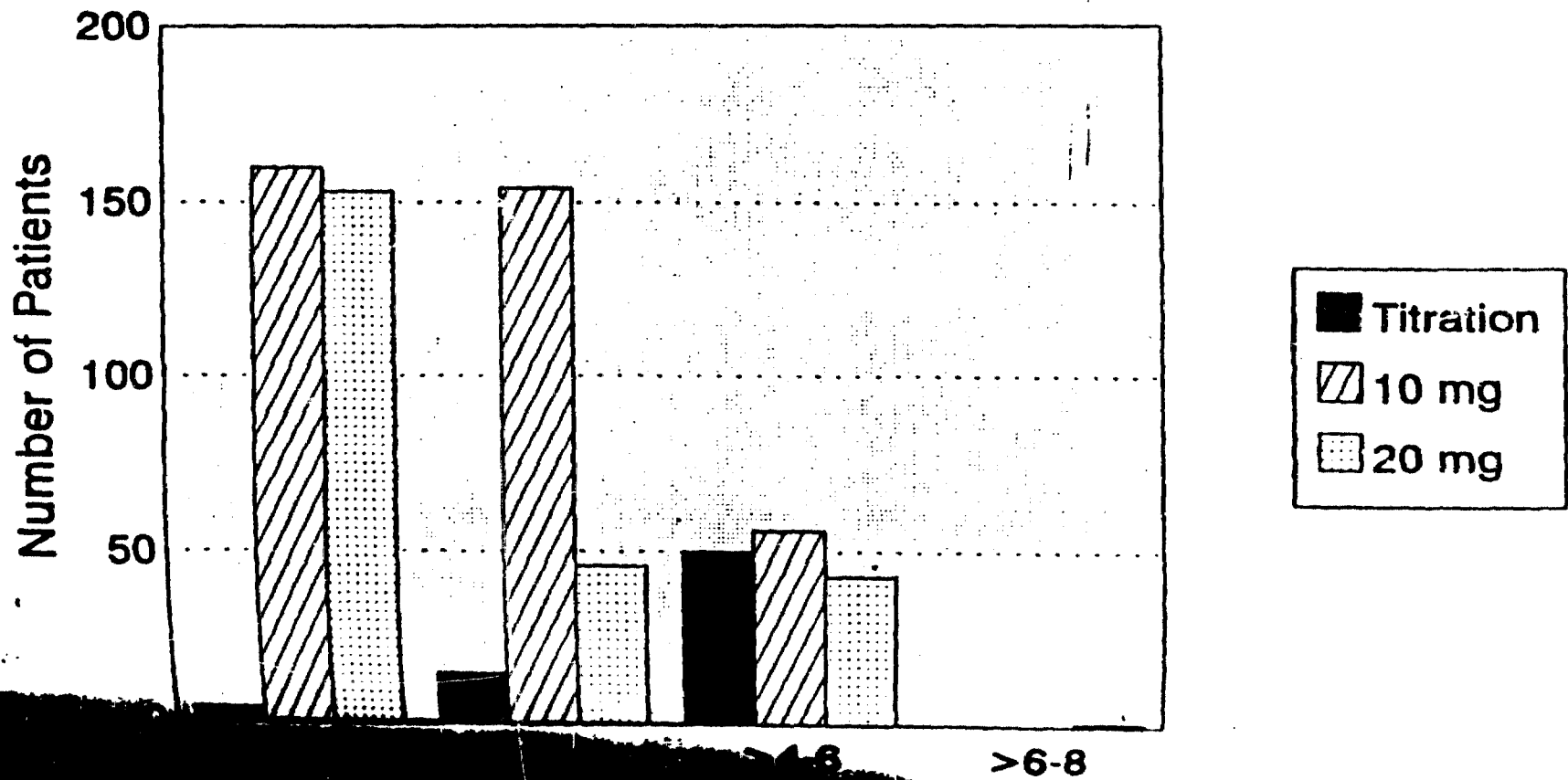


FIGURE 3D: CONTROLLED CLINICAL TRIALS

DURATION OF THERAPY: Asthma

Tabs/caps: Cetirizine 10 and 20 mg

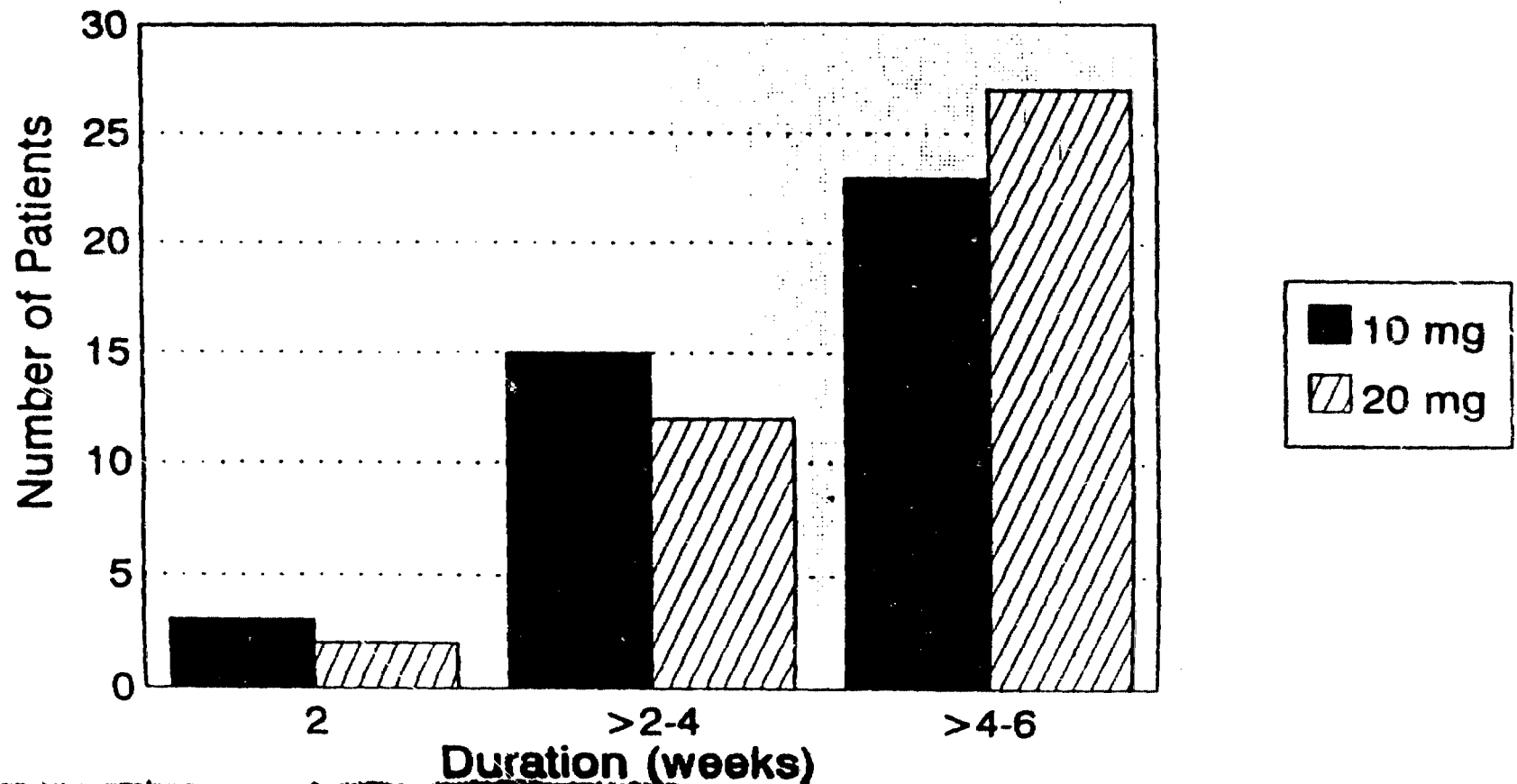


Table 4. Incidence of Adverse Experiences in Patients Treated in Placebo-Controlled U.S. Clinical Trials-Cetirizine vs. Placebo¹

	<u>Cetirizine</u> (N=1369)	<u>Placebo</u> (N=821)
Total Number of Patients with Adverse Experiences (% of Patients)	641 (46.8)	323 (39.3)
Total Number of Patients Discontinued Because of Adverse Experiences (% of Patients)	36 (2.6)	22 (2.7)

¹ Includes all studies except LTT-1 and last two months (open phase) of PAR-3.

TABLE Q.4: INCIDENCE OF ADVERSE EXPERIENCES (INCIDENCE $\geq$ 2 %) IN PLACEBO-CONTROLLED FIXED DOSE SAR/PAR STUDIES

ADVERSE EXPERIENCES	CETIRIZINE COMBINED	PLACEBO	ASTENIZOLE	TERFENADINE	CHLORPHENIR.	LORATADINE
	NO. PTS. (%)	NO. PTS. (%)	NO. PTS. (%)	NO. PTS. (%)	NO. PTS. (%)	NO. PTS. (%)
TOTAL NO. OF PATIENTS	1997	1117	91	147	158	82
NO. OF PTS. WITH ADVERSE EXPERIENCES	845 (42.2%)	419 (37.5%)	43 (47.3%)	51 (34.7%)	74 (53.6%)	13 (15.9%)
HEADACHE	346 (17.0%)	217 (19.4%)	26 (28.6%)	24 (16.3%)	26 (18.0%)	6 (7.3%)
SOMNOLENCE	274 (13.7%)	66 (5.9%)	4 (4.4%)	7 (4.8%)	30 (21.7%)	6 (7.3%)
FATIGUE	118 (5.9%)	38 (3.4%)	0 (0.0%)	5 (3.4%)	0 (0.0%)	2 (2.4%)
MOUTH DRY	93 (4.7%)	25 (2.2%)	2 (2.2%)	4 (2.7%)	14 (10.1%)	0 (0.0%)
PHARYNGITIS	45 (2.3%)	26 (2.3%)	0 (0.0%)	2 (1.4%)	6 (4.3%)	0 (0.0%)
NAUSEA	44 (2.2%)	37 (3.3%)	1 (1.1%)	3 (2.0%)	3 (2.2%)	0 (0.0%)
DIZZINESS	34 (1.7%)	18 (1.6%)	1 (1.1%)	5 (3.4%)	7 (5.1%)	0 (0.0%)
EPISTAXIS	24 (1.2%)	12 (1.1%)	0 (0.0%)	0 (0.0%)	3 (2.2%)	0 (0.0%)
COUGHING	23 (1.2%)	10 (0.9%)	3 (3.3%)	1 (0.7%)	1 (0.7%)	0 (0.0%)
ABDOMINAL PAIN	21 (1.1%)	10 (0.9%)	1 (1.1%)	2 (1.4%)	4 (2.9%)	0 (0.0%)
NERVOUSNESS	21 (1.1%)	11 (1.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)
DYSPEPSIA	20 (1.0%)	16 (1.4%)	1 (1.1%)	0 (0.0%)	4 (2.9%)	0 (0.0%)
RESPIRATORY DISORDER	20 (1.0%)	14 (1.3%)	0 (0.0%)	1 (0.7%)	4 (2.9%)	0 (0.0%)
DIARRHEA	14 (0.7%)	11 (1.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (1.2%)
RHINITIS	13 (0.7%)	6 (0.5%)	2 (2.2%)	2 (1.4%)	2 (1.4%)	0 (0.0%)
APPETITE INCREASED	11 (0.6%)	3 (0.3%)	3 (3.3%)	1 (0.7%)	0 (0.0%)	0 (0.0%)

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TABLE 9.7: LISTING OF ALL REPORTED ADVERSE EXPERIENCES FOR PATIENTS DISCONTINUED DUE TO ADVERSE EXPERIENCES IN CONTROLLED STUDIES
INDICATION: ALLERGIC SKIN

STUDY/PROTOCOL NUMBER	GRANT NUMBER	PATIENT NUMBER	DRUG	FINAL DOSE	DAYS ON DRUG	AGE	SEX	ADV. EXP. (WHO INCLUDED TERM)	SEVERITY

* DAYS ON DRUG= LAST DATE OF MED - FIRST DATE OF MED +1

TABLE 0.7: LISTING OF ALL REPORTED ADVERSE EXPERIENCES FOR PATIENTS DISCONTINUED DUE TO ADVERSE EXPERIENCES IN CONTROLLED STUDIES
INDICATION: ALLERGIC SKIN

STUDY/PROTOCOL NUMBER	GRANT NUMBER	PATIENT NUMBER	DRUG	FINAL DOSE	DAYS ON DRUG	AGE	SEX	ADV. EXP. (WHO INCLUDED ?)	SEVERITY

* DAYS ON DRUG= LAST DATE OF MED - FIRST DATE OF MED +1

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TABLE Q.7: LISTING OF ALL REPORTED ADVERSE EXPERIENCES FOR PATIENTS DISCONTINUED DUE TO ADVERSE EXPERIENCES IN CONTROLLED STUDIES
INDICATION: SAR/PAR

STUDY/PROTOCOL NUMBER	GRANT NUMBER	PATIENT NUMBER	DRUG	FINAL DOSE	DAYS ON DRUG #	AGE	SEX	ADV. EXP. (WHO INCLUDED TERM)	SEVERITY
.....									

DAYS ON DRUG: LAST DATE OF MED - FIRST DATE OF MED #1

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TABLE 0.7: LISTING OF ALL REPORTED ADVERSE EXPERIENCES FOR PATIENTS DISCONTINUED DUE TO ADVERSE EXPERIENCES IN CONTROLLED STUDIES
INDICATION: SAR/PAR

STUDY/PROTOCOL NUMBER	GRANT NUMBER	PATIENT NUMBER	DRUG	FINAL DOSE	DAYS ON DRUG	AGE	SEX	ADV. EXP. (WHO INCLUDED TERM)	SEVERITY

TABLE 0.7: LISTING OF ALL REPORTED ADVERSE EXPERIENCES FOR PATIENTS DISCONTINUED DUE TO ADVERSE EXPERIENCES IN CONTROLLED STUDIES
INDICATION: ASTHMA

STUDY/PROTOCOL NUMBER	GRANT NUMBER	PATIENT NUMBER	DRUG	FINAL DOSE	DAYS ON DRUG N	AGE	SEX	ADV. EXP. (WHO INCLUDED TERM)	SEVERITY

* DAYS ON DRUG= LAST DATE OF MED - FIRST DATE OF MED +1

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TABLE 2.7: LISTING OF ALL REPORTED ADVERSE EXPERIENCES FOR PATIENTS DISCONTINUED DUE TO ADVERSE EXPERIENCES IN CONTROLLED STUDIES

INDICATION: SAR/PAR

STUDY/PROTOCOL NUMBER	GRANT NUMBER	PATIENT NUMBER	DRUG	FINAL DOSE	DAYS ON DRUG #	AGE	SEX	ADV. EXP. (WHO INCLUDED TERM)	SEVERITY

DAYS ON DRUG= LAST DATE OF MED - FIRST DATE OF MED +1

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TABLE 0.7: LISTING OF ALL REPORTED ADVERSE EXPERIENCES FOR PATIENTS DISCONTINUED DUE TO ADVERSE EXPERIENCES IN CONTROLLED STUDIES
INDICATION: SAR/PAR

STUDY/PROTOCOL NUMBER	GRANT NUMBER	PATIENT NUMBER	DRUG	FINAL DOSE	DAYS ON DRUG	AGE	SEX	ADV. EXP. (MMO INCLUDED TERM)	SEVERITY
		19							

- THIS UN DRUG: LAST DATE OF MED - FIRST DATE OF MED +1

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TABLE 9.7: LISTING OF ALL REPORTED ADVERSE EXPERIENCES FOR PATIENTS DISCONTINUED DUE TO ADVERSE EXPERIENCES IN CONTROLLED STUDIES

INDICATION: SAR/PAR

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STUDY/PROTOCOL NUMBER	GRANT NUMBER	PATIENT NUMBER	DRUG	FINAL DOSE	DAYS ON DRUG	AGE	SEX	ADV. EXP. (WHO INCLUDED TERM)	SEVERITY
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■ DAYS ON DRUG: LAST DATE OF MED - FIRST DATE OF MED +1

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TABLE 0.7: LISTING OF ALL REPORTED ADVERSE EXPERIENCES FOR PATIENTS DISCONTINUED DUE TO ADVERSE EXPERIENCES IN CONTROLLED STUDIES
 INDICATION: SAR/PAR

STUDY/PROTOCOL NUMBER	GRANT NUMBER	PATIENT NUMBER	DRUG	FINAL DOSE	DAYS ON DRUG	AGE	SEX	ADV. EXP. (WHO INCLUDED TERM)	SEVERITY

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TABLE 9.7: LISTING OF ALL REPORTED ADVERSE EXPERIENCES FOR PATIENTS DISCONTINUED DUE TO ADVERSE EXPERIENCES IN CONTROLLED STUDIES

INDICATION: SAB/PAR

STUDY/PROTOCOL NUMBER	GRANT NUMBER	PATIENT NUMBER	DRUG	FINAL DOSE	DAYS ON DRUG	AGE	SEX	ADV. EXP. (WHO INCLUDED TERM)	SEVERITY

■ DAYS ON DRUG: LAST DATE OF MED - FIRST DATE OF MED +1

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TABLE 0.4: INCIDENCE OF ADVERSE EXPERIENCES (INCIDENCE >= 2 %) IN PLACEBO-CONTROLLED FIXED DOSE SAR/PAR STUDIES

ADVERSE EXPERIENCES	CETIRIZINE COMBINED		PLACEBO		ASTemizOLE		TERFENADINE		CHLORPHENIR.		LORATADINE	
	NO. PTS. (X)	NO. PTS. (X)	NO. PTS. (X)	NO. PTS. (X)	NO. PTS. (X)	NO. PTS. (X)	NO. PTS. (X)	NO. PTS. (X)	NO. PTS. (X)	NO. PTS. (X)	NO. PTS. (X)	NO. PTS. (X)
TOTAL NO. OF PATIENTS	1997	1117	91	147	158	82						
NO. OF PTS. WITH ADVERSE EXPERIENCES	843 (42.2%)	419 (37.5%)	45 (47.9%)	51 (34.7%)	74 (53.6%)	15 (18.9%)						
HEADACHE	348 (17.0%)	217 (19.4%)	26 (28.6%)	24 (16.8%)	26 (18.8%)	6 (7.8%)						
SORE THROAT	270 (13.7%)	66 (5.9%)	4 (4.0%)	7 (4.8%)	50 (21.7%)	6 (7.3%)						
FATIGUE	118 (5.9%)	88 (7.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)						
MOUTH DRY	93 (4.7%)	25 (2.2%)	2 (2.2%)	4 (2.7%)	14 (10.1%)	0 (0.0%)						
PHARYNGITIS	45 (2.3%)	26 (2.3%)	0 (0.0%)	2 (1.4%)	6 (4.3%)	0 (0.0%)						
NAUSEA	44 (2.2%)	37 (3.3%)	1 (1.1%)	3 (2.0%)	3 (2.2%)	0 (0.0%)						
DIZZINESS	34 (1.7%)	18 (1.6%)	1 (1.1%)	5 (3.4%)	7 (5.1%)	0 (0.0%)						
EPISTAXIS	24 (1.2%)	12 (1.1%)	0 (0.0%)	0 (0.0%)	3 (2.2%)	0 (0.0%)						
COUGHING	23 (1.2%)	10 (0.9%)	3 (3.3%)	1 (0.7%)	1 (0.7%)	0 (0.0%)						
ABDOMINAL PAIN	21 (1.1%)	10 (0.9%)	1 (1.1%)	2 (1.4%)	4 (2.9%)	0 (0.0%)						
NERVOUSNESS	21 (1.1%)	11 (1.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)						
DYSPEPSIA	20 (1.0%)	16 (1.4%)	1 (1.1%)	0 (0.0%)	4 (2.9%)	0 (0.0%)						
RESPIRATORY DISORDER	20 (1.0%)	14 (1.3%)	0 (0.0%)	1 (0.7%)	4 (2.9%)	0 (0.0%)						
DIARRHEA	14 (0.7%)	11 (1.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (1.2%)						
RHINITIS	13 (0.7%)	6 (0.5%)	2 (2.2%)	2 (1.4%)	2 (1.4%)	0 (0.0%)						
APPETITE INCREASED	11 (0.6%)	3 (0.3%)	3 (3.3%)	1 (0.7%)	0 (0.0%)	0 (0.0%)						

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TABLE 0.4: INCIDENCE OF ADVERSE EXPERIENCES (INCIDENCE >= 2 %) IN PLACEBO-CONTROLLED FIXED DOSE SAR/PAR STUDIES

ADVERSE EXPERIENCES	PLACEBO						CETIRIZINE					
	NO. PTS. (X)	1.25 MG	2.5 MG	5 MG	10 MG	20 MG	NO. PTS. (X)	1.25 MG	2.5 MG	5 MG	10 MG	20 MG
TOTAL NO. OF PATIENTS	1117	79	79	822	980	270	1117	79	79	822	980	270
NO. OF PTS. WITH ADVERSE EXPERIENCES	419 (42.2%)	13 (16.5%)	13 (16.5%)	193 (37.8%)	449 (48.4%)	153 (56.7%)	419 (42.2%)	13 (16.5%)	13 (16.5%)	193 (37.8%)	449 (48.4%)	153 (56.7%)
HEADACHE	217 (17.0%)	5 (6.3%)	6 (7.6%)	92 (17.4%)	177 (17.7%)	55 (20.4%)	217 (17.0%)	5 (6.3%)	6 (7.6%)	92 (17.4%)	177 (17.7%)	55 (20.4%)
SOMNOLENCE	66 (5.7%)	1 (1.3%)	2 (2.5%)	52 (10.0%)	143 (14.5%)	71 (26.3%)	66 (5.7%)	1 (1.3%)	2 (2.5%)	52 (10.0%)	143 (14.5%)	71 (26.3%)
FATIGUE	38 (3.0%)	0 (0.0%)	0 (0.0%)	25 (4.9%)	67 (6.8%)	22 (8.1%)	38 (3.0%)	0 (0.0%)	0 (0.0%)	25 (4.9%)	67 (6.8%)	22 (8.1%)
MOUTH DRY	25 (1.9%)	1 (1.3%)	0 (0.0%)	21 (4.0%)	52 (5.3%)	17 (6.3%)	25 (1.9%)	1 (1.3%)	0 (0.0%)	21 (4.0%)	52 (5.3%)	17 (6.3%)
PHARYNGITIS	26 (2.3%)	0 (0.0%)	0 (0.0%)	9 (1.7%)	29 (2.9%)	6 (2.2%)	26 (2.3%)	0 (0.0%)	0 (0.0%)	9 (1.7%)	29 (2.9%)	6 (2.2%)
NAUSEA	37 (2.9%)	2 (2.5%)	0 (0.0%)	0 (0.0%)	25 (2.5%)	0 (0.0%)	37 (2.9%)	2 (2.5%)	0 (0.0%)	0 (0.0%)	25 (2.5%)	0 (0.0%)
DIZZINESS	10 (1.7%)	0 (0.0%)	0 (0.0%)	7 (1.3%)	24 (2.4%)	2 (0.7%)	10 (1.7%)	0 (0.0%)	0 (0.0%)	7 (1.3%)	24 (2.4%)	2 (0.7%)
EPISTAXIS	12 (1.2%)	1 (1.3%)	1 (1.3%)	9 (1.7%)	10 (1.0%)	1 (0.4%)	12 (1.2%)	1 (1.3%)	1 (1.3%)	9 (1.7%)	10 (1.0%)	1 (0.4%)
COUGHING	10 (1.3%)	0 (0.0%)	0 (0.0%)	3 (0.6%)	15 (1.5%)	0 (0.0%)	10 (1.3%)	0 (0.0%)	0 (0.0%)	3 (0.6%)	15 (1.5%)	0 (0.0%)
ABDOMINAL PAIN	10 (1.1%)	0 (0.0%)	1 (1.3%)	1 (0.2%)	16 (1.6%)	2 (0.7%)	10 (1.1%)	0 (0.0%)	1 (1.3%)	1 (0.2%)	16 (1.6%)	2 (0.7%)
NERVOUSNESS	11 (1.1%)	0 (0.0%)	1 (1.3%)	3 (0.6%)	11 (1.1%)	0 (0.0%)	11 (1.1%)	0 (0.0%)	1 (1.3%)	3 (0.6%)	11 (1.1%)	0 (0.0%)
DYSPEPSIA	16 (1.0%)	2 (2.5%)	1 (1.3%)	4 (0.8%)	9 (0.9%)	6 (2.2%)	16 (1.0%)	2 (2.5%)	1 (1.3%)	4 (0.8%)	9 (0.9%)	6 (2.2%)
RESPIRATORY DISORDER	14 (1.0%)	0 (0.0%)	0 (0.0%)	4 (0.8%)	10 (1.0%)	3 (1.1%)	14 (1.0%)	0 (0.0%)	0 (0.0%)	4 (0.8%)	10 (1.0%)	3 (1.1%)
DIARRHEA	11 (0.7%)	0 (0.0%)	0 (0.0%)	4 (0.8%)	7 (0.7%)	1 (0.4%)	11 (0.7%)	0 (0.0%)	0 (0.0%)	4 (0.8%)	7 (0.7%)	1 (0.4%)
RHINITIS	6 (0.7%)	0 (0.0%)	0 (0.0%)	3 (0.6%)	9 (0.9%)	1 (0.4%)	6 (0.7%)	0 (0.0%)	0 (0.0%)	3 (0.6%)	9 (0.9%)	1 (0.4%)
APPETITE INCREASED	3 (0.6%)	0 (0.0%)	0 (0.0%)	2 (0.4%)	7 (0.7%)	0 (0.0%)	3 (0.6%)	0 (0.0%)	0 (0.0%)	2 (0.4%)	7 (0.7%)	0 (0.0%)

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Table Q8B: Serious Foreign Adverse Experiences: Spontaneous Reports and Clinical Trials

Pfizer AE#	CASE SUMMARY	Country
1. N00114	Agranulocytosis: Clinical details are not available. The causality was determined by the treating physician to be not related to cetirizine.	France
2. N00115	40 year old female with somnolence and confusional state occurring immediately after taking cetirizine. The symptoms lasted 3 hours. Difficulty with balance and speech, and general fatigue also occurred. The patient took one dose of 10 mg of cetirizine for urticaria. There were no concomitant medications.	France
3. N00116	45 year old female with an episode of behavior disturbance after taking cetirizine (dose unknown). The patient opened a bottle of champagne and put the cork into her mouth. She placed table napkins in the refrigerator; and broke a magnesium ampule and poured the contents into her mouth. The symptoms resolved when the drug was stopped and recurred when cetirizine treatment was restarted. She has a history of anxiety, hypertension and "spasmophilia". Concomitant medications included captopril, calcium, magnesium and prazepam.	France
4. N00117	Necrotizing vasculitis in a male. The vasculitis improved when cetirizine was discontinued and was exacerbated when the drug was restarted. Concomitant medication included corgard and moduretic. Symptoms improved when Zyrtec (cetirizine) was discontinued and "deteriorated again when the 3-drug treatment was resumed". There was no further information on the basis of the diagnosis or outcome.	France
5. N00118	17 year old female with jaundice 3 to 4 days after taking 2 to 3 tablets of cetirizine for a rash. There were no laboratory reports, however prothrombin levels and "liver function" tests were elevated. The symptoms improved (after discontinuation of Zyrtec) but were still present on 2 months later.	UK

Table Q8B: Serious Foreign Adverse Experiences: Spontaneous Reports and Clinical Trials

Pfizer AE#	CASE SUMMARY	Country
6. N00119	37 year old female with angina pectoris. Chest pains occurred the first day of 20 mg of cetirizine treatment for "allergic reaction". There were no concomitant medication. The symptom improved after stopping the medication and recurred on restarting cetirizine.	Netherlands
7. N00120	Pharyngeal, laryngeal and tongue edema (?angioedema) in a 55 year old female. The reaction occurred after the first dose of 10 mg of cetirizine (for perennial allergic rhinitis) and disappeared when the drug was stopped after the second dose. There was a history of toleration of Hismanal and Teldane therapy.	France
8. N00121	11 year old patient with hallucinations. There were no clinical details available.	UK
9. N00122	17 year old patient with hallucinations. There were no clinical details available.	UK
10. **N00123	28 year old male with acute abdominal pain. The patient was hospitalized and a laparotomy was performed which showed gastritis.	UK
11. **N00124	16 year old female with allergic rhinitis developed intermittent anterior chest pain after seven weeks of treatment with 10 mg of cetirizine in a clinical trial. The patient completed the study and the chest pain persisted. The investigator's assessment of causality was unlikely related to cetirizine.	UK
12. N00125	20 year old male with neutropenia (3%) noted after one week of therapy with 10 mg of cetirizine and a local corticosteroid for eczema. The patient was hospitalized and the laboratory values returned to normal after one week. There was a history of hypertension. Concomitant medication included Sectral (acebutolol).	France
13. **N00126	66 year old male with a history of alcoholism who developed visual hallucinations and aggressive behavior after taking one dose of (10 mg) cetirizine for allergic rhinitis. Symptoms began two hours after taking cetirizine.	France

Table Q8B: Serious Foreign Adverse Experiences: Spontaneous Reports and Clinical Trials

Pfizer AE#	CASE SUMMARY	Country
14. N00127	30 year old patient with a history of epilepsy reported an "epileptic attack" after 2 days of treatment with cetirizine. The seizure resolved after stopping cetirizine. Concomitant medication included Epanutin and phenobarbital.	Ireland
15. N00132 IND Safety Report	17 year old male with transient increase of transaminases after treatment with 10 mg of cetirizine for rhinitis. There were no clinical details available.	France
16. N00173	47 year old female with syncopal episode following standing. The episode lasted for one-half hour. The patient took 10mg cetirizine for 10 days prior to the episode and continued cetirizine therapy after the adverse event. Past medical history of a "slight" abnormal EEG.	Netherlands
17. **N00188	Asthma and nasal congestion in a patient treated with 10 mg per day of cetirizine for 40 days. The patient had a history of asthma and perennial allergic rhinitis. Ventolin was a concomitant medication.	UK
18. **N00226	A male patient developed a "skin reaction" after sunbathing on an artificial sunbed. He took 10 mg of cetirizine. Skin erythema persisted and the patient took an additional 50 mg of cetirizine. Severe pruritus occurred after the 50 mg dose. This case was classified as an overdose by UCB and there are no other clinical details available.	Belgium
19. N00275	24 year old female took 150 mg cetirizine in a suicide attempt. Somnolence was reported. There were no other clinical signs and laboratory results were "normal". Determination of cetirizine blood levels by HPLC showed the whole blood concentration to be 0.34 microgram/ml (time relationship of sample to dosing is not known). This blood level compares with levels of 0.25 to 0.38 microgram/ml 1-1.5 hours after a single 10 mg dose of cetirizine.	France
20. N00276	21 year old female vomiting, abdominal pain and possible seizure after 20 mg cetirizine. The patient was hospitalized and appeared post-ictal. There was a history of malaria and no family history of seizure disorder. The event resolved. A subsequent EEG was normal.	UK

Table Q8B: Serious Foreign Adverse Experiences: Spontaneous Reports and Clinical Trials

Pfizer AE#	CASE SUMMARY	Country
21. N00277	68 year old female treated with 10 mg of Virlix (cetirizine) for urticaria. Urticaria, quincke's edema developed two hours after dosing. A rechallenge with cetirizine was positive for urticaria and facial edema. Concomitant medication included Aspro.	France
22. N00283	26 year old male treated with Zyrtec (cetirizine) for chronic idiopathic urticaria for six weeks. The patient developed angioedema and was hospitalized for one week. The physician's impression was that the angioedema was a part of the patient's disease and was unrelated to cetirizine. Cetirizine therapy was restarted without recurrence of angioedema.	Greece
23. N00292	A female patient took one tablet of cetirizine daily and fell asleep. The reporting doctor reported the sleep was equivalent to coma. There were no further details or follow-up information.	France
24. N00315	Appendicitis. No clinical details available.	UK
25. **N00318	Left sided chest pain, ankle edema and cardiovascular disorder were reported after 6 days of 10 mg daily cetirizine therapy. The patient was hospitalized and treated with Adalat. There was a past history of a mitral valvulotomy. The investigator did not attribute the adverse event to cetirizine.	UK
26. N00337 IND Safety Report	43 year old female was treated with 10 mg cetirizine for four days. She took enalapril as a concomitant medication. Eight days after discontinuation of cetirizine therapy the SGOT was "35 times normal", the SGPT was "18 times normal" and hyperbilirubinemia was reported. No specific laboratory values were given. The laboratory values returned to normal within two months. Hepatitis vaccine was previously given and the HBs antibody was 390 U and the anti-HCV was negative. There was also a history of obesity and vesicular-lithiasis (cholelithiasis).	France

Table Q8B: Serious Foreign Adverse Experiences: Spontaneous Reports and Clinical Trials

Pfizer AE#	CASE SUMMARY	Country
27. N00338	Hyperbilirubinemia in a male patient with a history of hepatitis. The serum bilirubin was 19.7 mg/l while taking cetirizine and the other liver function tests were normal. Three months after stopping cetirizine the serum bilirubin was 2.2 mg/l. No clinical details are available and it was noteworthy that the patient was not described as being jaundiced.	France
28. N00370	9 year old female with facial paralysis 10 to 15 days after starting cetirizine therapy for food allergy. Concomitant medication included cortisone.	Switzerland
29. N00431	31 year old female with hypotension after 3 days of 10mg daily cetirizine therapy. She had a history of urticaria and there was no concomitant medication. She previously took cetirizine for 4 days.	Germany
30. N00438	35 year old female with nausea and retching after the first dose of 10 mg cetirizine. Four weeks later she had an episode of "circulatory collapse" and unconsciousness after a single dose of cetirizine. The patient was not hospitalized and recovered.	Germany
31. N00467	31 year old female who took 10 mg cetirizine daily from July 16, 1990 to July 20, 1990. On August 2, 1990 she had a positive pregnancy test and was 6 weeks amenorrheic. An ultrasound was performed and did not show any fetus. It was concluded that there was a complication of "nidation in this patient treated with Zyrtec" by the treating physician and the patient underwent induced w. uterine bleeding.	Germany
32. N00479	Hallucination during treatment with cetirizine. No clinical details are available.	UK
33. N00524	71 year old male with eczema and an allergy history who had an elevated prothrombin time during treatment with 10 mg/day of cetirizine. The prothrombin rate increased from 37 - 40% to 53 - 56%. Concomitant medication included Previscan (fludione), Vasumine (tocopherol-troxrutine), Lipanthyl (fenofibrate).	France

Table Q8B: Serious Foreign Adverse Experiences: Spontaneous Reports and Clinical Trials

Pfizer AE#	CASE SUMMARY	Country
34. N00535	20 year old female with a history of "sun allergy" who developed "severe hypotension" lasting 2 hours after a single 5 mg dose of cetirizine. Ten hours prior to taking cetirizine, she took a dose of terfenadine.	France
35. N00542	A 33 year old male developed "questionable" allergy symptoms related to an infection. The patient was treated with "cortotavegil" and 10 mg cetirizine. Flushing, swelling and a bullous eruption developed on the second day of treatment. Pruritus also was present. The patient had a history of relapsing allergic rash. Concomitant medication also included cod liver oil.	Germany
36. N00546 IND Safety Report	12 year old female with increased sweating, hypotension, sinus tachycardia and anxiety. The event began 30 minutes after taking 10mg cetirizine. The patient had taken cetirizine the previous day without any difficulty. The systolic blood pressure was 60 mm and the diastolic was "almost zero". She was hospitalized and treated and carotid massage. She was discharge the following morning. The impression was that this event was suggestive of anaphylaxis.	UK
37. N00570	Facial paralysis and diplopia in a male patient. There was a past history of the same event "some years" ago.	France
38. N00590	41 year old male with extrasystole. The patient was treated with Teldanex (terfenadine) from 1989 to April 15, 1991. He was switched to cetirizine. The patient became acutely ill and another doctor sent the patient to the hospital. ECG showed frequent extrasystole. Cetirizine was withdrawn. One month after stopping cetirizine the patient was again hospitalized for management of the extrasystole. Concomitant medication included Iliadin.	Norway
39. **N00641	29 year old male with allergic rhinitis developed cold symptoms followed facial cellulitis and elevated blood glucose. He was treated with Erythromycin. The investigator felt the adverse events were unlikely to be related to cetirizine therapy.	UK

Table Q8B: Serious Foreign Adverse Experiences: Spontaneous Reports and Clinical Trials

Pfizer AE#	CASE SUMMARY	Country
40. **N00650	45 year female increased alkaline phosphatase, from 179 to 409 IU/L (change for normal to 1.5 times normal) associated with drowsiness, headache, dry mouth and respiratory tract infection. The SGPT (ALT) increased from 29 to 58 (normal to 1.45 times normal) and the calcium was slightly elevated to 1.83 (0.8-1.45). There was no concurrent medication and the causality was not assessed by the investigator.	UK
41. **N00651	12 year old male accidental fall off a wall while playing. He was admitted to a hospital. There were no details about the hospitalization. The patient recovered and the investigator felt the event was unlikely to be related to cetirizine therapy.	UK
42. **N00653	Respiratory tract infection. Concomitant medication included Codimal. There was a history of a frozen shoulder.	UK
43. N00717	35 year old female noted depersonalization, stupor, and dizziness after a single intake of 10mg cetirizine. The symptoms resolved. She took Hismanal for 3 weeks up to the day before starting cetirizine. Concomitant medication included moduretic and ventolin.	UK
44. 9100891 ¹	42 year old female had <u>loss of vision</u> in her right eye (people were blurred or missing on the right side) for 10 minutes. This occurred in the morning, 10-15 minutes after the first dose of 10 mg of cetirizine and associated with a frontal headache. That afternoon she had an upset stomach and minor cramps. Cetirizine was stopped and the symptoms resolved.	Canada
45. N00785	41 year old female treated with Zyrtec (cetirizine) had angioedema, <u>thrombocytopenia</u> , anemia and leukocytosis. Concomitant medications included <u>Jasix</u> and <u>oxazepam</u> . The reporting physician considered the <u>cetirizine</u> as a possible cause of the adverse events, but did not conclude and therefore formally report the adverse events by completing the pharmacovigilance form.	Netherlands
46. N00875	Severe asthenia and "unbalanced antiepileptic therapy" requiring hospitalization of a 12 year old male on Depakane and cetirizine.	France

Table Q8B: Serious Foreign Adverse Experiences: Spontaneous Reports and Clinical Trials

Pfizer AE#	CASE SUMMARY	Country
47. N00909	Hallucinations in a 12 year old child treated with Zyrtec (cetirizine).	Belgium
48. N00912 IND Safety Report	Gingival Bleeding and thrombocytopenia in a 23 year old male treated with 10 mg cetirizine daily "since June 1991". The platelet count was 16,000 in May 1992. The patient was admitted to a hospital and treated with methylprednisolone. The patient recovered and was discharged in four days. Concomitant medication included ketotifen.	Belgium
9. N00980'	Strong episodes of vertigo resulting in a fall and requiring discontinuation of cetirizine.	France
50. N00982 <i>IND Safety report</i>	Hemolytic anemia in a 45 year old male treated with 20 mg daily from February to March 1992 (exact dates were not specified, but +/- 14 days stated). Laboratory results showed a low hemoglobin and serum haptoglobin; elevated LDH, bilirubin, and reticulocyte count; and a positive direct Coombs test. There were no concomitant medication, but he used alcohol moderately. The reaction "abated" after stopping cetirizine.	Germany
51. N00984	68 year old female with pruritus and a macular eruption on the forearms on week after stopping 10mg Virlix (cetirizine). She had been taking cetirizine from May 7 to June 8, 1992. The rash spreaded to one leg and the thorax. The patient was hospitalized for one day because of laryngeal discomfort. Concomitant medication included lorazepam.	France
52. N00985	36 year old female with decreased vision during treatment with 10mg cetirizine. There are no clinical details available.	Sweden



Table Q8B: Serious Foreign Adverse Experiences: Spontaneous Reports and Clinical Trials

Pfizer AE#	CASE SUMMARY	Country
53. **N01049	26 year old female was treated with cetirizine in a comparative study sponsored by Schering Plough. Initial pregnancy test was negative. She received 10 mg cetirizine daily for 9 days (11/27 -12/5/92). There was no menses in 12/92. Pregnancy test was 118,000 U/L (normal 16,000-200,000) on 1/5/93 and the ultrasound of the pelvis showed two fetuses and "no cardiac activity" on 1/9/93. A repeat ultrasound on 1/15/93 revealed the same results. The investigator concluded that a double fetal death occurred possibly related to cetirizine therapy. The patient underwent a medical abortion.	France

**Serious foreign clinical trial adverse events.

These cases do not meet FDA criteria for serious, but were noteworthy.

TABLE 0.9: SCOT LAB SUMMARY IPRE - TO MAX. INCREASE DURING TREATMENT OR UP THROUGH 2 WEEKS POST TREATMENT)
 - ALL TABLETS/CAPSULE STUDIES

DRUG	DAILY DOSE	TOT. PTS.	FREQUENCY (%) DISTRIBUTION OF LAB. READINGS AS BELOW (L), WITHIN (M), OR ABOVE (H) THE NORMAL RANGE												
			ML	LL	MM	MM	LM	MM	MM	MM	MM	MM	MM	MM	
CETIRIZINE	5	418	-	0.24	-	0.72	95.22	0.24	-	-	-	-	1.20	2.39	-
CETIRIZINE	10	1257	-	0.16	-	2.07	95.72	0.08	-	-	-	-	1.27	2.33	-
CETIRIZINE	15	50	-	-	-	1.72	87.93	-	-	-	-	-	6.90	3.05	-
CETIRIZINE	20	536	-	-	-	1.68	90.86	-	-	-	-	-	2.05	5.01	-
CETIRIZINE	YTHR.	300	-	-	0.20	1.00	90.22	0.56	-	-	-	-	1.00	6.15	-
CETIRIZINE	COMBINED	2047	-	0.11	0.25	1.67	92.77	0.34	-	-	-	-	1.56	3.50	-
PLACILLO		1010	-	0.21	0.21	1.00	90.03	0.20	-	-	-	-	1.00	1.62	-
ASPIRIZOLE	10	100	-	-	-	0.71	97.14	-	-	-	-	-	0.71	1.03	-
CHLORPHENIRAMINE	16	133	-	-	-	3.01	90.90	-	-	-	-	-	1.50	4.51	-
CHLORPHENIRAMINE	YTHR.	12	-	-	-	0.33	91.67	-	-	-	-	-	-	-	-
DIPHENHYDRAMINE	YTHR.	70	-	1.03	1.03	1.43	92.06	-	-	-	-	-	-	2.06	-
HYDROXYZINE	YTHR.	66	-	1.50	-	7.69	84.62	-	-	-	-	-	1.50	4.62	-
LOXITAPINE	10	63	-	-	-	1.59	95.24	-	-	-	-	-	3.17	-	-
TERFENADINE	120	100	-	-	-	0.69	94.00	-	-	-	-	-	1.39	3.07	-
TERFENADINE	YTHR.	20	-	-	-	-	100	-	-	-	-	-	-	-	-

* ML - FIRST LETTER (M) REPRESENTS BASELINE VALUE; SECOND LETTER (L) REPRESENTS THE MAXIMUM INCREASE DURING OR AFTER TREATMENT.

TABLE Q-10: SCOT LAS SUMMARY (PRE - TO MAX. INCREASE BEFORE TREATMENT OR UP THROUGH 2 WEEKS POST TREATMENT)
 - ALL SYMPTOM STUDIES

DRUG	DAILY DOSE	TOT. PTS.	FREQUENCY (%) DISTRIBUTION OF LAS. READINGS AS BELOW (L), WITHIN (N), OR ABOVE (H) THE NORMAL RANGE											
			HL	LL	HN	LN	HN	LN	HN	LN	HN	LN		
CETIZINE	1.25	76	-	-	1.32	78.79	-	2.63	5.26	-	-	-	-	-
CETIZINE	2.5	76	-	-	1.32	68.16	-	5.26	5.26	-	-	-	-	-
CETIZINE	5	106	-	-	4.72	86.79	-	4.72	3.77	-	-	-	-	-
CETIZINE	10	177	-	0.56	3.95	84.18	-	4.52	6.78	-	-	-	-	-
CETIZINE	COMBINED	435	-	0.23	3.22	86.67	-	4.37	5.52	-	-	-	-	-
PLACED		168	-	-	1.19	94.64	-	1.79	2.34	-	-	-	-	-
CYCLOPENTIMINE	6	61	-	-	3.28	93.44	-	1.64	1.64	-	-	-	-	-

* HL - FIRST LETTER (H) REPRESENTS BASELINE VALUE; SECOND LETTER (L) REPRESENTS THE MAXIMUM INCREASE BEFORE OR AFTER TREATMENT.

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TABLE Q.11C: SCOT LAB SUMMARY (PRE - TO MAX. INCREASE IN TIME INTERVAL DURING TREATMENT OR UP THROUGH 2 WEEKS POST TREATMENT - ALL TABLETS/CAPSULE STUDIES BY DURATION OF THERAPY

DRUG	DAILY DOSE	DURATION OF THERAPY IN WEEKS	TOT. PTS. NUM	FREQUENCY (%) DISTRIBUTION OF LAB. READINGS AS BELOW (L), WITHIN (M), OR ABOVE (H) THE NORMAL RANGE									
				ML*	LL	MM	12H	LN	MM	MH	LN	MH	LH
CETIRIZINE	5	UP TO 2 WEEKS	150	-	0.0	-	0.0	94.2	0.0	1.7	1.7	-	-
		>2 - 4 WEEKS	136	-	-	-	2.2	75.6	-	0.7	1.5	-	-
		>4 - 12 WEEKS	206	-	-	-	1.0	95.1	-	1.0	2.9	-	-
CETIRIZINE	10	UP TO 2 WEEKS	432	-	-	-	2.8	92.6	1.2	2.3	1.0	-	-
		>2 - 4 WEEKS	623	-	0.8	-	1.6	94.5	0.2	0.6	2.6	-	-
		>4 - 12 WEEKS	002	-	-	-	2.0	94.0	-	1.0	2.2	-	-
CETIRIZINE	15	UP TO 2 WEEKS	3	-	-	-	-	100.0	-	-	-	-	-
		>2 - 4 WEEKS	24	-	-	-	7.4	80.9	-	1.9	2.9	-	-
		>4 - 12 WEEKS	09	-	-	-	2.0	85.7	-	0.2	0.1	-	-
CETIRIZINE	20	UP TO 2 WEEKS	200	-	-	-	1.0	89.3	-	3.2	5.7	-	-
		>2 - 4 WEEKS	166	-	-	-	1.2	92.0	-	1.0	4.2	-	-
		>4 - 12 WEEKS	170	-	-	-	2.2	93.3	-	0.6	3.9	-	-
CETIRIZINE	TITR.	UP TO 2 WEEKS	37	-	-	-	2.7	89.2	-	2.7	5.4	-	-
		>2 - 4 WEEKS	209	-	-	-	-	95.7	0.5	0.5	3.5	-	-
		>4 - 12 WEEKS	220	-	-	0.3	1.3	94.1	0.3	1.3	2.0	-	-
		>12 WEEKS	230	-	-	0.4	-	94.0	0.4	0.4	3.9	-	-
CETIRIZINE	COMBINED	UP TO 2 WEEKS	072	-	0.1	-	2.1	91.6	0.7	2.5	3.0	-	-
		>2 - 4 WEEKS	1100	-	0.3	-	1.6	94.4	0.2	0.0	2.0	-	-
		>4 - 12 WEEKS	1105	-	-	0.1	1.6	94.0	0.1	1.3	2.9	-	-
		>12 WEEKS	230	-	-	0.4	-	94.0	0.4	0.4	3.9	-	-
PLACEDO		UP TO 2 WEEKS	471	-	0.6	0.2	1.9	92.0	-	3.2	1.5	-	-
		>2 - 4 WEEKS	616	-	0.2	0.2	1.3	95.0	0.2	1.5	1.0	-	-
		>4 - 12 WEEKS	559	-	0.4	0.4	1.4	95.7	0.2	1.4	1.6	-	-

* ML - FIRST LETTER (H) REPRESENTS BASELINE VALUE; SECOND LETTER REPRESENTS THE MAXIMUM INCREASE DURING OR AFTER TREATMENT.
 MH IF LAB DATE PASSED LAST DATE OF MEDICATION, DURATION OF THERAPY = LAST DATE OF MED. - FIRST DATE OF MED. +1
 MHNA PATIENT IS INCLUDED IN ALL INTERVALS IN WHICH SCOT WAS DETERMINED.

TABLE 8.11C: SCOT LAB SUMMARY (PRE - TO MAX. INCREASE IN TIME INTERVAL DURING TREATMENT OR UP THROUGH 2 WEEKS POST TREATMENT)
 - ALL TABLET/CAPSULE STUDIES BY DURATION OF THERAPY

DRUG	DAILY DOSE	DURATION OF THERAPY OR UP THROUGH 2 WEEKS POST TREATMENT	TOT. PTS. n=	FREQUENCY (%) DISTRIBUTION OF LAB. READINGS AS										
				ML#	MC	LL	MM	NN	LN	MM	NN	LN	LN	
ASTemizole	10	UP TO 2 WEEKS	19	-	-	-	5.3	89.5	-	5.3	-	-	-	-
		>2 - 4 WEEKS	112	-	-	-	98.2	-	-	-	-	1.8	-	
		>4 - 12 WEEKS	14	-	-	-	100.0	-	-	-	-	-	-	
Chlorpheniramine	16	UP TO 2 WEEKS	13	-	-	-	-	92.3	-	7.7	-	-	-	
		>2 - 4 WEEKS	119	-	-	-	3.4	91.6	-	6.0	-	4.2	-	
		>4 - 12 WEEKS	48	-	-	-	6.3	91.7	-	-	-	2.1	-	
Chlorpheniramine	TITR.	UP TO 2 WEEKS	1	-	-	-	100	-	-	-	-	-	-	
		>4 - 12 WEEKS	11	-	-	-	100.0	-	-	-	-	-	-	
Diphenhydramine	TITR.	UP TO 2 WEEKS	3	-	-	-	-	100.0	-	-	-	-	-	
		>2 - 4 WEEKS	14	-	-	-	7.1	92.9	-	-	-	-	-	
		>4 - 12 WEEKS	58	-	1.7	1.7	-	94.8	-	-	-	1.7	-	
		>12 WEEKS	36	-	-	-	-	97.2	-	-	-	2.8	-	
Hydroxyzine	TITR.	UP TO 2 WEEKS	9	-	-	-	33.3	55.6	-	11.1	-	-	-	
		>2 - 4 WEEKS	10	-	-	-	100.0	-	-	-	-	-		
		>4 - 12 WEEKS	47	-	2.1	-	4.3	87.2	-	-	-	6.4	-	
Loratadine	10	UP TO 2 WEEKS	32	-	-	-	-	96.9	-	3.1	-	-		
		>2 - 4 WEEKS	31	-	-	-	3.2	93.5	-	3.2	-	-		
Terfenadine	120	UP TO 2 WEEKS	10	-	-	-	10.0	90.0	-	-	-	-		
		>2 - 4 WEEKS	22	-	-	-	4.5	86.4	-	-	-	9.1		
		>4 - 12 WEEKS	118	-	-	-	-	95.7	-	1.7	-	2.6		
Terfenadine	TITR.	UP TO 2 WEEKS	1	-	-	-	-	100.0	-	-	-	-		
		>4 - 12 WEEKS	19	-	-	-	-	100.0	-	-	-	-		

* ML - FIRST LETTER (M) REPRESENTS BASELINE VALUE; SECOND LETTER REPRESENTS THE MAXIMUM INCREASE DURING OR AFTER TREATMENT.
 ** IF LAB DATE PASSED LAST DATE OF MEDICATION, DURATION OF THERAPY = LAST DATE OF MED. - FIRST DATE OF MED. *1
 ***A PATIENT IS INCLUDED IN ALL INTERVALS IN WHICH SCOT WAS DETERMINED.

TABLE Q.11D: SCOT LAB SUMMARY (PRE - TO MAX. INCREASE IN TIME INTERVAL DURING TREATMENT OR UP THROUGH 2 WEEKS POST TREATMENT)
 - ALL SYRUP STUDIES BY DURATION OF THERAPY

DRUG	DAILY DOSE	DURATION OF THERAPY **	TOT. PTS.***	FREQUENCY (%) DISTRIBUTION OF LAB. READINGS AS BELOW (L), WITHIN (N), OR ABOVE (H) THE NORMAL RANGE								
				ML#	ML	LL	LN	LN	LN	HN	HN	LN
CETIRIZINE	1.25	UP TO 2 WEEKS	6	-	-	-	-	83.3	-	16.7	-	-
		>2 - 4 WEEKS	18	-	-	-	5.4	77.8	-	-	16.7	-
		>4 -12 WEEKS	53	-	-	-	1.9	94.3	-	1.9	1.9	-
CETIRIZINE	2.5	UP TO 2 WEEKS	6	-	-	-	16.7	66.7	-	16.7	-	-
		>2 - 4 WEEKS	14	-	-	-	7.1	78.6	-	7.1	7.1	-
		>4 -12 WEEKS	60	-	-	-	1.7	98.0	-	3.3	5.0	-
CETIRIZINE	5	UP TO 2 WEEKS	11	-	-	-	18.2	54.5	-	27.3	-	-
		>2 - 4 WEEKS	42	-	-	-	7.1	83.3	-	7.1	2.4	-
		>4 -12 WEEKS	55	-	-	-	1.6	92.7	-	-	5.5	-
CETIRIZINE	10	UP TO 2 WEEKS	66	-	-	-	4.5	87.9	-	1.5	6.1	-
		>2 - 4 WEEKS	111	-	6.9	-	3.6	82.0	-	6.3	7.2	-
CETIRIZINE	COMBINED	UP TO 2 WEEKS	89	-	-	-	6.7	82.0	-	6.7	4.5	-
		>2 - 4 WEEKS	105	-	0.5	-	4.9	81.6	-	5.9	7.0	-
		>4 -12 WEEKS	168	-	-	-	1.8	92.3	-	1.8	4.2	-
PLACEBO		UP TO 2 WEEKS	55	-	-	-	-	96.4	-	-	3.6	-
		>2 - 4 WEEKS	58	-	-	-	-	98.3	-	1.7	-	-
		>4 -12 WEEKS	57	-	-	-	3.5	89.5	-	3.5	3.5	-
CHLORPHENIRAMINE	6	UP TO 2 WEEKS	12	-	-	-	8.3	91.7	-	-	-	-
		>2 - 4 WEEKS	49	-	-	-	2.0	93.9	-	2.0	2.0	-

ML - FIRST LETTER (M) REPRESENTS BASELINE VALUE; SECOND LETTER REPRESENTS THE MAXIMUM INCREASE DURING OR AFTER TREATMENT.
 ** IF LAB DATE PASSED LAST DATE OF MEDICATION, DURATION OF THERAPY = LAST DATE OF MED. - FIRST DATE OF MED. +1
 ***A PATIENT IS INCLUDED IN ALL INTERVALS IN WHICH SCOT WAS DETERMINED.

FILE: CSF1P11J
 DATE: 03/10/93 8:51:49

TABLE Q.15A: SCOT LAB SUMMARY (NUMBER OF PATIENTS WHO CHANGED FROM NORMAL TO HIGH FOR THE MAX DURING TREATMENT THROUGH 2 WEEKS POST TREATMENT) ALL STUDIES BY DURATION OF THERAPY

DRUG	DAILY DOSE	FORMULATION	TOT. PTS. #	DURATION OF THERAPY AT TIME OF MAX CHANGE##	MULTIPLES OF UPPER LIMIT OF NORMAL			
					>1 - 2 X NO. PTS. (%)	> 2 - 3 X NO. PTS. (%)	> 3 - 7 X NO. PTS. (%)	> 7 X NO. PTS. (%)
CETIRIZINE	1.25	SYRUP	73	>2 - 4 WEEKS >4 -12 WEEKS	3(4.11%) 1(1.37%)	0(- %) 0(- %)	0(- %) 0(- %)	0(- %) 0(- %)
CETIRIZINE	2.5	SYRUP	71	>2 - 4 WEEKS >4 -12 WEEKS	1(1.41%) 3(4.23%)	0(- %) 0(- %)	0(- %) 0(- %)	0(- %) 0(- %)
CETIRIZINE	5	SYRUP	96	>2 - 4 WEEKS >4 -12 WEEKS	1(1.04%) 3(3.13%)	0(- %) 0(- %)	0(- %) 0(- %)	0(- %) 0(- %)
CETIRIZINE	10	SYRUP	162	UP TO 2 WEEKS >2 - 4 WEEKS	4(2.47%) 0(0.00%)	0(- %) 0(- %)	0(- %) 0(- %)	0(- %) 0(- %)
CETIRIZINE	COMBINED SYRUP		402	UP TO 2 WEEKS >2 - 4 WEEKS >4 -12 WEEKS	4(1.00%) 13(3.23%) 7(1.74%)	0(- %) 0(- %) 0(- %)	0(- %) 0(- %) 0(- %)	0(- %) 0(- %) 0(- %)
CETIRIZINE	5	TABLET/CAPSULE	409	UP TO 2 WEEKS >2 - 4 WEEKS >4 -12 WEEKS	2(0.49%) 2(0.49%) 6(1.47%)	0(- %) 0(- %) 0(- %)	0(- %) 0(- %) 0(- %)	0(- %) 0(- %) 0(- %)
CETIRIZINE	10	TABLET/CAPSULE	1209	UP TO 2 WEEKS >2 - 4 WEEKS >4 -12 WEEKS	6(0.50%) 18(1.50%) 5(0.41%)	0(- %) 1(0.08%) 1(0.08%)	0(- %) 1(0.08%) 2(0.17%)	0(- %) 0(- %) 0(- %)
CETIRIZINE	15	TABLET/CAPSULE	53	>4 -12 WEEKS	2(3.77%)	0(- %)	0(- %)	0(- %)
CETIRIZINE	20	TABLET/CAPSULE	516	UP TO 2 WEEKS >2 - 4 WEEKS >4 -12 WEEKS	15(2.91%) 5(0.97%) 6(1.16%)	1(0.19%) 1(0.19%) 0(- %)	0(- %) 1(0.19%) 0(- %)	0(- %) 0(- %) 0(- %)
CETIRIZINE	TITR.	TABLET/CAPSULE	345	UP TO 2 WEEKS >2 - 4 WEEKS >4 -12 WEEKS >12 WEEKS	2(0.58%) 5(1.45%) 4(1.16%) 0(0.00%)	0(- %) 0(- %) 2(0.58%) 1(0.29%)	0(- %) 0(- %) 0(- %) 0(- %)	0(- %) 0(- %) 0(- %) 0(- %)
CETIRIZINE	COMBINED TABLET/CAPSULE		2532	UP TO 2 WEEKS >2 - 4 WEEKS >4 -12 WEEKS >12 WEEKS	25(0.99%) 25(0.99%) 23(0.91%) 0(0.00%)	1(0.04%) 2(0.08%) 3(0.12%) 1(0.04%)	0(- %) 2(0.08%) 2(0.08%) 0(- %)	0(- %) 0(- %) 0(- %) 0(- %)

#NUMBER OF PATIENTS WHO HAD NORMAL BASELINE AND POST LAB VISIT.

##IF LAB DATE PASSED LAST DATE OF MEDICATION, DURATION OF THERAPY=LAST DATE OF MED. - FIRST DATE OF MED. +1

FILE: CSF1P15B

DATE: 03/10/93 8:26:03

TABLE Q.15A: SCOT LAB SUMMARY (NUMBER OF PATIENTS WHO CHANGED FROM NORMAL TO HIGH FOR THE MAX DURING TREATMENT THROUGH 2 WEEKS POST TREATMENT) ALL STUDIES BY DURATION OF THERAPY

DRUG	DAILY DOSE	FORMULATION	TOT. PTS.#	DURATION OF THERAPY AT TIME OF MAX CHANGE##	MULTIPLES OF UPPER LIMIT OF NORMAL			
					>1 - 2 X NO.PTS.(%)	> 2 - 3 X NO.PTS.(%)	> 3 - 7 X NO.PTS.(%)	> 7 X NO.PTS.(%)
PLACEBO		SYRUP	163	UP TO 2 WEEKS	2(1.25%)	0(- %)	0(- %)	0(- %)
				>4 -12 WEEKS	2(1.25%)	0(- %)	0(- %)	0(- %)
PLACEBO		TABLET/CAPSULE	1371	UP TO 2 WEEKS	4(0.29%)	0(- %)	2(0.15%)	0(- %)
				>2 - 4 WEEKS	6(0.44%)	2(0.15%)	1(0.07%)	0(- %)
				>4 -12 WEEKS	7(0.51%)	0(- %)	1(0.07%)	0(- %)
ASTEMIZOLE	10	TABLET/CAPSULE	130	>2 - 4 WEEKS	2(1.48%)	0(- %)	0(- %)	0(- %)
CHLORPHENIRAMINE	6	SYRUP	50	>2 - 4 WEEKS	1(1.72%)	0(- %)	0(- %)	0(- %)
CHLORPHENIRAMINE	16	TABLET/CAPSULE	127	>2 - 4 WEEKS	5(3.94%)	0(- %)	0(- %)	0(- %)
				>4 -12 WEEKS	1(0.79%)	0(- %)	0(- %)	0(- %)
DIPHENHYDRAMINE	TITR.	TABLET/CAPSULE	60	>4 -12 WEEKS	1(1.47%)	0(- %)	0(- %)	0(- %)
				>12 WEEKS	1(1.47%)	0(- %)	0(- %)	0(- %)
HYDROXYZINE	TITR.	TABLET/CAPSULE	59	>4 -12 WEEKS	2(3.39%)	0(- %)	1(1.69%)	0(- %)
TERFENADINE	120	TABLET/CAPSULE	141	>2 - 4 WEEKS	2(1.42%)	0(- %)	0(- %)	0(- %)
				>4 -12 WEEKS	3(2.13%)	0(- %)	0(- %)	0(- %)

##NUMBER OF PATIENTS WHO HAD NORMAL BASELINE AND POST LAB VISIT.

##IF LAB DATE PASSED LAST DATE OF MEDICATION, DURATION OF THERAPY=LAST DATE OF MED. - FIRST DATE OF MED. +1

FILE: CSF1P150

DATE: 03/10/95 8:26:04

TABLE Q.12A: SCOT LAB SUMMARY (PRE -TO MAX. INCREASE DURING TREATMENT OF UP THROUGH 2 WEEKS POST TREATMENT)
 - ALL TABLETS/CAPSULE STUDIES INCLUDE ONLY WOMEN (AGE >= 12 YRS)

DRUG	DAILY DOSE	TOT. PTS.	FREQUENCY (%) DISTRIBUTION OF LAB. READINGS AS BELOW (L), WITHIN (N), OR ABOVE (H) THE NORMAL RANGE								
			ML#	ML	LL	NH	NN	LH	NH	NN	LH
CETIRIZINE	5	171	-	0.58	-	-	96.49	0.30	1.17	1.17	-
CETIRIZINE	10	606	-	-	-	1.65	95.71	0.33	0.33	1.90	-
CETIRIZINE	15	22	-	-	-	-	90.91	-	4.55	4.55	-
CETIRIZINE	20	255	-	-	-	1.57	92.94	-	0.78	4.71	-
CETIRIZINE	TITR.	210	-	-	-	0.95	91.90	0.95	0.95	5.24	-
CETIRIZINE	COMBINED	1264	-	0.00	-	1.27	94.54	0.40	0.71	3.01	-
PLACEBO		728	-	0.14	0.27	1.24	56.29	-	0.96	1.10	-
ASTENIZOLE	10	92	-	-	-	-	100	-	-	-	-
CHLORPHENIRAMINE	16	58	-	-	-	5.24	89.47	-	2.43	2.43	-
CHLORPHENIRAMINE	TITR.	8	-	-	-	-	100	-	-	-	-
DIPHENHYDRAMINE	TITR.	33	-	-	-	3.03	96.97	-	-	-	-
HYDROXYZINE	TITR.	41	-	2.44	-	2.44	92.68	-	-	2.44	-
LORATADINE	10	38	-	-	-	-	97.37	-	2.43	-	-
TERFENADINE	120	81	-	-	-	-	97.53	-	1.23	1.23	-
TERFENADINE	TITR.	14	-	-	-	-	100	-	-	-	-

* ML - FIRST LETTER (H) REPRESENTS BASELINE VALUE; SECOND LETTER REPRESENTS THE MAXIMUM INCREASE DURING OR AFTER TREATMENT.

FILE: CSF1P12A

DATE: 03/08/93 12:23:34

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FEB 23 1994

Addendum to Medical Officer Review

N 19835

Drug: cetirizine tablets

Sponsor: Pfizer

Correspondence: N (AM) July 15, 1993

Subject: Revisions to the MOR dated October 22, 1993.

Date: February 22, 1994

Medical Officer reviewer: Ana M. Saavedra-Delgado, M.D.

Handwritten signature: Ana M. Saavedra-Delgado
Handwritten date: Feb 22, 1994

The Sponsor's submission of July 15, 1993 is the response to our April 19, 1993 questions regarding cetirizine safety issues.

The MOR reviewed volumes 53, 54, and 55 of the original NDA submission of June 30, 1988 for the preparation of the original MOR review.

1. Cetirizine - CNS - Population Higher Risk - page 20 and 35

In the original MOR in page 20 it reads:

Even though in the population database of patients >12 years in controlled studies, Table 1 (Appendix 2), there is no difference in the frequency of central and peripheral nervous system disorders, between patients that receive cetirizine (all patients, all doses included) and placebo, for this same population the frequency of reported psychiatric disorders is almost twice for patient receiving cetirizine (17.6%) versus those receiving placebo (9.2%).

We had not made this observation before (unless somnolence is included in this category), and perhaps the events listed under this term now were grouped differently before. It would be particularly relevant if terms such as depression were included in this category. This observation is seen with about the same frequency in males (16.5% vs 8.9%, Table 2) and in females (18.6% vs 9.4%, Table 3-Appendix 2). These results would also be more meaningful if they had been reported in terms of the dose of cetirizine used in addition to the reported format.

The Sponsor should be able to explain this observation in greater detail, including relation to the dose of cetirizine used.

A list of terms included under this observation needs to be submitted by the Sponsor, with the corresponding frequencies per term specified.

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It should read:

Even though in the population database of patients >12 years in controlled studies, Table 1 (Appendix 2), there is no difference in the frequency of central and peripheral nervous system disorders, between patients that received cetirizine (all patients, all doses included) and placebo, for this same population the frequency of reported psychiatric disorders is almost twice for patient receiving cetirizine (17.6%) versus those receiving placebo (9.2%). We had not made this observation before (unless somnolence is included in this category). This observation is seen with about the same frequency in males (16.7% cetirizine vs 8.9% placebo, Table 2) and in females (18.6% cetirizine vs 9.4% placebo, Table 3-Appendix 2). These results would also be more meaningful if they had been reported in terms of the dose of cetirizine used in addition to the reported format.

In the integrated summary of the original NDA submission (June 30, 1988) the Summary of Adverse Experiences by WHO preferred term, for patients treated in placebo controlled U.S. Clinical trials, lists only one report of depression out of 1369 patients, in cetirizine treated patients, Table 5.

In the Safety Update of Jan 30, 1992, depression is reported by 3 out of 2113 patients in randomized, fixed-dose, US trials (Table F 11 vol 1). In the cumulative database (NDA and post NDA U.S. studies) by duration of treatment: 5/2533 (up to 2 weeks), 4/1716 (3-4 weeks), 2/1031 (5-12 weeks), 1/237 (13-6 mo) in Table F 13, vol 1.

In the safety update of 5/12/93, the term depression as such did not appear, probably due to the fact that the incidence was <2%.

A list of terms included under the grouping "psychiatric disorders" needs to be submitted by the Sponsor, with an update of the corresponding frequencies per term. These results should also be reported in terms of the dose and duration of treatment in addition to the reported format.

In the original MOR in page 35 it reads:

4. Even though in the population database of patients >12 years in controlled studies, Table 1, there is no difference in the frequency of central and peripheral nervous system disorders, between patients that receive cetirizine (all patients, all doses

included) and placebo, for this same population the frequency of reported psychiatric disorders is almost twice for patient receiving cetirizine (17.6%) versus those receiving placebo (9.2%).

We had not made this observation before (unless somnolence is included in this category), and perhaps the events listed under this term now, were grouped differently before. It would be particularly relevant if terms such as depression were included in this category. This observation is seen with about the same frequency in males (16.5% vs 8.9%, Table 2) and in females (18.6% vs 9.4%, Table 3). These results would also be more meaningful if they had been reported in terms of the dose of cetirizine used in addition to the reported format.

The Sponsor should be able to explain this observation in greater detail, including relation to the dose of cetirizine used.

A list of terms included under this observation needs to be submitted by the Sponsor, with the corresponding frequencies per term specified.

It should read:

For patients >12 years in controlled studies, the frequency of reported psychiatric disorders is almost twice for patient receiving cetirizine (17.6%) versus those receiving placebo (9.2%). This observation is seen with about the same frequency in males (16.7% cetirizine vs 8.9% placebo), and in females (18.6% cetirizine vs 9.4% placebo).

A list of terms included under the grouping "psychiatric disorders" needs to be submitted by the Sponsor, with an update of the corresponding frequencies per term. These results should be reported by dose, gender and duration of treatment.

2. Reviewer's comment to case report 85-N-0047:

In the original MOR p.33, 7 a., it reads:

a. For the CRF of patient 85-N-0042 #13 please resubmit pages 12 1744, 1750 1753 and 1754. CRF photocopy was too light to read.

Reviewer's comments:

It is likely that the decrease in platelet count in this patient could be related to the study drug, cetirizine. Thrombocytopenia has been reported in two other patients from the foreign spontaneous reports, one in association with oxazepam and luscix N00785 and another in patient N00912 with ketotifen (16,000). Thrombocytopenia has not been included in the labeling, and it should.

The reviewer's comment for this case should read:

It cannot be ruled out that cetirizine could have contributed to a decrease in platelet count in this patient. However this patient did not experience thrombocytopenia.

There are two foreign spontaneous case reports of thrombocytopenia in patients using cetirizine concomitantly with other drugs: N00785 (oxazepam and lasix) and N00912 (ketotifen). Thrombocytopenia does not need to be included in the labeling.

The following paragraph in page 38 should be deleted:

Serious adverse events:

12. From the data set of discontinued patients it is likely that the decrease in platelet count in patient 85-N-0042 #13 could be related to the study drug, cetirizine. Thrombocytopenia has been reported in two other patients from the foreign spontaneous reports, one in association with oxazepam and lasix N00785 and another in patient N00912 with ketotifen (16,000). Thrombocytopenia has not been included as a potential rare adverse event in the labeling, and it should.

3. Amendment to MOR comments p.34 in reference to item #8, regarding the failure to report 4 symptoms (omissions) in the adverse event tables, that were originally reported in the CRF of 4 of 72 patients that discontinued studies due to adverse events.

In the original MOR Reviewer's comment to response for #8, page 34, it reads:

8. The following questions refer to the discontinued patients from original NDA studies due to adverse events:

Reviewer's comments:

If in the CRFs of the discontinued patients due to adverse events, that were reviewed by a clinical research associate, by the department of quality assurance personnel and a physician, there were 4 omissions, that I could easily detect, out of 72 patients (6%), then one wonders what is the omission rate for the rest of the safety data base, whose CRF are not usually submitted as part of the NDA. If, in addition, one considers that the patients did not fill out in their diaries information about the adverse events, we have to conclude that the safety data base that we have available for review, underestimates the incidence of adverse events.

It should read:

Reviewer's comments:

In the integrated safety summary of the original

submission vol 84 page 10 51) it is stated that "all reported ADEs have been included regardless of their severity or relationship to study drug", the same is stated in the safety update from 1/30/92, vol 1 p 2 15).

It is not clear to this reviewer now, if the adverse events that were considered to be related to a concurrent illness by the investigator were excluded from the adverse event tables (all events in all patients). It would be expected that patients with a significant pre-existent concurrent illnesses were excluded from the controlled studies, and that the number of patients with a concurrent illness participating in these controlled studies (other than atopic conditions) would be small. Therefore if this translates into underreporting of adverse events then it could have been more prevalent in the area of associated concurrent atopic conditions (sinus infections, sinus headaches, asthma symptoms). We need clarification on this regard, from the Sponsor. If symptoms of concurrent illness were excluded from the adverse event tables that we have for review, the original CRFs need to be reviewed again to capture this information, and new adverse event tables submitted.

Adverse events were not recorded in the patient's diaries of most of these controlled studies. This would underestimate the incidence of adverse events. This reviewer recommends that the Sponsor reports adverse events at an incidence of 1% or above, rather than the proposed 2% and above incidence, in the labeling.

In page 38 the following paragraph should be deleted:

Incidence of adverse events:

13. If in the Tables that correspond to the adverse events from CRF of the discontinued patients due to adverse events, that were reviewed by a clinical research associate, by the department of quality assurance personnel and by a physician, there were 4 omissions, that I could easily detect, out of 72 patients (6%). This questions what is the omission rate for the rest of the safety data base, whose CRF are not usually submitted as part of the NDA. If, in addition, one considers that in the majority of placebo control trials, patients did not fill out in their daily diaries information about the adverse events, we have to conclude that the safety data base that we have available for review, underestimates the incidence of adverse events. Therefore, adverse reaction at a lower incidence than 2%, possibly 1% should be incorporated in the labeling.

The paragraph under Incidence of adverse events (#13) should read:

a. It is not clear to this reviewer now, if the adverse

events that were considered to be related to a concurrent illness by the investigator were excluded from the adverse event tables (all events in all patients). This needs to be clarified. If symptoms of concurrent illness were excluded from the adverse event tables that have been submitted, the Sponsor needs to submit new adverse event tables based on the results of a new review of the original CRFs from all controlled studies to include all adverse events including those related to concurrent illnesses.

b. Adverse events were not recorded in the patient's diaries of most of these controlled studies. This would underestimate the incidence of reported adverse events. The adverse events report in the labeling should include those at an incidence of 1% or above, rather than the proposed 2% and above incidence.

4. Referring to potential immunologic cross-reactivity to cetirizine in patients sensitive piperazines:

In the original MOR in page 24, it reads:

Both hydroxyzine and cetirizine have a piperazine structure. Although we are not aware of studies that show direct crossreactivity to hydroxyzine or cetirizine in patients sensitive to piperazine(s), it would be prudent to alert patients that have developed hypersensitivity to piperazine or to piperazine substituted products they could have the potential for showing crossreactivity to hydroxyzine and cetirizine, and that they should be adequately evaluated by a physician before initiation of treatment with cetirizine.

Further studies in this area are warranted.

It should read:

Both hydroxyzine and cetirizine have a piperazine structure. Although we are not aware of studies that show direct crossreactivity to hydroxyzine or cetirizine in patients sensitive to piperazine(s), it would be prudent to alert patients that have developed hypersensitivity to piperazine or to piperazine substituted products they could have the potential for showing crossreactivity to hydroxyzine and cetirizine, and that they should be adequately evaluated by a physician before initiation of treatment with cetirizine.

We would like the Sponsor to follow up the postmarketing reports of adverse events where the etiologic factor

could be attributed to an immunologic or to an allergic reaction to cetirizine, by documenting the presence or absence of a positive history of an allergic or immunologic reaction to other piperazine related structures in these patients.

In page 37 at the end of the following paragraph it should be added:

Both hydroxyzine and cetirizine have a piperazine structure. Although we are not aware of studies that show direct crossreactivity to hydroxyzine or cetirizine in patients sensitive to piperazine(s), it would be prudent to alert patients that have developed hypersensitivity to piperazine or to piperazine substituted products they could have the potential for showing crossreactivity to hydroxyzine and cetirizine, and that they should be adequately evaluated by a physician before initiation of treatment with cetirizine.

We would like the Sponsor to follow up the postmarketing reports of adverse events where the etiologic factor could be attributed to an immunologic or to an allergic reaction to cetirizine, by documenting the presence or absence of a positive history of an allergic or immunologic reaction to other piperazine related structures in these patients.

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Medical Officer Review

NDA 19,835

Cetirizine Tabs

Sponsor: Pfizer

Subject: Response to April 19, 1993 Safety Questions

Correspondence dates: N (AM)

Submission: July 15, 1993
Received: July 19, 1993
Review completed: October 22, 1993

A Saavedra-Delgado MD
Oct 25, 1993
Cy Bunkle 2/23/94

Medical Officer Reviewer: Ana M. Saavedra-Delgado, M.D.

The subject of this MOR is to review the Sponsor's response to our April 19, 1993 questions regarding cetirizine's safety issues. The conclusions of this review (p. 35-39) will be incorporated into the MOR integrated safety review and in the labeling as appropriate.

see
Dr. D. B.
note id
2/22/94
for clarity

The questions that were posed to the Sponsor appear in bold type, followed by their response and the MOR comments.

1. Has the cetirizine -CNS interaction been adequately studied? Is there be a population at higher risk that needs to be identified? Has the potential for cetirizine to interact with antiepileptic drugs? other CNS depressants? been properly studied?

Response:

The Sponsor considers that this interaction has been adequately addressed. Nine clinical pharmacology studies were submitted evaluating the effects of cetirizine on the CNS. Of these 8, were single dose studies. Seven studied cetirizine effects on performance as measured by vigilance performance testing, critical flicker fusion frequency, stroop word test and simulated driving reaction times. In CP-21, when Multiple Sleep Latency Test was measured with doses up to 20 mg of cetirizine there was no significantly increase in day time sleepiness. Study CP-28, with a multiple dose portion of 7 days, did not show any differences between 10 mg cetirizine and 20 mg hydroxyzine BID, in psychomotor tests results.

In terms of interactive studies with CNS depressants, they have conducted three single dose studies, two with ethanol and one with diazepam. In these studies,

psychometric methods were used, and in general the 10 mg cetirizine dose did not show potentiation.

CP-35 studied 10 mg single dose of cetirizine + 0.8 ml/kg ethanol on performance tests (short term memory, attention and concentration). Cetirizine did not potentiate the ethanol effects.

CP-36 studied the combination of 10 mg single dose of cetirizine + ethanol vs. placebo + ethanol. In only 1/6 tests performed there was a paradoxical response. The other psychometric tests did not show potentiation.

CP-37 was also a single dose (10 mg cetirizine) 4 way cross over: 5 mg diazepam, 10 mg cetirizine, placebo, and 5 mg diazepam + 10 mg cetirizine. The combination showed poor concentration compared to placebo but not additional to the results of the single components.

Since patients with diseases that required antiepileptic drugs or CNS depressants were generally excluded from cetirizine studies, the population studied with concurrent medication that had CNS activity was small, 49 patients. In these the adverse event profile did not show increased frequency of CNS adverse events.

The Sponsor cannot identify a higher risk population for CNS effects based on the overall safety database. There are no increased frequency of CNS effects by gender or age.

Reviewer's comments:

Cetirizine-CNS interaction:

The Sponsor has submitted the results of 9 clinical trials that study the interaction CNS-cetirizine interaction. Of these 9 studies 8 have been single dose studies. A brief assessment of from this reviewer perspective on the clinical significance of the results of these studies follow.

CP-21 Study # 85-N-0110 Vol 53, section 8, pages 426-465

Title: Cetirizine effects on objective measures of daytime sleepiness and performance.

Population: 60 healthy males and females (ages 21-45)

Design: single dose, double blind, randomized to one of 5 parallel groups

5 mg cetirizine (N=13), 10 mg cetirizine (N=13), 20 mg cetirizine (N=11), hydroxyzine 25 mg (N=12), placebo (N=11).

Assessments: MSLT every two hours, 30 minute vigilance test (video).

Results: Patients on hydroxyzine had slower reaction times and were significantly more sedated than placebo for at least 4 hours after treatment.

Reviewer's Comments: In the analysis of the MSLT results, the Sponsor has compared the absolute values on drug for the first 5 interval versus those of placebo. See Sponsor's Table 3 (Appendix 1). A low value (min) indicates that there is less time needed to fall asleep and therefore is an assessment of daytime sedation.

In this comparison only hydroxyzine is significantly different from placebo in terms of sedation. However, if we allow for a later onset of cetirizine's action in terms of sedation and do not count the first 2 hour interval, then it would appear that from 4-8 hours post dose the values on cetirizine, although not as markedly decreased as with hydroxyzine, would be less than placebo, and therefore clinically significant in terms of daytime sedation. This is particularly seen in the 20 mg and 5 mg dose.

In the Sponsor's Table 5 (Appendix 1), self-rating of sleepiness and mood during the day, expressed as group means across the day. The individual dose mean values for cetirizine are not statistically significantly different from placebo, but they show a trend towards an increase in the mean with increasing doses of cetirizine, particularly in the linear sleepiness scale.

In summary, the results of this study suggest that cetirizine does not produce daytime sedation when the mean results are taken into consideration. However, when the individual timepoints are considered, this conclusion is not so apparent, since in at least 2 out of 5 timepoints, the results suggest that cetirizine is producing daytime sedation. In addition, with the lack of concurrent PK data in this study it is hard to evaluate the effect that increasing drug concentration on individual subjects would have on the parameters measured. Therefore, the results of this study should not be used to indicate that cetirizine does not produce daytime sedation.

CP-22 Study # 84-N-0091 vol. 53, section 8, pp. 466-492

Title: The Relative Antihistaminic and Psychomotor Effects of Hydroxyzine and Cetirizine.

Population: 12 atopic healthy males (20-35 years)

Design: single dose, double blind, 4-way cross-over study, placebo controlled, randomized by Latin square design.

10 mg cetirizine, 20 mg cetirizine, hydroxyzine 25 mg and placebo.

(capsules)

Assessments: critical flicker frequency, stroop word testing and visual analog scales. Skin test (multitest) response to sequential skin tests to histamine and plasma levels of cetirizine and hydroxyzine were obtained.

Results: Hydroxyzine produced significant changes in the 3 CNS parameters measured, these were significantly related to hydroxyzine concentrations (at 2 and 4 hours). Neither doses of cetirizine (10 or 20 mg) produced any significant change in the CNS parameters measured. The three active treatments produced an equivalent suppression of the skin wheal response. Subjective complaints of tiredness, fatigue and sleepiness occurred 12x following hydroxyzine, 2x placebo, 1x cetirizine 10 mg and 2x cetirizine 20 mg.

All active drugs significantly reduced the histamine skin test response at 4, 12, and 24 hours after administration. There were no significant differences between the effect of hydroxyzine and cetirizine at these time points.

"Hydroxyzine concentrations reach average peak concentrations of 29+- 17 ng/ml, and were highest at 2 hours for all 12 subjects, then exhibited a biexponential decline with a mean 14 hours terminal half life. Metabolite (cetirizine) concentrations following oral hydroxyzine displayed a variable time to reach peak, with mean peak concentrations of 145 +- 35 ng/ml. The decline of cetirizine concentrations following hydroxyzine dosing was similar to the decline of parent hydroxyzine concentrations. "

"The disposition of cetirizine when administered orally is very different from its disposition following oral administrations of hydroxyzine. Peak concentrations were achieved by one hour for both the 10 and 20 mg doses. Peak concentrations following the 20 mg dose were 580.4 +- 203 ng/ml and following the 10 mg dose were 257+-148 ng/ml. Serum concentrations then declined, with a terminal half life of 6.6 and 7.7 hours for the 10 and 20 mg dose respectively."

Reviewer's comments: The available data that we have in this study is presented as the mean for each group in figure form. The individual patient values were not submitted. Restricting our comments to the data submitted, we agree with the Sponsor that in this study cetirizine does not show an interaction in these psychomotor tests. However, the validity of this tests to be able to accurately reflect daytime sedation is in question.

CP-23 Study #86-M-0059 Vol. 53, section 8, pp.493-518

Title: A Double-Blind Dose Ranging Study to Compare the Effects of Cetirizine and Diphenhydramine on Simulated Driving Performance and Other Measures of Cognitive Function.

Population: 15 male volunteers (19-45 years)

Design: single dose, double-blind, 5 way crossover, placebo controlled, randomized by Latin square design.

5 mg cetirizine, 10 mg cetirizine, 20 mg cetirizine,

diphenhydramine 50 mg and placebo.

Assessments: driving simulator, simulated accident avoidance, digit symbol substitution, stroop word testing, trials B maze tracking, visual analog scale, and Stanford Sleepiness Scale.

Results: There were large inter subject variability at baseline. In the visual analog scale, diphenhydramine produced more sedation than any other cetirizine dose. The Stanford Sleepiness Scale demonstrated greater subjective sleepiness following diphenhydramine than any dose of cetirizine. Driving simulation: cetirizine doses similar to placebo, diphenhydramine 2x placebo. Simulated driving time: cetirizine subject's reaction time did not differ from those on placebo, those subjects on diphenhydramine had increases in simulated driving time greater than placebo. In the digit symbol substitution and stroop word testing there was no difference between any of the treatment studied and placebo.

Reviewer's comments: Although in the above results the subjective assessment and the driving tests favor only the potential of diphenhydramine to produce sedation, after looking at the individual data submitted for the Stanford Sleepiness Test, 6/15 subjects receiving 10 mg of cetirizine scored 3 or more. In this subjective test a score of 3 or more indicates that significant daytime somnolence is present. In view of the subjective individual subject results the sensitivity of the driving assessment test as conducted in this study to predict daytime sedation is in question.

The individual patient data for the rest of the tests was not submitted. The negative results for all treatments in the digit symbol substitution and stroop word testing argue against the effectiveness and validity of these tests to show antihistaminic sedative effects.

Therefore the results of this study taken as a group and looking at individual subject data, do not support the claim that cetirizine at the doses tested does not have a sedative effect.

CP-24 Study # DE85M033E vol.53, section 8, pp.519-539

Title: Quantitative EEG and Neuropsychological Effects of P071, 5-20 mg single oral doses. CMS "Toxicity" Study in Normal Volunteers.

Population: 8 male volunteers (22-+ 3.2 years)

Design: single dose, double-blind, 5 way crossover, placebo controlled, randomized by Latin square design.

5 mg P071, 10 mg P071, 20 mg P071 and placebo.

Assessments: EEG, memory and attention tests (short term retention test for sequence letters, backwards digit span test, first and last name test, immediate retention tests for sequence of colors), Critical Flicker-fusion Frequency (CFF), heart rate and BP, subjective symptoms.

Results: EEG: not possible to outline any time ongoing or dose relation possibly consistent with a CNS effect; memory and attention tests and CFF: in general no effect different from placebo.

Reviewer's comments: In terms of subjective symptoms 2/8 receiving 5 and 20 mg of cetirizine respectively, reported feeling drowsy. One of the subjects dosed with 10 mg reported feeling fatigued and one reported feeling drowsy. None of the subjects receiving placebo reported these effects. The duration of the events were not submitted.

Although no direct EEG effect was demonstrated in this small study, subjective symptoms indicate that individual subjects did experience sedation. Again the validity of the tests selected to show sedation in the absence of a positive antihistamine control, is in question. Therefore, the results of this study should not be used to claim the lack of sedative effects by cetirizine.

CP-25 Report #DR87A151 vol. 53 Section 8, pp 611-655

Title: A Comparative Study of Cetirizine 10 mg versus Terfenadine 60 mg.

Population: 9 males (20-30 yrs)

Design: single dose, double blind, randomized, cross-over, patient follow up for 6 hrs post dose

cetirizine 10 mg, terfenadine 60 mg and placebo capsules

Assessments: EEG, visual scales (good condition-high fatigue), skin tests through 6 hours

Results: EEG at 6 hrs slight central effect, similar to a reduction in vigilance for terfenadine; visual scale: no difference between treatments according to summary. However, in Table XIV, there appears to be an effect seen 6 hours post dose.

Reviewer's comments: In this small study of 6 hrs follow up there is no difference reported between treatments in terms of EEG.

Reviewing the visual scale results, the ^{appendix 1)} summary reports no difference between treatments. Table XIV, with individual subject data show that there are differences between placebo and the two active treatments, 6 hrs. post dose in terms of fatigue, even though there may be no significant difference between terfenadine 60 mg and cetirizine 10 mg. It could be concluded from the individual subject results, that in this study, when subjects received cetirizine 10 mg or terfenadine 60 mg, they experienced mild fatigue compared to when placebo was used.

CP-26 Report# DE85M033F vol.53, Section 8, pp 656-685

Title: Comparative Study of the Peripheral Anti H₁ Effects and the Central Nervous System Effects of P071 and Terfenadine.

Population: 12 pts with rhinitis (7males, 5 females)

Design: single dose, double blind, randomized, cross-over, patient follow up for 5 hrs post dose, wash-out period 48 hrs between treatments.

P071:10 mg, terfenadine 180 mg and placebo

Assessments: psychometric testing; cognitive, coupled video objects; self rated vigilance; skin tests to histamine.

Results: no difference between treatments in the psychometric testing and in the self rated vigilance.

Reviewer's comments: In this small study the short wash out period between doses (48 hrs), post drug follow up (5 hrs), lack of positive control, questionable validity of the psychomotor tests used, put in question the conclusion the lack of CNS effects after single dose use of terfenadine 180 mg and cetirizine 10 mg.

CP-3 Report # DIE86E212 vol 53, section 8, pp 686-712

Title: Comparative Study of the Peripheral and Central Effects of Terfenadine and Cetirizine 2HCL.

Population:

Terfenadine 60 mg: 9 healthy volunteers (5 males, 4 females, ages 22-52)

Terfenadine 120 mg: 7 healthy volunteers (4 males, 3 females, ages 22-47)

Terfenadine 180 mg: 9 healthy volunteers (4 males, 5 females, ages 25-50)

Design: three different group of volunteers were used for the three single dose trials where terfenadine at different doses was compared to 10 mg of cetirizine- capsules

- 1) Terfenadine 60 mg: double blind, cross over, randomized, follow up for 24 hours
- 2) Terfenadine 120 mg: open, cross over, randomized, subjects follow up for 4 hours
- 3) Terfenadine 180 mg: double blind, cross over, randomized, follow up for 6 hours

Assessments: Studies 1 and 3: visual scale for sedation; lack of movement coordination; cutaneous reactivity to histamine. Study 2: cutaneous reactivity to histamine.

Results: In terms of CNS effects only the results of the double blind studies 1 and 3 were reported. In terms of sedation reported using visual analog scales there was no difference between treatments. Individual subject data was not included.

In the spontaneous reports:

Study 1: placebo: 1 subject: sleepiness and heavy head -4 hr

terf. 60 mg: 2 subjects--altered attention-concentration
 cetirizine 10 mg: none
 Study 3: placebo: 1 fatigue- 3hrs (male)
 terf. 180 mg: 1 drowsiness (male)
 1 altered attention-concentration (male)
 cetirizine 10 mg: 1 drowsiness and dry mouth (female)

Reviewer's comments: These three small studies, using 48 hrs wash out between doses, attempt to compare the central effects of cetirizine 10 mg with increasing doses of terfenadine. Only the results of cutaneous reactivity to histamine are reported for Study #2.

When the CNS effects of cetirizine 10 mg are compared to terfenadine 60 and 180 mg in double blind studies, using a visual analog scale for sedation, no difference is observed between treatments. Individual subject data was not submitted. There are however differences between treatments observed by spontaneous subject reporting. In these two studies the results favor cetirizine. It is surprising that only 2 subjects receiving 180 mg of terfenadine reported adverse events. The short follow up for this study may be responsible for the few reported adverse events.

Multiple Dose Studies:

CP-28 Report #DE35M033G vol. 54, section 8 pp.713-837

Title: Peripheral Antihistaminic Activity and Central Effects of Two Antihistamines: Cetirizine 2HCL and Hydroxyzine.

Population: 12 healthy volunteers (3 males and 9 females, ages 22-38 years of age)

Design: double blind, randomized, multiple cross over study using single and multiple dose schedules; duration 1 week. The wash-out period between doses or treatment tested was not stated in the submitted material.

cetirizine 10 mg, hydroxyzine 20 mg and placebo tablets

Assessments: visual scales (0-100 mm): alertness, concentration, tiredness, sleepiness, tenseness, restlessness, and lack of comfort; psychometric tests: tapping, reaction times and maze; skin test to histamine were also performed.

Results: Using the mean data from the above tests to measure CNS effects, only hydroxyzine when given as single dose showed an effect in three of the visual scale parameters measured: sleepiness, alertness and tiredness. Hydroxyzine did not show a significant difference from placebo in the psychomotor tests used after single or multiple doses. Cetirizine 10 mg was not found to be significantly different from placebo in the visual scales for sleepiness. In multiple dosing, no difference was observed between the three treatments regimens.

Reviewer's comments: When individual subject data is

examined:

Single Dose:

3 cetirizine treated subjects (3/12, 25%) report a score of less than 50, or (+) sleepiness: Subject 3 (18), 7 (48) and 12 (37).

6 hydroxyzine treated subjects (6/12, 50%) report a score of less than 50: Subject 2(1), 3(30), 7 (11), 8 (0), 9 (8) and 13 (34)

1 placebo treated (1/12, 8%), Subject 3 (39), scored under 50.

No significant CNS effects difference is observed between all three treatments with the psychomotor tests used.

Multiple Dose:

No significant CNS effects difference is observed between all three treatments with the psychomotor tests used or with the use of the visual scales.

We agree with the study investigator's conclusion: "subjective testing using the visual analog scales proves to be more sensitive than the psychomotor testing, and it allows to evidence undesired central effects after single dose administration, and in this case quite particularly with hydroxyzine" The investigators recognize that the psychomotor testing used lacked sensitivity to answer whether after repetitive dosing, subjective habituation occurred, or in other words, whether the subjects did not get used to living with a sedative effect. Unless appropriate psychomotor testing that can differentiate between this two effects is validated, the subjective adverse event reporting in clinical trials should be the parameter used to assess sedation after multiple dose antihistamine administration.

General reviewer's comments on studies submitted to evaluate cetirizine-CNS effects:

In the single doses studies conducted to assess cetirizine's CNS effects, only on CP-21 the MSLT (multiple sleep latency test) was used. The MSLT is probably the most effective test of the ones now available to detect daytime sedation. In this study three doses of cetirizine were studied (5, 10, and 20 mg). The results expressed as the mean of the first five measurements of the MSLT done at 2 hour intervals did not show any difference between the doses of cetirizine studied and placebo. However the results at 4 and 6 hours post dose if independently assessed,

then could show a possible dose effect trend with a significant difference from placebo shown by cetirizine 20 mg at 4 hrs post dose.

In CP-22 and 23 a variety of psychomotor tests were used to compare the effects of cetirizine (5, 10 and 20 mg) to diphenhydramine 50 mg and hydroxyzine 25 mg and placebo. No difference was seen in the reported mean results between cetirizine and placebo. In CP-23 however, when the individual data for the Stanford Sleepiness Scale was presented, 4/10 subjects a dose of 10 mg of cetirizine had a score of 3 or more, indicating the presence significant daytime sedation.

CP-24 tried to quantitate the CNS effect of cetirizine (5, 10, and 20 mg) versus placebo, using a set of psychomotor tests to measure memory and attention. No difference was observed between treatments. The subjective symptom assessments showed that 2/8 subjects (25%) taking 5 and 20 mg cetirizine, reported feeling drowsy, no patient on placebo complained of drowsiness.

The CNS effects of cetirizine 10 mg and terfenadine (60, 120 and 180 mg) were compared to placebo in three small, cross-over studies, CP-25, 26 and 27. EEG, visual scales for sedation and psychomotor tests were used. In these tests, there was no difference between cetirizine and placebo noted. For terfenadine 60 mg a slight central effect, similar to a reduction in vigilance was noted. A wash-out period of 48 hrs was used for these studies. If individual data for the visual scale of fatigue is examined for study CP-25, it would appear that both cetirizine 10 mg and terfenadine 60 mg at 6 hours show a difference compared to placebo. However at higher doses no effect was noted in the psychomotor tests used or in the self rated vigilance or visual scales for sedation. In CP-26 the short wash out period between doses (48 hrs), post drug follow up (5 hrs), lack of positive control, questionable validity of the psychomotor tests used, put in question the conclusion the lack of CNS effects after single dose use of terfenadine 180 mg and cetirizine 10 mg. In CP-27, when the CNS effects of cetirizine 10 mg are compared to terfenadine 60 and 180 mg in double blind studies, using a visual analog scale for sedation, no difference is observed between treatments. Individual subject data was not submitted. There are however differences between treatments observed by spontaneous subject reporting. In these two studies the results favor cetirizine. It is surprising that only 2 subjects receiving 180 mg of terfenadine reported adverse events. The short follow up for this study may be responsible for the few reported adverse events.

In CP-28 we agree with the study investigator's conclusion: "subjective testing using the visual analog scales proves to be more sensitive than the psychomotor testing, and it allows to evidence undesired central effects after single dose

administration, and in this case quite particularly with hydroxyzine" In this study the investigators recognize that the psychomotor testing used lacked sensitivity to answer whether after repetitive dosing, subjective habituation occurred, or in other words, whether the subjects did not get used to living with a sedative effect. Unless appropriated psychomotor testing that can differentiate between these two effects is validated, the subjective adverse reporting in clinical trials should be the parameter used to assess sedation after multiple dose antihistamine administration.

Cetirizine-CNS Depressants

The complete submission to the NDA for these three studies was reviewed. The next section will consist of a study summary for each study and reviewer's comments. All three studies were conducted in Europe. CP-35 and CP-37 were conducted by the same research group.

Cetirizine/ethanol:

CP-35 Report # CE86A201 vol 54, section 8 pp 951-1108

Title: Interaction between alcohol and P071. A psychopharmacological Study.

Population: 36 healthy volunteers (15 females, 21 males 19-25 years of age)

Design: randomized, double blind, placebo controlled, single dose, cross over study

One large dose of alcohol (0.8ml/kg or 0.6312 gm/Kg), 10 mg of P071, or placebo.

Subjects received the placebo or cetirizine dose and 40 minutes later the dose of alcohol or placebo drink. Testing was started 1 hour 30 min after.

Assessments: glycemia level, drug levels at the end of the session and the following assessments:

Collective Tests:

Bourdon Wiersma Test (attention)

work rate

work rate evolution over time

inaccuracy

evolution degree of inaccuracy

attention index

evolution attention index

Feldmarkierungstest (concentration)

work rate

inaccuracy

evolution of work rate over time
 evolution of degree of inaccuracy
 productivity fluctuations
Aufmerksamkeits-Belastungstest (attention+concentration)
 work rate
 degree of inaccuracy
 fluctuation in productivity
Lern-und Gedachtnis (learning and short-term memory)
 total retention score
 retention scores for pictures
 retention scores for verbal elements

Individual Tests:

Crawford Small Parts Dexterity Test (hand-eye coordination)
 Inventory of subjective health
 Mood scale
 visual analog scale
 self assurance and fatigue scale
 Estimation of the experimental condition
 state trait anxiety inventory

Results:

It took significantly longer for subjects taking the drink containing the alcohol to finish their drink. Subjects were quite accurate in their estimation as to whether they had received alcohol or not. In this sense blinding was broken.

Subjective health. In this global there was no difference as to whether they had received alcohol or not. However in the individual questions alcohol made subjects feel:

less up to scratch
 less capable of coping with their work rhythm
 more tired
 more sleepy and drowsy
 more apathetic
 more fatigued than they should
 more dizzy

Bourdon Wierma Test (attention). Alcohol only showed a positive effect on the work rate, counteracting the learning-order effect. There were no positive effects for P071 or for combination. For the other parameters tested there were significant order effects, showing that as subjects repeated the tests their scores improved. The investigators conclude that subjects slow down their work rate in order to keep accuracy within acceptable boundaries.

Feldmarkierungstest (concentration). Although alcohol had a positive effect for work rate and inaccuracy, there were positive order or learning effects for all parameters tested. The investigators conclude that under alcohol subjects prove to work less hard and to become more inaccurate than when not under its influence.

Aufmerksamkeits-Belastungstest (attention+concentration). Alcohol did not effect the expected results of this test. There were order - learning effects that counteracted the expected effects.

Lern-und Gedachtnis (learning and short-term memory). Alcohol had a positive effect on total retention score and retention score for verbal elements. However also in this tests there were positive learning effects for all parameters measured. Therefore, as subjects

repeated the tests they got better at it.

The investigators conclude that "due to the sequence effects noted throughout the experiment one cannot state in general terms that the medication treatment did not have any effect. One can merely state that the 10 mg medication treatment did not have more depressant properties than the placebo treatment. Yet both medication treatments might have possibly impaired some of the performances measured by the battery of psychological testing."

Reviewer's comments:

Only one dose of cetirizine was used (10 mg). The blinding was not maintained in this study in terms of alcohol intake but it was apparently maintained in terms of P071 (cetirizine 10 mg). The validity of the subjective data is therefore questionable. There are about 17 objective parameters measured but no a "p priori" primary endpoint was selected. There were substantial learning-sequence effects for most of the objective tests used in this cross over study, that put into question the validity of these results.

Only mean data was submitted for all parameters measured. Adequate pharmacokinetic data was not collected. We do not know what happened to the plasma levels through out the study or if there were any PK interactions. The time to recovery of alcohol impairment, a potential PD interaction was not explored. Only one dose of the proposed (5-20mg) was used. Among other tests that have been found to be meaningfully effected by alcohol intake, like the standing steadiness test, was not done.*

In conclusion the deficiencies in this study (blinding not maintained in terms of the subjective assessments and sequence - learning effects in the objective assessments, inadequate PK data collection) limit its usefulness to adequately assess ethanol-cetirizine interactions and provide adequate labeling recommendations.

* Franks H.M., Hensley V.R., Hensley W.J. et al. The Interaction between ethanol and antihistamines. The Medical Journal of Australia, 1: 449-452, 1978.

CP-36 Report # DE85M038 vol. 55, sect 8, pp. 1,108-

Title: Influence of an "Antihistamine I-Ethanol" Association upon Alertness

Population: 8 male subjects (21-27 yrs of age)

Design: Double blind, randomized, 2 period crossover study, with a 7 day wash-out period

ethanol 1.5 ml/kg (0.048gm/kg) then 0.75 ml/kg to insure rate of

0.50 to 1.00 gm/L (11-22 nmol/L) for 4 hours
cetirizine 10 mg capsules and placebo

Assessments:

anxiety scale of Catell
complex figure of Ray
visual retention test of Benson
series of figure
Luneau stereotest
Code test
simple reaction time (visual - auditory)
alcoholometer Lion SD₂

The psychometric tests were done once, while the reaction times were done 6 times per session.

Results:

In terms of alcohol concentration measurements no significant differences were observed between the placebo period and the cetirizine period at each measured time, 0.5-8 hrs post dose.

The reaction time to auditory stimulus was significantly prolonged in 5/8 subjects when comparing the cetirizine period (ethanol-cetirizine) to placebo period (ethanol/placebo) period for the test performed 2.5 hrs post dose. It was also positive in 3/8 at 1.5 hrs post dose. However by 4.5 hrs post dose, for 4/8 subjects it was significantly prolonged and in 4/8 subjects the reaction time was significantly shortened.

In 2/8 subjects the ethanol-cetirizine combination appeared to produce through out this test a pronounced prolongation effect. In 2/8 subjects the opposite was true.

With the exception of the reaction time to stimulus, the above psychometric assessments did not distinguished any differences between treatments (alcohol-cetirizine, alcohol-placebo).

Reviewer's comments:

This study has a number of limitations that impact on the extrapolation of its results to a general population: small and limited population, multiple assessments and no primary efficacy endpoint chosen "a priori", lack of a single cetirizine placebo and placebo alcohol arms, failure to validate the tests chosen with positive controls such as diphenhydramine or a diphenhydramine-alcohol combination.

As has been reported* the auditory reaction time has been found to be affected by antihistamine-ethanol interactions. The fact that this results may have shown that within the small sample of male patients studied, there seems to be a wide variety of response to this interaction and that some subjects may be significantly more sensitive to it than others, deserves further study to clarify this possibility and to define the extent of it.

The fact that the other psychometric studies did not find differences between the two regimens, does not imply that no actual differences exists. The fact that positive learning- sequence effects were found in some tests and that perhaps the optimal time according to actual peak plasma cetirizine-ethanol levels was not taken into consideration into the study design, limit the usefulness of extrapolating the results of this study into the general population. The limitations noted should be taken into consideration for the design of future clinical trials to study this interaction.

Cetirizine/diazepam (Valium):

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Title: "P071:Valium. A Study on Interaction Effects."

Part 1. Validation Study

Population: 16 healthy volunteers (10 males, 6 females, 19-25 years of age)

Design: The research group conducting this study is the same group that conducted the ethanol-cetirizine study, CP-35.

Part 1: Validation study, diphenhydramine study: single dose (0, 25, 50 , 75 100 and 125 mg), double blind, using the same psychometric assessments to be used in part 2.

Medication (Valium or placebo, cetirizine or placebo) were administered concurrently at 10:45 AM and tests were started at 2 PM.

Assessments: glycemia levels were obtained pre-dose, serum collected for drug concentrations at the end of the testing session.

Collective Tests:

Bourdon Wiersma Test (attention)

work rate
work rate evolution over time
inaccuracy
evolution degree of inaccuracy
attention index
evolution attention index

Feldmarkierungstest (concentration)

work rate
inaccuracy
evolution of work rate over time
evolution of degree of inaccuracy
productivity fluctuations

Lern-und Gedachtnis (learning and short-term memory)

total retention score
retention scores for pictures
retention score for verbal elements

Individual Tests:

Wiener Reaktionsgerat: reaction time to visual stimuli and to a

combination of visual and auditory stimuli
 Mental alertness under conditions of high work load
 Inventory of subjective health
 Mood scale
 visual analog scale, scored scale
 Subjective feeling of self assurance and fatigue
 Estimation of the experimental condition
 state trait anxiety inventory

Analysis: two analysis were done, one comparing the results of the test through linear regression using the results of the different doses and another comparing the different scores that the same subjects obtained during this study with the ones obtained a year prior under no drug (historical, non-concurrent control).

Results: will be presented in a table form, following the description of Part 2.

Only the following tests were considered to be sensitive to antihistamine effects and will be used in Part 2; this decision was based on having at least one of its dependent measures sensitive to the antihistaminic effects of diphenhydramine:

Statistically Positive results:

Bourdon Wiersma Test (attention)
 + inaccuracy
 Feldmarkierungstest (concentration)
 + work rate
 + work evolution
 Wiener Reaktionsgerat: reaction time to visual stimuli and to a combination of visual and auditory stimuli
 + visual stimuli by themselves
 Mood scale
 + visual analog scale; (-) when compared to non concurrent control
 + score scale; (-) when compared to non concurrent control
 Subjective feeling of self assurance and fatigue
 + fatigue; (-) when compared to non concurrent control
 + self assurance, (-) when compared to non concurrent control

Part 2. P071:Valium Interaction.

Population: 33 initially, completed: 28 healthy volunteers (16 males, 12 females, 19-35 yrs of age)

5 withdrawals: N=3 no explicit reasons, N=1 illness, N=1 teaching problems)

Design: double blind, randomized, 4 period cross-over, one week wash-out

Medications: (placebo or 10 mg P071, placebo or Valium 5 mg) given at 11:10 AM, test sessions begun at 2:00PM

The duration of the Bourdon Wiersma Test (attention), was changed from 5 to 15 min, and the reaction time test was extended for 2x the time used in the validation part.

Assessments: glycemia pre-dose and drug levels at the end of testing

session

Bourdon Wiersma Test (attention)
 Feldmarkierungstest (concentration)
 Wiener Reaktionsgerät: reaction time to visual stimuli and to a
 combination of visual and auditory stimuli
 Mood scale
 visual analog scale, scored scale
 Subjective feeling of self assurance and fatigue
 Estimation of the experimental condition
 state trait anxiety inventory

Results:

- Patients receiving Valium were quite accurate in their estimations of the Valium treatment, when serum concentrations increased the subjects could provide a more accurate estimation as to whether they had received Valium. For subjects receiving P071 this did not occur.
- The mean time from dose administration to end of test session was 4 hours and 47 min.
- Clinical observations: 7/28 (25%) subjects fell asleep (5 females and 2 males) when they took Valium. Four had received Valium + P071 and 3 received Valium and placebo.

Table of Results of Analysis of Variance : significant main effects for
 -37

	Benadryl	Valium	P071	V:P071
mood scale				
analog scale	+	+	- ¹	-
scored scale	+	trend	-	-
fatigue	+	+	trend	- ²
self assurance	+	+	-	-
Bourdon Wiersma				
work rate	-	-*	-*	-*
work rate				
evolution	-	-*	-*	-*
inaccuracy	+	-*	-* ³	-*
evolution				
degree				
inaccuracy	-	-	-	-
attention				
index	-	**	-*	-*
evolution				
attention				
index	-	-*	-* ³	-*
Feldmarkierungstest				
work rate	+	-*	-*	-*
work rate				
evolution	+	-*	-*	-*
inaccuracy	-	-	+ ⁴	-
evolution of				
inaccuracy	-	-	+ ⁴	-
productivity				
fluctuations	-	-*	-*	-*

Wiener Reaktionsgerat				
visual	+	-*	-* ⁵	-*
mistakes excess	-	-	-	-
mistakes omissions	+	+	trend	+ ⁶
visual+auditory	-	-	-	-
mean # of mistakes	-	-*	+*	+*

* order main effect: learning effect

(1) subjects report to feel less well as the concentration of P071 in their blood sample is more pronounced.

(2) when contrasting the experimental condition with the baseline condition it becomes apparent that subjects feel more fatigued in the experimental condition versus the baseline condition (p=0.009).

(3) subjects make more errors and become less attentive as the concentration of P071 becomes more pronounced in their blood: p=.001 and p=0.006, respectively.

(4) the degree of inaccuracy decreased when subjects took P071 with either Valium or Valium placebo.

(5) subjects reacted less quickly to the light stimulus when the P071 concentration in their blood was more pronounced, p=0.04.

(6) the contrast between the Valium- P071 10 mg and other treatments proves to be meaningful, p=0.04.

Reviewer's comments:

In this study several of the deficiencies that were noted in the two previous studies ethanol-cetirizine interaction were addressed in the study design: validation of the psychomotor assessments with a study using a positive control, inclusion of a separate Valium, cetirizine and placebo arms, and expansion of the population studied.

However, the following are deficiencies are noted in the study design: failure to maintain blinding in terms of Valium; multiple endpoints and failure to chose a primary endpoint "a priori"; inclusion of measures in the efficacy analysis that were not found to be affected by antihistamines in the validation study; failure to study the time to recovery of Valium impairment, a potential PD interaction was not explored. Only one dose of the proposed 5-20mg dose range was used.

Subjective symptoms. When subjects were taking Valium they felt less well, less self assured and more fatigued, furthermore they felt they were receiving Valium and 7/28 fall asleep. The addition of P071 does not start to make a difference unless the P071 serum concentration is taken into consideration, and this is only true for the feeling of fatigue.

Objective psychometric assessments:

Bourdon Wiersma. In the validation study only inaccuracy was affected by the use of Benadryl, in this study this and most other parameters studied are significantly affected by main order effects or learning effects, making this test inadequate to measure attention deficits. However, even with these deficiencies, subjects make more errors and become less attentive as the concentration of P071 becomes more pronounced in their blood.

Feldmarkierungstest. When this test to measure concentration in the validation study only the work rate was affected. In this study this measurement was affected by order main effects - learning effects and no difference was seen between treatments. When inaccuracy was measured, the subjects receiving P071 regardless of whether they were receiving Valium or not the inaccuracy decreased. The investigators did not have an explanation for this effect.

Wiener Reaktionsgerat. In the validation study, Benadryl clearly affected the reaction to the visual stimuli. In the interaction study, the main effects are main order or learning effects affect the subjects response. In terms of P071, subjects reacted less quickly to the light stimulus when the P071 concentration in their blood was more pronounced, $p=0.04$. The errors of omission were the ones found to be mostly affected in the response to this test. A statistically significant interaction between P071 and Valium was found, with subjects making more errors of omission when they were under both treatments.

The investigators argue that only 1/16 of the objective assessments was affected by the Valium-cetirizine interaction and that its clinical meaning is in question. However, it is important to recall that only 5/16 of these assessments were statistically affected by increasing doses of Benadryl and therefore these were the only ones validated, and this particular one was one of those five.

In another one of these five assessments, accuracy in the Bourdon Wiersma test, P071 serum values correlated with inaccurate responses. In remaining 3/5, main order effects - learning effects, had more effect on the results than the treatments given. Therefore, these reflect deficiencies in the study design.

The fact that no other positive interaction is found in the objective assessments done, does not mean that there are none. The time to recovery of Valium impairment, for example, a potential meaningful PD interaction was not explored and the full

range of proposed dosing for cetirizine was not studied.

In conclusion, the above study has serious limitations to be considered as the study to define potential clinical and objective interactions between cetirizine and Valium and provide adequate labeling recommendations. The interaction of cetirizine and CNS depressant drugs using single doses in the full range of proposed dosing and steady state conditions needs to be adequately assessed.

Cetirizine-CNS- Population Higher Risk

Even though in the population database of patients >12 years in controlled studies, Table 1 (Appendix 2), there is no difference in the frequency of central and peripheral nervous system disorders, between patients that receive cetirizine (all patients, all doses included) and placebo, for this same population the frequency of reported psychiatric disorders is almost twice for patient receiving cetirizine (17.6%) versus those receiving placebo (9.2%).

We had not made this observation before (unless somnolence is included in this category), and perhaps the events listed under this term now were grouped differently before. It would be particularly relevant if terms such as depression were included in this category. This observation is seen with about the same frequency in males (16.5% vs 8.9%, Table 2) and in females (18.6% vs 9.4%, Table 3-Appendix 2). These results would also be more meaningful if they had been reported in terms of the dose of cetirizine used in addition to the reported format.

The Sponsor should be able to explain this observation in greater detail, including relation to the dose of cetirizine used. A list of terms included under this observation needs to be submitted by the Sponsor, with the corresponding frequencies per term specified.

Cetirizine-antiepileptic drugs

The Sponsor does not have an adequate study or database to address the interaction with cetirizine with antiepileptic drugs. The reports of: interaction with antiepileptic therapy N00875, N00127, seizure N00276 and N00127, included in the serious foreign reports included in Table Q8.B of the 3/12/93 submission prompted this question to the Sponsor. This potential interaction should be reflected in the labeling, Phase IV studies should address this issue.

2. Has the potential for cetirizine to induce allergic-immunologic reactions adequately studied? Is the incidence of these different from hydroxyzine? Please make a listing of patients with possible allergic/immunologic reactions to cetirizine that had a prior hx of reactions to other drugs.

Response:

Specific studies to evaluate cetirizine as an inducer of allergic immunologic reactions were not performed.

In a search done for patients in U.S. studies, >12 yrs, with a history of drug allergy and with pertinent WHO coded adverse events: pruritus, any rash, urticaria, allergic reaction and angioedema, twenty patients were selected. Of these, 15 that received placebo, and 5 that received cetirizine had a reaction. Causality was not established in any of the cases. The five cetirizine treated patients with hx of reactions to drugs that had an allergic reaction were:

ATP-1, 88N0069 #11, allergic reaction severe
 SAR-2, 85N0051 #18, pruritus, mild
 URT-1, 85N0041 #20, rash, moderate
 SAR-1, 84N0063 #15, rash erythematous, moderate
 PRU-2, 86N0202 #37, urticaria, mild

The Sponsor concludes that the US database does not indicate that cetirizine is frequently associated with allergic immunologic reactions compared to placebo.

In the database collected electronically on hydroxyzine since 1987, for allergic-immunologic reaction, there were 27 cases of spontaneous adverse events. These included two allergic reactions and one case of anaphylaxis. These reports originated from more than 200 million patient treatment days over the last five years.

Allergic-immunologic reactions may occur during treatment with cetirizine or hydroxyzine, however the incidence of such a reaction is very low for either drug.

Studies evaluating cross-sensitization reaction between cetirizine and either piperazines or ethylenediamines were not performed.

Cross sensitization between hydroxyzine and ethylenediamines have been reported and are expressed as skin reactions. A review of the cetirizine safety database for skin reactions was performed. There were 6 cetirizine serious foreign spontaneous reports:

N00120, N00226, N00277, N00785, and N00984 --(Executive Summary Table Q8A and 8B, 3/12/93)- These come from a database of >600 million standard daily doses of cetirizine. There is no information in these reports form a previous history of drug reactions to piperazines or ethylenediamines.

A search of Medline, Cancerlit, Health and Aidline databases, there were no literature reports of a cetirizine-ethylenediamine or cetirizine-piperazine cross-sensitization reaction.

While cross-sensitization cannot be excluded, it appears unlikely.

Reviewer's comments:**Allergic-immunologic reactions:**

The Sponsor interpreted the allergic - immunologic reactions term in our question as referring only to those allergic reactions that were caused by an immunologic mechanism. Even though we wanted to receive information on this group of reactions, we also wanted to have a record on immunologic reactions that would have been associated with the use of cetirizine. These would include, but not be limited to autoimmune reactions such as: vasculitis, neutropenias, etc.

Allergic, Type I:

Allergic Type I reactions to cetirizine: It is a possibility, it has been reported, however the reported frequency is very low. In the package insert patients have been alerted to avoid using cetirizine if they have a known hypersensitivity to it or any of its ingredients, or to its parent compound, hydroxyzine. This has been included in the proposed labeling.

Cetirizine/hydroxyzine/ethylenediamine**Cetirizine/hydroxyzine**

Of a search done from an electronically collected database by Pfizer since 1987 on spontaneous reports to hydroxyzine, there were 27 reports. The terms searched were allergy, pruritus, any rash, urticaria, angioedema and vasculitis. Of these reports: two were considered by the sponsor to be allergic reactions and an additional one was an anaphylactic reaction. Asthma was not one of the search terms.

In this search according to Table 6 (Appendix 3), there were 6 cases of reported urticaria, 2 of pruritus, 2 of pruritus and rash and 5 of rash. Even though, the population that formed the basis for this search was more than 200 million patients treatment days over the last five years, the results of this search indicate that there can be allergic and immunologic reactions to hydroxyzine and that cetirizine would have the potential to cross react and produce similar reactions in sensitized patients. As noted above, this has been acknowledged in the Contraindication section of the annotated package insert.

Hydroxyzine/ethylenediamine:

Reports of hydroxyzine cross reactivity with ethylenediamine are acknowledged. The Sponsor considers reactions to ethylenediamines to be expressed only as skin reactions. There have been literature reports of asthma to inhalation of

ethylenediamine dust, so the possibility of causing asthma, although could be very rare, in sensitized patients exists; asthma was not included in the Sponsor's search.

According to the Sponsor, since there were only 6 serious foreign spontaneous reports for skin reactions in the cetirizine data base, and since the literature search databases failed to show drug interaction between cetirizine/ethylenediamine, the Sponsor concludes that the possibility of cross-sensitization between cetirizine and ethylenediamine appears unlikely.

Since it has already been reported that patients that are sensitive to ethylenediamine have had cross-reactions with hydroxyzine, then it should follow that patients sensitized to ethylenediamine should be alerted of the possibility of potential allergic reactions to cetirizine, even though at the present time there are no data either by spontaneous foreign reports or by literature search that this interaction has been reported.

Other Immunologic Reactions:

The Sponsor does not mention searching for other terms that could be considered as more specific for other immunologic reactions, such as:

hematologic: hemolytic anemia, thrombocytopenia,
neutropenia, agranulocytosis
skin: vasculitis

In Table 6 with the 27 reports of allergic reactions to hydroxyzine discussed above, included is a case of vasculitis to hydroxyzine, along with 3 cases of rash and fever, and 2 cases of epidermal necrolysis.

The mechanism to explain the above and the following reports found in Table Q&.B of the 3/12/93 submission was not addressed:

hematologic anemia: N00982
thrombocytopenia: N00912, N00785
neutropenia: N00125
agranulocytosis: N00114

It has also been reported that ethylenediamine can cross reacts with piperazine.(1,2) The Sponsor does not address the potential cross reactivity between hydroxyzine and piperazines. The importance of considering immunologic reactions to piperazine and to piperazine class drugs is that immunologic reactions other than those limited to the skin have been reported.

Allergic-immunologic and immunologic cross-reactions to piperazine and potentially to piperazine-substituted phenothiazine drugs were not adequately addressed by the Sponsor

in this discussion. Reported reactions to piperazine include: respiratory symptoms ⁽³⁾ and thrombocytopenia ⁽⁴⁾.

Both hydroxyzine and cetirizine have a piperazine structure. Although we are not aware of studies that show direct crossreactivity to hydroxyzine or cetirizine in patients sensitive to piperazine(s), it would be prudent to alert patients that have developed hypersensitivity to piperazine or to piperazine substituted products they could have the potential for showing crossreactivity to hydroxyzine and cetirizine, and that they should be adequately evaluated by a physician before initiation of treatment with cetirizine.

Further studies in this area are warranted.

(1) Zuidema J. Pharm-Weekbl-Sci. Ethylenediamine, profile of a sensitizing excipient. 7(4):134-40, 1985

(2) Eedy D.J., Contact Dermatitis. Angioneurotic oedema following piperazine ingestion in an ethylenediamine-sensitive subject. 28 (1):48-9, 1993.

(3) Hagmar, L. et al. Piperazine-induced occupational asthma. J Occup Med. 24 (3):193-7, 1982.

(4) Cork M.J, et al. Pruritus ani, piperazine and thrombocytopenia. British Medical Journal. 301(6765):1398, 1990.

3. Has the weight-dose relationship and incidence of adverse events been adequately studied in the adult population?

After reviewing the CFRs of patients that discontinued the studies it appears that there could be a relationship between weight and adverse events. Since drowsiness or somnolence are the most frequent these seem to stand out. There seems to be more patients under 125 lb or above 180 if male or above 150 if female that discontinue the studies due to adverse events. This would be particularly noticeable in the general 12-24 yr. old population with a leaner body mass.

a. In the discontinued patient data set (NDA and post NDA) could you look at the % of patients on cetirizine vs placebo that discontinued studies due to adverse events and in particular due to somnolence, that were under 125lb or >150lb if female and >180lb if male and compare it to see if these are real effects.

Results:

The rate of discontinued patients due to adverse events:

Due to all adverse events:

	cetirizine	placebo
females <125 lb	5% (14/280)	2.6% (4/157)
>150 lb	3.2% (14/438)	2.2% (7/313)
males <125 lb	4.8% (3/63)	2.9% (1/35)
>180 lb	2.2% (11/491)	2.1% (6/284)

Due to somnolence:

females <125 lb	1.1% (3/280)	1.3% (2/157)
>150 lb	1.8% (8/438)	0
males <125 lb	3.2% (2/63)	2.9% (1/35)
>180 lb	0.6% (3/491)	0.4% (1/284)

The Sponsor concludes that the above data do not indicate that lower weight individuals have a higher rate of discontinuation due to adverse effects or somnolence when compared to heavier patients.

Reviewer's comments:

We were interested in getting more information regarding weight -age- gender relationships by looking at the data set of patients that discontinued studies due to adverse effects. I agree with the Sponsor in that there does not seem to be a higher rate of discontinuation due to adverse effects and in particular somnolence when the lower weight individuals are compared to the heavier patients.

However, for cetirizine treated males and females with lower weight (<125 lb) the rate of discontinuation due to adverse events is higher than the 2.9% (72/2513) rate observed when all patients included in placebo -controlled trials are considered. This is particularly seen in the female group treated with cetirizine. This group had a discontinuation rate of 5% (14/280). In the same weight category, placebo treated female patients had a discontinuation rate of 2.6% (4/157). The Sponsor did not compare these two groups statistically.

Only in the group of cetirizine treated females weighing >150 is the discontinuation rate due to somnolence appreciably higher than for those patients in the same weight category treated with placebo; 1.8% (8/438) vs 0% (0/313) and this discontinuation rate is higher than for those patients with a lower weight category 1.1% (3/280) vs. 1.3% (2/157) for cetirizine and placebo treated patients respectively. This observation, presuming that the cetirizine dose was constant would contradict the effects seen in the general population in which clinically there is a dose response in terms of sedation with increasing doses of cetirizine.

Other factors that need to be taken into consideration include: dose, length or trial duration and duration of treatment. A patient may be willing to tolerate and adverse effect of moderate to severe severity if the trial is of short

duration but decide not to if it is going to last for 4 weeks or more.

More definite answers will be found to these questions when additional PK-PD relationship in terms of adverse effects that take into considering weight-gender interactions in wider populations are done. The above preliminary observations should be compared to the results from analysis of PK data obtained in Phase IV trials.

b. Using the data set of all patients in controlled studies, could you look at the frequency of adverse events and in particular somnolence in patients using cetirizine in terms of age 12-24 and compare it to that in ages 12-65. Is this different to what is seen in placebo treated patients?

Results:

Adverse events:

Age(yrs)	cetirizine	placebo
12-24	38.3% (210/549)	34.9% (98/281)
25-65*	44% (810/1841)	38.0% (428/1127)
12-65*	42.7% (1020/2390)	37.4% (526/1408)

Somnolence:

Age(yrs)	cetirizine	placebo
12-24*	14.6% N=549	6.4% N=281
25-65*	15.5% N=1841	6.9% N=1127
12-65*	15.3% N=2390	6.8% N=1408

* $p < 0.001$

The incidence of adverse events for cetirizine treated patients age 12-24 yrs was similar to placebo treated patients. In the other two age groups the patients reported significantly more adverse events than the respective placebo groups. The frequencies for adverse events between the three age groups was comparable.

The incidence of somnolence for the three age groups was significantly more than placebo (twice as much). The frequency of somnolence for the three age groups was comparable.

c. Using the data set of all patients in controlled studies could you look at the frequency of adverse events of patients using cetirizine by body weight and gender <125, 125-150, >150-180, >180lbs. and compare it to the frequency found in the general population in this data set? Is this different to what is seen in placebo treated patients?

Overall incidence of adverse events for patients >12 yrs of age in placebo controlled studies was 42.8% for cetirizine treated patients and 36.6% for placebo treated patients.

Adverse events:

	cetirizine	placebo
females	47.1% (561/1192)	41.5% (321/773)
males	39% (515/1321)	31.3% (228/728)

The placebo adjusted rate 47.1-41.5= 7.7% for males and 5.6% for females is not different p=0.404

Incidence of Adverse events by weight and Sex; Sponsor's Table page 7. The median dose of cetirizine was 10 mg.

Sex	Treatment	<125	>125-150	>150-180	>180
male	cet.	34.9% N=63	33.6% N=220	39.7% N=544	41.3% N=491
	placebo	28.6% N=35	24.0% N=125	31.3% N=284	34.9% N=284
female	cet.	43.9% N=280	50.4% N=470	50.0% N=256	40.1% N=182
	placebo	36.9% N=157	40.6% N=303	46.9% N=179	1.8% N=134

Female patients had a higher incidence of adverse events than male patients treated with cetirizine or placebo in each weight group, with the exception of patients weighing more than 180 lbs. The incidence of adverse events by weight and sex were comparable to the overall frequency in the general population of patients in placebo controlled studies.

Reviewer's comments:

In the above summary table if the placebo adjusted rate is calculated for the different categories, it is apparent that the difference found in adverse events between cetirizine and placebo decreases as the weight increases >150 lb, showing a negative dose relationship with increasing weight. This difference is more apparent in the female patients than in the male patients, raising up the question again as to whether female patients are more sensitive to the drug effects because of gender.

Sex	Treatment	<125	>125-150	>150-180	>180
male	cet.	34.9% N=63	33.6% N=220	39.7% N=544	41.3% N=491
	placebo	28.6% N=35	24.0% N=125	31.3% N=284	34.9% N=284
		6.3%	9.6%	8.4%	6.4%
female	cet.	43.9% N=280	50.4% N=470	50.0% N=256	40.1% N=182
	placebo	36.9% N=157	40.6% N=303	46.9% N=179	41.8% N=134

7.0% 9.8% 3.1% -0.7%

More definite answers will be found to these questions when additional PK-PD relationship in terms of adverse effects that take into consideration age-weight-gender interactions in wider populations are done. The above preliminary observations should serve to prompt and direct further PK data collection and analyses of these interactions from data obtained in Phase IV trials.

4. Was Table 9A in the executive summary of April 1993 created using the data from Table Q.7 in March 12, 1993 submission? If not, please submit a new table using this information?

The data set of Table 9A -discontinued patients includes all patients >12 yrs of age from all U.S. placebo controlled trials.

In Table Q.7, three pediatric trials and 2 active control trials (SAR-8 and SAR-Kaiser) were included.

5. The following questions relate to the review of the individual case report forms from deaths in foreign studies:

a. Please submit the appendix that it is referred to in page 9 3723 (vol 82 of 116) of the investigator report on the evolution of liver function tests from patient PCNSA111 #3 from Dr. Buyse, we were unable to locate it.

This patient was a 71 yr female with history of spinocellular epithelioma, impaired liver function without evidence of metastasis at study entry. A dose of 10 mg of cetirizine was given.

Visit #	T.bili. ULN=1mg/dl	GGT 18IU/l	Alk.phos. 200IU/l	SGOT 19IU/l
Baseline	2.8	284	420	-
5 (3 mo)	3.8	263	505	-
8 (6 mo)	5.0	317	542	41

This patient was removed from the study for evaluation of metastatic spinocellular epithelioma with ascites. The clinical summary translation was provided.

Reviewer's comments:

After a review of the case summary it is important to note that this patient had pruritus for 4 yrs prior to study entry, that the spinocellular epithelioma was from the nose. At inclusion the concomitant medication was indomethacin 100 mg/day. It was not until the 5 clinic visit or 3 mo after the start of therapy that the patient pruritus began to improve with change from severe to moderate. The patient and investigator global opinion

regarding treatment during all this time was that it was bad. It was not until 4 mo after treatment, visit 6th, that the pruritus and scratching lesions subsided, having then a light score and a good global evaluation; the effectiveness of treatment in terms of pruritus continued though visit 8th or 6 mo after treatment initiation; thereafter pruritus returned and the treatment for pruritus was not noted to be efficacious. The patient continued on the study 2 months after visit 8th, when she was admitted for check up of liver metastasis of nasal spinocellular carcinoma and ascites.

It would be hard to ascertain whether in this patient cetirizine had a role in the worsening of LFTs or if it all was due to the her epithelioma. However with a history of 4 yrs of pruritus without evidence of metastasis it would be possible to speculate if the treatment for pruritus (cetirizine) had anything to do with the acceleration of the metastatic process.

b. Please submit copies of all source documents from patient PCN84A111 #27 from Dr. Gomme (page 9 3556, vol 82 of 116), that would refer to concomitant medication, cardiovascular evaluations or EKGs, at the time that this patient was receiving cetirizine.

A translation into English of the CRF is provided. There is no data in the CRF to clarify events other than the patient had an EKG at entry read as regular rhythm EKG with lateral ischemia and that she died before the third visit, 20 days after study entry of cardiac arrest. No other concomitant medications are noted on the chart. Labs included a normal K at entry, Bp 140/80 with pulse 80/min, 15 days post initiation pulse 80/min and BP=125/7.

Reviewer's comments:

The presence of ASHD is confirmed in this patient. The BP recording of day 15 was probably an error. We do not know if the patient was hospitalized during the cardiac arrest. No further information is provided. With the lack of records surrounding the patient's death, the potential role that cetirizine may have had is not at all clear.

c. What were the glucose levels of patient PCN84A 111 #17 from Dr. Gomme (p. 3546, vol 82 of 116) before and during ceterizine treatment.

This patient was diabetic and had CHF, at entry (5/9/84) her regular treatment included insulin, digoxin and hydrochlorothiazide+triamptere. At entry her glucose level was 182 mg/100 ml and on 9/20/84 or 4 mo after treatment initiation it was 90 mg/100 ml.

On 8/27/84 the investigator noticed cyanosis of the 3rd and 4th toes and

the patient was treated with flunazarine, smoking was also noted. The patient died 12/11/84, twelve days after right leg amputation for diabetic gangrene.

Reviewer's comment:

The patients glucose level reported during treatment is not elevated. A summary clinical report was given, a translation of the CFR was not submitted. However even though this blood glucose level during treatment may have been an unusual low one, it would appear that in this case the patient's underlying medical conditions (diabetes and CHF) would have been the predominant factors contributing to the patients gangrene and death.

d. Were cetirizine blood levels obtained on Dr. Gomme's patients PCN34A111 # 4 and PNC 34A111 #7 (p. 9 3540 and 9 3542, vol 82 of 116)?

No drug monitoring was done in this study.

e. Could the statistical significant decreases in systolic blood pressure during the first two months (mean=13 torr) found in patients that participated in -32 contribute to poor perfusion in this group of elderly patients, particularly CNS?

The mean change in blood pressure decrease is within what is seen in the ambulatory population. Its relationship to poor perfusion is possible but only an speculation.

Reviewer's comments:

Although it is only a speculation, it should be clarified with appropriate monitoring in elderly patients, in a placebo controlled study during Phase IV.

6. The following questions refer to the discontinued patients from post NDA studies due to adverse events:

Please refer to volumes 6-9 of the January 30, 1992 submission.

a. For patient 89N0115 #222 (URT-3) the investigator felt that this episode of faintness, heart racing and vomiting could have been a vasovagal response, more details are needed to rule out syncope. Please obtain all source documents relating to this episode.

Patient had hx of orthostatic symptoms in 1980. On 7/18/90, she "blacked out" for a split second while in the shower. She did not fall or injure herself. She got out of the shower and felt nausea and vomited. By that afternoon the patient was "99% back to normal". Evaluation of the syncope was discussed with the patient but she declined.

Reviewer's comment:

This 33 y/o female patient with chronic urticaria participated in URT-3 study and received 10 mg cetirizine for 2 days. The patient did pass out once prior in 80's after getting out of bed too fast.

7/18/90 , 4PM "At approx. 6:40 Am, while taking a shower, patient blacked out (very conscious of blacking out). Seat down to avoid falling. Happened in a slip second. Pt. got out of shower to lay on floor. Immediately felt sick to her stomach. Got to commode and vomited. Pt. laid back on floor, felt "racing heart" rate. By 3:30 pm, was 99% back to normal. Felt sluggish all day."

On enrollment BP was 110/76. On 7/23/90 she was evaluated by the investigator. At this time BP 120/80, pulse was 100/min, weight 159. She had taken two doses of the study medication one on 7/16 and 7/17, the last dose at 10:40 PM. No concomitant medication recorded. On the termination visit clinical note it is recorded that the patient after the initial episode felt better for the rest of the day except for a few spells of her heart "racing". She denied any other symptoms- no hx or sx of cold, flu, or GI upset. No hx of dizziness or fainting spells in the recent past. She attributed her fainting episode to possibly a reaction to the study drug, since she says she "often has bad reactions to medications". Further workup for syncopal episode was discussed with the patient but she elected to defer it.

The investigator thought that the cause for the fainting was most likely a vasovagal episode. However this explanation would not explain the patient symptoms of "few spells of heart "racing" during the day. No EKG was obtained, so there is no objective evidence that this could have been related to effects of QT prolongation, however the hx of the episode could be compatible with it.

Clinical studies to evaluate QT prolongation in normal volunteers at doses up to 60 mg of cetirizine and doses of 20 mg with erythromycin or ketoconazole have been completed and complete study reports were recently submitted for review. Preliminary review indicates that by itself at doses up to 60 mg or with erythromycin, cetirizine does not prolong the QT_c interval. In the cetirizine - ketoconazole interaction study, both drugs prolong the QT_c interval by approx. 8 msec. The

significance of these findings awaits further discussions.

b. Was induction of sleep apnea for patient 9080028 #31 (SAR-8), obese, with intermittent episodes of waking up at night with shortness of breath, considered? If not, could the investigator contact patient and give a follow up in this regard?

The patient did not sleep apnea symptoms.

Reviewer's comments:

Agree with investigator's evaluation.

c. For patient 88-N-0064 #24 (ATP-1) with CHF and ASHD, a change in diuretics 15 prior to starting cetirizine was considered to be responsible for worsening of the CHF. However no changes in physical exam were seen at study initiation by the investigator. Please obtain copies of emergency room records for this patient.

In the submitted ER visit of this patient on 9/7/89 to The Children's Hospital of Alabama no worsening of CHF was recorded. The patient complained of stomach pain all day with vomiting earlier in the morning but better at the time of the visit. The patient was on digoxin and diazide. Blood sample for digoxin was obtained but results were not reported. The patient was D/C, and asked to take one additional thiazide during the night and to omit the digoxin until the following day.

Reviewer's comments:

This record does not appear to indicate the presence of worsening CHF. Therefore the reason for discontinuation is unclear but does not appear to be worsening of CHF.

d. For patient 88-N-0065 #015 (ATP-1) please clarify if the patient's disorientation was secondary to drowsiness or to a general confused state after taking the second dose of cetirizine 20 mg?

It was the investigator's impression that the "confused state" was due to drowsiness.

Reviewer's comments:

Agree with the Sponsor's evaluation.

e. For patient 90-N-0024 #68 (PEDS-3) with increased urination, we were unable to locate the patient's daily diary. Please submit a copy.

Reviewer's comments:

Patient received cetirizine syrup in the evenings. There is no record of when increased urination occurred -all day, night? This adverse event did not resolve until one week after study discontinuation. This is a rare event but is one that has been observed previously with antihistamines. However, the duration of the effect after discontinuation of the study drug, makes the drug by itself a less plausible cause of it.

7. The following questions refer to the discontinued patients due to abnormal lab:

Original NDA submission. Please refer to Volumes 109-115 of original NDA for specific CRFs.

a. For the CRF of patient 85-N-0042 #13 please resubmit pages 12 1744, 1750 1753 and 1754. CRF photocopy was too light to read.

This 21 y/o male patient with chronic urticaria, had 136,000 platelets on screening (6/30/86). On 7/6/86 they were reported as adequate. At the end of week 2 (7/23/86) he reported a feeling of malaise for 1 day from 7/21 to 7/22. On 7/23 the platelet count was 114,000. At the end of week 4 (7/29/86) the platelet count continued to stay low, 113,000, and the patient was dropped from the study. No concomitant medications.

The results of repeat platelet counts follow:

7/31/86	117,000.
8/6/86	125,000
2/15/88	151,000

Reviewer's comments:

It is likely that the decrease in platelet count in this patient could be related to the study drug, cetirizine. Thrombocytopenia has been reported in two other patients from the foreign spontaneous reports, one in association with oxazepam and lasix N00785 and another in patient N00912 with ketotifen (16,000). Thrombocytopenia has not been included in the labeling, and it should.

Post original NDA submission. Please refer to volumes 6-9 of the January 30, 1992 submission.

b. For patient 89N0107 #187, with increase in direct and indirect bilirubin, follow up records are needed.

The Sponsor was unable to contact patient by telephone or registered mail.

8. The following questions refer to the discontinued patients from original NDA studies due to adverse events:

Please refer to Volumes 109-115 of original NDA for specific CRFs and to Table Q.7 from the March 12, 1993 submission.

a. For patient 85-N-0051 #6 (SAR-2) please clarify why dizziness was not included in the table although it is mentioned in the diary card and in the clinical summary. Patient was also on theodur.

b. For patient 85-N0066 #8 (SAR-3) only nausea is listed in the Table Q.7. However the patient experienced a "sinus headache " after the first dose. Headache was not included as an adverse event. Please clarify.

c. For patient 84-N0053 #14 (PAR-1) on synthroid for hypothyroidism, moodiness and decrease energy that appear in the clinical summary, were not included in Table Q.7. Please clarify.

d. For patients 84-N-0114 # 30 (PAR-1) increase of asthma symptoms was not included in Table Q.7. Please clarify.

Sponsor: "No explanation can be offered as to why these effects were not included in Table Q.7. It is important to note, however, that the following guideline may have impacted on the decision at the time of CRF review: Signs or symptoms that were due to a concurrent illness were not included in adverse event tables. This guideline may explain the omissions for two of the four patients (84N0053 #14 and 84N0114 #30)".

Reviewer's comments:

If in the CRFs of the discontinued patients due to adverse events, that were reviewed by a clinical research associate, by the department of quality assurance personnel and a physician, there were 4 omissions, that I could easily detect, out of 72 patients (6%), then one wonders was is the ommision rate for the rest of the safety data base, whose CRF are not usually submitted as part of the NDA. If, in addition, one considers that the patients did not fill out in their diaries information about the adverse events, we have to conclude that the safety data base that we have available for review, underestimates the incidence of adverse events.

Reviewer's recommendations regarding labeling of the package insert based on the review of the material in this submission:

Cetirizine-CNS interaction:

1. Cetirizine is a sedating antihistamine. Unless appropriated psychomotor testing is validated, the subjective adverse reporting in clinical trials should be the parameter used to assess sedation after multiple dose antihistamine administration.

Cetirizine -CNS depressants

2. **Cetirizine/ethanol interaction.** The limitations noted in the two clinical trials that study the ethanol-cetirizine interaction, question the validity of their conclusions and therefore these results should not be considered to be the final conclusions regarding this interaction. The Sponsor should commit themselves to adequately study this interaction during the post marketing. From the results of these studies it cannot be concluded that cetirizine does not increase alcohol -induced impairment of motor and mental performance as indicated in the proposed labeling.

3. **Cetirizine/diazepam (Valium).** The submitted study, has serious limitations to be considered as the study to define potential clinical and objective interactions between cetirizine and Valium and provide adequate labeling recommendations. Therefore, it cannot be concluded that cetirizine does not increase Valium-induced impairment of motor and mental performance as indicated in the proposed labeling.

The interaction of cetirizine and CNS depressant drugs using single doses in the full range of proposed dosing and steady state conditions needs to be adequately assessed.

Cetirizine-CNS- Population Higher Risk

4. Even though in the population database of patients >12 years in controlled studies, Table 1, there is no difference in the frequency of central and peripheral nervous system disorders, between patients that receive cetirizine (all patients, all doses included) and placebo, for this same population the frequency of reported psychiatric disorders is almost twice for patient receiving cetirizine (17.6%) versus those receiving placebo (9.2%).

We had not made this observation before (unless somnolence is included in this category), and perhaps the events listed under this term now, were grouped differently before. It would be particularly relevant if terms such as depression were

included in this category. This observation is seen with about the same frequency in males (16.5% vs 8.9%, Table 2) and in females (18.6% vs 9.4%, Table 3). These results would also be more meaningful if they had been reported in terms of the dose of cetirizine used in addition to the reported format.

The Sponsor should be able to explain this observation in greater detail, including relation to the dose of cetirizine used. A list of terms included under this observation needs to be submitted by the Sponsor, with the corresponding frequencies per term specified.

Cetirizine-antiepileptic drugs

5. The Sponsor does not have an adequate study or database to address the interaction with cetirizine with antiepileptic drugs. The reports of: interaction with antiepileptic therapy N00875, N00127, seizure N00276 and N00127, included in the serious foreign reports included in Table Q8.B of the 3/12/93 submission prompted this question to the Sponsor. This potential interaction should be reflected in the labeling, Phase IV studies should address this issue.

Allergic -Immunologic Reactions

6. The Sponsor interpreted the allergic - immunologic reactions term in our question as referring only to those allergic reactions that were caused by an immunologic mechanism. Even though we wanted to receive information on this group of reactions, we also wanted to have a record on immunologic reactions that would have been associated with the use of cetirizine. These would include, but not be limited to autoimmune reactions such as: vasculitis, neutropenias, etc.

Allergic, Type I:

7. Allergic Type I reactions to cetirizine: It is a possibility, it has been reported, however the reported frequency is very low. In the package insert patients have been alerted to avoid using cetirizine if they have a known hypersensitivity to it or any of its ingredients, or to its parent compound, hydroxyzine.

Cetirizine/hydroxyzine/ethylenediamine

Cetirizine/hydroxyzine

8. There can be allergic and immunologic reactions to hydroxyzine and cetirizine has have the potential to cross react and produce similar reactions in sensitized patients. As noted above, this has been acknowledged in the Contraindication section of the annotated package insert.

Hydroxyzine/ethylenediamine:

9. Reports of hydroxyzine cross reactivity with ethylenediamine are acknowledged. The Sponsor considers reactions to ethylenediamines to be expressed only as skin reactions. There have been literature reports of asthma to inhalation of ethylenediamine dust, so the possibility of causing asthma, although could be very rare, in sensitized patients exists; asthma was not included in the Sponsor's search.

Since it has already been reported that patients that are sensitive to ethylenediamine have had cross-reactions with hydroxyzine, then it should follow that patients sensitized to ethylenediamine should be alerted of the possibility of potential allergic reactions to cetirizine, even though at the present time there are no data either by spontaneous foreign reports or by literature search that this interaction has been reported.

Both hydroxyzine and cetirizine have a piperazine structure. Although we are not aware of studies that show direct crossreactivity to hydroxyzine or cetirizine in patients sensitive to piperazine(s), it would be prudent to alert patients that have developed hypersensitivity to piperazine or to piperazine substituted products they could have the potential for showing crossreactivity to hydroxyzine and cetirizine, and that they should be adequately evaluated by a physician before initiation of treatment with cetirizine.

Other Immunologic Reactions:

10. This topic was not adequately discussed. A case report of vasculitis to hydroxyzine is among the cases presented from the included electronic data search. However, the possible mechanisms of action were not addressed. The following reports in cetirizine treated patients found in Table Q8.B of the 3/12/93 submission was not addressed:

hematologic anemia:	N00982
thrombocytopenia:	N00912, N00785
neutropenia:	N00125
agranulocytosis:	N00114

The fact that other immunologic reactions to cetirizine can occur needs to be addressed and possible mechanisms of action adequately explored.

Allergic-immunologic and immunologic cross-reactions to piperazine and potentially to piperazine-substituted phenothiazine drugs were not adequately addressed by the Sponsor in this discussion. Among the case reports to piperazine in the literature are: respiratory symptoms and thrombocytopenia. Further studies in this area are warranted.

Relations between gender/weight/adverse events:

11. Female patients had a higher incidence of adverse events than male patients treated with cetirizine or placebo in each weight group, with the exception of patients weighing more than 180 lbs. The incidence of adverse events by weight and sex were comparable to the overall frequency in the general population of patients in placebo controlled studies.

However, if the placebo adjusted rate is calculated for the different weight categories, it is apparent that the difference found in adverse events between cetirizine and placebo decreases as the weight increases >150 lb, showing a negative dose relationship with increasing weight. This difference is more apparent in the female patients than in the male patients, raising up the question again as to whether female patients are more sensitive to the drug effects because of gender.

More definite answers will be found to these questions when proper PK-PD relationship in terms of adverse effects that take into consideration age-weight-gender interactions in wider populations are done. The above preliminary observations should serve to prompt and direct further PK data collection and analyses of these interactions from data obtained in Phase IV trials.

Serious adverse events:

12. From the data set of discontinued patients it is likely that the decrease in platelet count in patient 85-N-0042 #13 could be related to the study drug, cetirizine. Thrombocytopenia has been reported in two other patients from the foreign spontaneous reports, one in association with oxazepam and lasix N00785 and another in patient N00912 with ketotifen (16,000). Thrombocytopenia has not been included as a potential rare adverse event in the labeling, and it should.

Incidence of adverse events:

13. If in the Tables that correspond to the adverse events from CRF of the discontinued patients due to adverse events, that were reviewed by a clinical research associate, by the department of quality assurance personnel and by a physician, there were 4 omissions, that I could easily detect, out of 72 patients (6%). This questions what is the omission rate for the rest of the safety data base, whose CRF are not usually submitted as part of the NDA. If, in addition, one considers that in the majority of placebo control trials, patients did not fill out in their daily diaries information about the adverse events, we have to conclude that the safety data base that we have available for review, underestimates the incidence of adverse events. Therefore, adverse reaction at a lower incidence than 2%, possibly 1%

should be incorporated in the labeling.

Adverse events in the elderly

14. It is very likely that the mean change in blood pressure decrease seen in the foreign clinical trial that studied pruritus (URB-32) is within what is seen in the ambulatory population. Its relationship to poor perfusion is possible, but at the present time only an speculation. However, since the present database in elderly patients is so small, although it is only a speculation, it should be clarified with appropriate blood pressure monitoring in elderly patients, in a placebo controlled study during Phase IV.

TABLE 3. MULTIPLE SLEEP LATENCY TESTS (MSLT) -- GROUP MEANS AND STANDARD DEVIATIONS.

	DRUG														
	C05			C10			C20			H25			PLA		
	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD
SLT MEAN (First 5)	13	6.6	3.4	13	8.3	3.5	10	7.8	4.7	12	4.5	2.9	11	8.4	5.6
SLT 0930	13	9.3	5.2	13	13.0	5.1	10	12.1	7.2	12	5.0	2.8	11	10.6	6.4
SLT 1130	13	6.0	3.6	13	7.5	4.4	10	6.1	2.6	12	3.7	2.5	11	8.0	6.3
SLT 1330	13	4.8	3.2	13	6.9	5.4	10	6.3	5.7	12	4.3	3.5	11	7.4	7.1
SLT 1530	13	5.5	5.0	13	6.7	4.0	10	5.2	4.6	12	3.8	3.0	11	6.9	7.8
SLT 1730	13	7.6	5.5	13	7.3	4.9	10	8.6	6.9	12	5.9	5.3	11	6.9	6.2
SLT 1830	13	13.2	6.7	13	14.8	8.8	10	13.0	6.8	12	10.2	7.2	11	12.8	7.8

SLT: sleep latency test

Appendix 1 - Table 3

TABLE 5 (CONTINUED). SELF-RATINGS OF SLEEPINESS TAKEN EVERY TWO HOURS -- GROUP MEANS BY TIME OF DAY

	DRUG														
	CET 05 mg			CET 10 mg			CET 20 mg			HYDROX 25			PLACEBO		
	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD
LSS 0930	13	26.3	17.8	13	35.8	19.5	10	42.2	20.4	12	32.5	16.8	11	34.3	17.1
LSS 1130	13	38.7	17.0	13	44.0	20.4	10	53.1	22.2	12	60.1	15.4	11	48.9	19.9
LSS 1330	13	33.5	21.0	13	37.0	24.8	10	47.8	29.1	12	49.3	22.9	11	45.3	17.9
LSS 1530	13	33.9	18.1	13	41.0	21.2	10	54.5	27.8	12	42.9	25.4	11	38.0	18.7
LSS 1730	13	32.7	24.8	13	34.2	19.7	10	56.2	24.8	12	36.3	21.1	11	40.3	19.0
SSS 0930	13	1.8	1.0	13	2.3	0.8	10	2.4	1.1	12	2.2	0.7	11	2.3	1.2
SSS 1130	13	2.8	1.1	13	3.0	1.2	10	3.0	1.2	12	3.8	1.3	11	3.1	1.3
SSS 1330	13	2.3	1.0	13	2.8	1.1	10	2.9	1.3	12	2.9	1.4	11	2.7	1.0
SSS 1530	13	2.4	1.0	13	2.5	0.7	10	3.3	2.0	12	2.8	1.7	11	2.4	0.9
SSS 1730	13	2.6	1.4	13	2.2	0.6	10	3.1	1.4	12	2.3	1.2	11	2.7	1.2

LSS: Linear sleepiness scale (0..99).
 SSS: Stanford sleepiness scale: 1=most alert, 7=most sleepy.

Appendix 1 - Table 5

TABLE XIV

Individual results expressed in mm, on a 0 to 100 scale

0 = absence of modification

- = deterioration

	Placebo		Terfenadine		Cetirizine	
	2 h	6 h	2 h	6 h	2 h	6 h
Mean±SD	1.5 ±2.1	-2.5 ±3.8	-0.8 ±1.6	-7.8 ±9.1	-0.1 ±0.3	-9.1 ±10.0

PLACEO-CONTROLLED ADULT (AGE > 12 YRS) STUDIES - ADV EXP

TABLE 1: INCIDENCE OF ADVERSE EXPERIENCE BY BODY SYSTEM

SEX GROUP: ALL PATIENTS
FORMULATION: TABLET/CAPSULE

ADVERSE EXPERIENCE	CETIRIZINE					PLACEBO				
	NO. PTS. (%)	NIL	MOD	SEV	NOT SPEC	NO. PTS. (%)	NIL	MOD	SEV	NOT SPEC
TOTAL NO. OF PATIENTS	2513					1501				
NO. OF PTS. WITH ANY AE	1076 (42.8%)					549 (36.6%)				
CENTR & PERIPH NERV SYST DISORDERS	457 (18.2%)	182	203	70	2	289 (19.3%)	123	109	56	1
* PSYCHIATRIC DISORDERS	442 (17.6%)	236	142	64	0	138 (9.2%)	66	49	23	0
BODY AS A WHOLE - GENERAL DISORDERS	202 (8.0%)	100	80	22	0	81 (5.4%)	21	41	17	2
GASTRO-INTESTINAL DISORDERS	144 (5.7%)	74	52	17	1	102 (6.8%)	44	41	17	0
AUTONOMIC NERVOUS SYSTEM DISORDERS	141 (5.6%)	92	44	5	0	48 (3.2%)	23	13	4	0
RESPIRATORY SYSTEM DISORDERS	125 (5.0%)	57	56	12	0	64 (4.3%)	26	26	10	2
SKIN AND APPENDAGES DISORDERS	45 (1.8%)	20	17	8	0	44 (2.9%)	18	12	14	0
VISION DISORDERS	28 (1.1%)	18	7	3	0	11 (0.7%)	6	3	2	0
HEARING AND VESTIBULAR DISORDERS	20 (0.8%)	11	7	2	0	12 (0.8%)	8	4	0	0
CARDIOVASCULAR DISORDERS, GENERAL	17 (0.7%)	11	5	1	0	8 (0.5%)	6	1	1	0
MUSCULO-SKELETAL SYSTEM DISORDERS	15 (0.6%)	3	9	3	0	5 (0.3%)	1	3	1	0

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PLACEBO-CONTROLLED ADULT (AGE >= 12 YRS) STUDIES - ADV EXP
 =====

TABLE 2: INCIDENCE OF ADVERSE EXPERIENCE BY BODY SYSTEM

SEX GROUP: MALE
 FORMULATION: TABLET/CAPSULE

ADVERSE EXPERIENCE	CETIRIZINE					PLACEBO				
	NO. PTS. (%)	MIL	MOD	SEV	NOT SPEC	NO. PTS. (%)	MIL	MOD	SEV	NOT SPEC
TOTAL NO. OF PATIENTS	1321					1728				
NO. OF PTS. WITH ANY AE	515 (39.0%)					228 (13.2%)				
*PSYCHIATRIC DISORDERS	220 (16.7%)	129	65	26	0	65 (8.9%)	30	26	9	0
CENTR & PERIPH NERV SYST DISORDERS	207 (15.7%)	86	95	24	2	113 (15.5%)	54	44	15	0
BODY AS A WHOLE - GENERAL DISORDERS	87 (6.6%)	43	36	8	0	36 (4.9%)	12	18	6	0
AUTONOMIC NERVOUS SYSTEM DISORDERS	64 (4.8%)	40	15	1	0	11 (1.5%)	5	5	1	0
GASTRO-INTESTINAL DISORDERS	62 (4.7%)	36	18	7	1	40 (5.5%)	15	19	6	0
RESPIRATORY SYSTEM DISORDERS	53 (4.0%)	29	21	3	0	26 (3.6%)	6	14	5	1
SKIN AND APPENDAGES DISORDERS	21 (1.6%)	8	8	5	0	13 (1.8%)	7	4	2	0
VISION DISORDERS	15 (1.1%)	11	4	0	0	5 (0.7%)	2	2	1	0
HEARING AND VESTIBULAR DISORDERS	8 (0.6%)	6	1	1	0	8 (1.1%)	5	3	0	0
MUSCULO-SKELETAL SYSTEM DISORDERS	8 (0.6%)	3	3	2	0	1 (0.1%)	0	1	0	0

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Appendix 2, Table 2.

TABLE 3: INCIDENCE OF ADVERSE EXPERIENCE BY BODY SYSTEM

SEX GROUP: FEMALE
 FORMULATION: TABLET/CAPSULE

ADVERSE EXPERIENCE	CETIRIZINE					PLACEBO				
	NO. PTS. (%)	MIL	MOD	SEV	NOT SPEC	NO. PTS. (%)	MIL	MOD	SEV	NOT SPEC
TOTAL NO. OF PATIENTS	1192					775				
NO. OF PTS. WITH ANY AE	561 (47.1%)					321 (41.5%)				
CENTR & PERIPH NERV SYST DISORDERS	250 (21.0%)	96	100	46	0	176 (22.8%)	69	65	41	1
*PSYCHIATRIC DISORDERS	222 (18.6%)	107	77	38	0	73 (9.4%)	36	23	14	0
BODY AS A WHOLE - GENERAL DISORDERS	115 (9.6%)	57	44	14	0	45 (5.8%)	9	23	11	2
GASTRO-INTESTINAL DISORDERS	62 (5.2%)	30	34	10	0	62 (8.0%)	29	22	11	0
AUTONOMIC NERVOUS SYSTEM DISORDERS	77 (6.5%)	44	29	4	0	29 (3.8%)	10	0	3	0
RESPIRATORY SYSTEM DISORDERS	72 (6.0%)	20	35	9	0	30 (3.9%)	20	12	5	1
SKIN AND APPENDAGES DISORDERS	24 (2.0%)	12	9	3	0	31 (4.0%)	11	0	12	0
VISION DISORDERS	13 (1.1%)	7	3	3	0	6 (0.8%)	4	1	1	0
HEARING AND VESTIBULAR DISORDERS	12 (1.0%)	5	6	1	0	6 (0.8%)	3	1	0	0
REPRODUCTIVE DISORDERS, FEMALE	12 (1.0%)	4	6	1	1	3 (0.4%)	2	1	0	0

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Appendix 2. Table 3.

Table 6

HYDROXYZINE

ALLERGIC - IMMUNOLOGIC SPONTANEOUS ADVERSE EVENTS

CASE #	ADVERSE EVENT	PAST MEDICAL HISTORY	COUNTRY
L-3M190	Allergic Reaction	Menopause Osteoporosis Pruritus	US
9100357	Rash	NA ¹	Canada
9100356	Rash	NA	Canada
9000208	Pruritus	Acne Pustulosa Atopic dermatitis Prostatitis, unspecified	Japan
1705858	Rash, fever	Contact dermatitis	Japan
1705857	Urticaria	NA	Canada
1704503	Urticaria and joint swelling	NA	Sweden
1704498	Pruritus Rash	NA	Canada
1704496	Epidermal necrolysis	NA	Australia
L-3M1287	Rash, fever	Contact dermatitis Eczema	Japan
R2W688	Urticaria	Urticaria	US
R1W288	Urticaria	NA	US
R1K488	Pruritus Urticaria Rash	NA	US
R1G888	Pruritus Conjunctivitis Vomiting	NA	US
R1F1187	Urticaria	Urticaria	US

TABLE 6 (Cont'd)

CASE #	ADVERSE EVENT	PAST MEDICAL HISTORY	COUNTRY
9201969	Rash Skin discoloration Fever Abnormal hepatic function	Urticaria Thyroiditis Gastritis	Japan
R7H1092	Anaphylactic reaction	NA	US
9302054	Urticaria	NA	US
9301460	Rash and swelling	NA	US
9300404	Epidermal Necrolysis	Insomnia	Japan
R18M992	Dermatitis	NA	US
R18W692	Urticaria	NA	US
R6K1092	Photosensitive reaction	Anxiety	US
R2H1191	Allergic reaction	Contact dermatitis Eczema	US
R1K491	Rash	Skin eruption	US
R10R892	Rash Purpura	NA	US
R1J291	Rash	Systemic Lupus	US
NA - not available			

Aug. NDA 19-835
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 Cantel/155
 Himmel/155
 Delgado/155
 Joliet/155

Leadet

Medical Officer Review

OCT 27 1992

NDA 19,835

Drug: Reactine (cetirizine tablets)

Sponsor: Pfizer

Document reviewed: Amendment to an pending NDA Application;
Study 89CE16-0448.

Correspondence dates:

Submission: September 16, 1991
Assigned: August 12, 1992
Review Completed: October 20, 1992

Medical Officer Reviewer: Ana M. Saavedra-Delgado, M.D.

Handwritten signature and date: 10/21/92

Reviewer's Trial # 1 Sponsor's protocol # 89CE16-0448

Title: "A double-blind parallel multisite study of the safety and efficacy of cetirizine 5 mg and 10 mg qAM versus placebo in the treatment of patients with perennial allergic rhinitis."

Handwritten initials: 9/13/92

Objective/Rationale

Handwritten date: 10/21/92

This is the fourth pivotal trial conducted to demonstrate the efficacy and safety of cetirizine for the treatment of perennial allergic rhinitis.

Design

Multicenter (12); see Appendix 1, Table 1, eight week, double-blind, randomized, placebo controlled study.

Protocol

Population

inclusion criteria: males and females of at least 12 years of age with a minimum two year history of perennial allergic rhinitis (PAR) and confirmed allergen sensitivity via RAST or skin tests to house dust, cat or dog dander, mites or molds. A total severity score of at least 8 (of a possible 21), based on 7 signs and symptoms of rhinitis (nasal congestion excluded), with at least one moderately severe nasal symptom (symptom not specified).

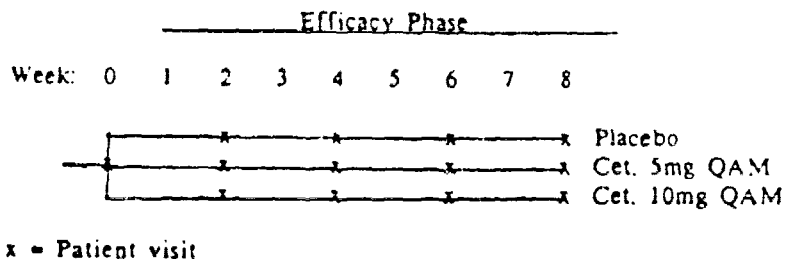
exclusion criteria: patients who are known to react symptomatically to seasonal allergens that would become prevalent during the course of their therapy, inability

to stop nasal steroids or cromolyn treatment for one week, an inability to discontinue treatment with antihistamines for **three days** prior to initiation, astemizole for 8 weeks.

Reviewer's comments: By using the inclusion criteria of only one symptom of moderate severity, the population studied needed to have only relatively mild symptoms, probably making it difficult for the patients to assess any great differences with treatment. The use of topical decongestants was not excluded, making this reviewer wonder about its relative use in this study and its implication in terms of efficacy. The minimum extent of daily exposure to perennial allergens was not specified, and with a population of relatively mild rhinitic patients the improvement in symptoms can be due to lack of exposure, rather than to medication.

study plan:

Table A. General Study Design



Reviewer's comments: In the design of this study patients should have been studied only during the winter months. As can be seen from Appendix 1, there were some centers that started their patients in April and had patients ending the study in June. Even though symptomatically they may not have been susceptible by history to seasonal aeroallergens such as trees during this time of the year, a number of sensitized patients could have been selectively reacting to seasonal molds.

study medication: tablet form

<u>Medication</u>	<u>Dose</u>	<u>Lot</u>
cetirizine	5mg	C6106
cetirizine	10mg	C6108
placebo	-	C8193

rescue medication: pseudoephedrine 60 mg Lot 9S2035

daily patient diary of the severity of each symptom over the previous 24 hours prior to each dose of study medication

signs and symptoms: nasal congestion, post-nasal discharge, itching of the nose, sneezing, watery nasal discharge, itching of the eyes and watering of the eyes. The severity of each sign and symptom was rated as :

- 0 (none - not present at all)
- 1 (mild - occasionally present; not troublesome),
- 2 (moderate - frequently present; annoying)
- 3 (severe - continuously present; interferes with work or sleep)

investigator assessment of above symptoms at entry of study(day 0), and after 2, 4, 6, and 8 weeks of treatment

global evaluations:an overall assessment of the effect of therapy, by the investigator in conjunction with the patient but without referring to the diary cards, at the end of the eight week treatment period, or at the time of discontinuation.

- 0 (no improvement or worse)
- 1 (slight, but insufficient improvement)
- 2 (definite improvement in signs and symptoms)
- 3 (highly effective)
- 4 (complete disappearance of signs and symptoms)

rescue decongestant: frequency and amount recorded on diary card. Use of topical decongestants was not excluded or recorded.

adverse experiences: volunteered or observed adverse experiences were recorded only at each study visit (day 1 and at weeks 2, 4, 6 and 8).

laboratory data: the following were done at entry and at the end of the study: SGOT, SGPT, BUN, total bilirubin, hematocrit and serum creatinine.

Endpoints

Efficacy:

Reviewer's comments

In the protocol used for this study, even though there is a description as to what efficacy evaluations are going to be performed, the Sponsor does not states or defines what will be the primary or secondary endpoints of this study.

It is only in the completed study report that this is stated. This, we could perhaps assume was due to an understanding that these endpoints would be the same as those that were considered in the previous perennial allergic rhinitis protocols and that they would be analyzed in the same way. It introduces however the question of an element of bias in the analysis.

It was stated in the completed study report that the primary endpoint was:

patient total symptom severity score, defined as 6 times the mean of the non-missing severities of all signs and symptoms other than nasal congestion. For each patient, weekly mean symptom severity score for each symptom was calculated. The weekly mean severity score was defined as the sum of the severity scores divided by the number of days of diary data for the week. If there was only data for less than three days, the mean weekly severity score was not calculated. Weekly total symptom severity scores were computed as the sum of the individual symptom weekly mean severities, provided that at least 5 symptoms had non missing values.

baseline severity - for each symptom was defined as the rating given by the investigator, in conjunction with the patient, at the screening (day 0) visit

Other endpoints: global evaluations and use of rescue medication

Safety:

Reviewer's comments:

Minimum safety evaluations were done in this study. Only volunteered or observed adverse experiences were recorded at each study visit (day 1 and at weeks 2, 4, 6 and 8). An adverse event log was not included in the daily patient diary. The frequency of somnolence and fatigue could have been underestimated.

In terms of the collected laboratory data, the following were done at entry and at the end of the study: SGOT, SGPT, BUN, total bilirubin, hematocrit and serum creatinine. No ECGs were done.

Statistical considerations

The Sponsor's proposed initial analysis was to use standard analysis of variance procedures appropriate to a model

involving a repeated measurement effect. If appropriate the physician baseline score would be entered as a covariate for both the physician's and the patient ratings.

The Sponsor analyzed patient weekly symptom scores (mean of daily diary scores) and biweekly investigator symptom scores using an analysis of covariance with factors treatment, center, and treatment by center interaction with baseline investigator assessment as a covariate.

A repeated measures analysis of covariance of all weekly assessment data was also performed.

The Sponsor also analyzed investigator global assessment of treatments using a Cochran-Mantel-Haenszel tests with centers as strata.

Results

Population enrolled/analyzed

There were 240 patients enrolled in the study; eighty patients were randomized to each of the placebo, 5 mg cetirizine and 10 mg cetirizine groups.

All patients that took at least three doses of study medication were evaluated for efficacy. Those that discontinued the study due to lack of efficacy, their final mean severity values were carried forward to subsequent weeks and included in the weekly and the repeated measures analyses. For those that discontinued the study for reasons other than lack of efficacy, were included in the weekly analyses prior to the time of discontinuance and excluded from the repeated measures analyses.

The Sponsor considered 230 patients evaluable for efficacy; 76/80 placebo, 78/80 5 mg cetirizine and 76/80 10 mg cetirizine. In 8/10 patients not evaluable for efficacy it was due to the prior or concomitant use of non approved medication; the other two patients did not return after the screening visit.

The treatment groups were comparable in demographic variables (age, weight, height, pulse, systolic BP, diastolic BP, temperature, duration of illness-years, sex and race). About 60% of patients were females in the treatment groups.

The baseline mean scores for the signs and symptoms of perennial allergic rhinitis were also comparable among treatment groups with the exception of nasal congestion in the 5 mg cetirizine group. The baseline means were 2.16 for

placebo, 2.37 for 5 mg cetirizine and 2.16 for the 10 mg group. See Appendix 1. Table 2, Sponsor's Table 6.

Reviewer's comments:

Although the statistical reviewer concludes in his review that this baseline difference should have little effect on the study conclusions since nasal congestion is not included in the efficacy analysis, I differ. It is interesting to note that this symptom was the only one with a mean severity score of 2 or above; the only symptom with a moderate severity mean as baseline in this study. One would expect therefore, the need to use regular decongestants by these patients in all treatment groups, but perhaps more in 5 mg cetirizine group, and especially in those with initial nasal congestion of severe severity. It is in 5 mg cetirizine treatment group, that the % of patients that use rescue medication through-out the study is greatest. Table 3. Sponsor's Table 12A.

When moderate to severe nasal congestion is present it is usually accompanied by post nasal drip or watery nasal discharge. It very well could be that in part the lack of effectiveness seen in the ceterizine 5 mg group is due to the lack of the study drug at this dose level to significantly affect these parameters. When nasal congestion was categorized as severe, the severity of post nasal drip and watery nasal discharge were usually at least of moderate severity therefore overriding the potential benefit in the others symptoms (sneezing, itchy nose, itchy eyes, watery eyes).

The use of oral nasal decongestants may affect the extent or severity of post nasal drip, the watery nasal discharge and may give the patient an increased sense of well being, which is felt within 3 hours of administration but does not usually persists. It would have been interesting to have patients compare their satisfaction with the rescue medication versus the ones used in the study. This of course, if the use of rescue medication was not discouraged.

Withdrawals

Fifty three patients (22%) discontinued the study prior to completing eight weeks of treatment: 19/80 patients (24%) on placebo, 22/80 (28%) on 5 mg cetirizine and 12/80 (15%) on 10 mg cetirizine. Appendix 1., Table 4, Sponsor's Table 4.

Unexpectedly, there are more reports of discontinuing

treatment secondary to adverse experiences and abnl labs in patients receiving 5 mg of cetirizine than in those receiving 10 mg.

Looking at individual data from all treatment groups in Table 2A and in Data Listing 5 of the Sponsor's Appendix E, in week 6 there are more withdrawals (11) than in the other weeks.

Efficacy endpoints outcomes

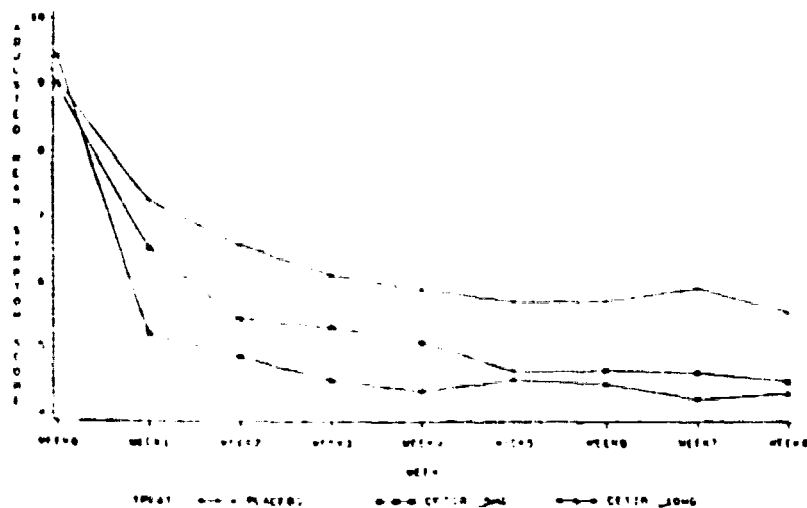
Patient diary data- The results of the mean total severity score on a weekly basis showed ceterizine 10 mg to be significantly better than placebo for weeks 1-4 and for weeks 6 and 8. Appendix 1, Table 5, Sponsor's Table 7A.

The only individual symptom in which ceterizine 10 mg was consistently significantly better than placebo over the first 4 weeks was sneezing.

As seen in Fig 1, the Sponsor's Figure 1A, mean total severity decreased from baseline values (Appendix 1, Table 2, Sponsor's Table 6) in all groups during the first 4 weeks, with more a more marked effect during the first week.

Fig 1 , Sponsor's Fig. 1A.

FIGURE 1A: ADJUSTED MEAN TOTAL SEVERITY BY STUDY WEEK - PATIENT ASSESSMENTS



The results for patients on ceterizine 5 mg were not different from those on placebo. Only at week 1, were the effects of the two ceterizine treatment groups significantly different, with a better improvement in total symptoms

scores for those patients on 10 mg cetirizine (using repeated measures analysis of covariance by study week, Appendix 1, Table 6, Sponsor's Table 7b-in this table patients that discontinued the study due to reasons other than lack of efficacy were not included).

Use of rescue medication - See Table 3, Sponsor's Table 12A. As mentioned above, the % of patients using oral nasal decongestants was greatest in the 5 mg cetirizine group, with average 44.6% patients using it over the study period. This difference was statistically significant at weeks 4 and 6. However the mean dose used was not more than the equivalent to two 30 mg/tabs per day in the ceterizine 5 mg group. The placebo group average was higher but did not reach the equivalent to three 30 mg tabs /day.

When the mean total symptom score for those that took rescue meds and for those patients that didn't was compared, there was a significant difference in response during weeks 1 and 2 that was primarily due to mean total severity among placebo patients.

Investigator's assessment - The improvement in mean total symptom severity score for the 10 mg cetirizine was only significantly better than placebo at the 2 week visit.

Only sneezing was thought to be improved in the 10 mg cetirizine vs placebo in weeks 4, 6 and 8. There was no difference in the mean total symptom severity scores or individual symptoms between the 5 mg group and placebo groups during treatment according to the investigator's assessment See Appendix 1, Table 7, Sponsor's Table 8b.

Investig. r's global efficacy rating - The physician's global assessment differed from the other evaluations in that a statistically significant difference favored 5 mg cetirizine over placebo.

A greater # of patients on cetirizine 5 mg were thought to have a fair to good response (slight to definite improvement) compared to placebo and cetirizine 10 mg.

The 10 mg cetirizine was not found to be significantly different from placebo, largely due to the percentage of patients (30%) showing no improvement. Twenty four percent of patients on cetirizine 10 mg and 15% of those on placebo received an excellent rating by the investigators (highly effective or complete disappearance of symptoms). See Appendix 1, Table 8, Sponsor's Table 11.

Reviewer's comments on efficacy

In this study the patients that were in the group that received 5 mg of cetirizine daily did as well as those that were on placebo, when the results from the patient's weekly assessment and the physician's clinic visit assessment were analyzed in terms of improvement in mean total symptom scores and individual symptoms.

As it was previously discussed, a higher baseline in nasal congestion in this group, may have contributed in some way to these negative results. It was only on the global physician assessment that cetirizine 5 mg did better than placebo and this was a subjective assessment by physicians at the end of the study. The difference on effect was mainly due to the % of patients that were felt to have a fair to good response (67%) compared to those that failed treatment (19%) or those with an excellent response (15%). However, the contribution of an initial higher baseline and a subjective assessment at the end of the study by the physicians cannot override the lack of response seen in terms of the main endpoints of efficacy throughout the study.

In conclusion, the results of this study do not support the use of 5 mg cetirizine for the intended indication of perennial allergic rhinitis.

In terms of the results in patients that received 10 mg of cetirizine, we have a positive response with a significant difference from placebo in the improvement in the mean total symptoms scores for the eight weeks of treatment. Weeks 1-4 and Week 7 showed a significant difference between both treatments (10 mg cetirizine vs placebo). Sneezing was the only individual symptom that followed this pattern.

In terms of the investigator assessment at two week intervals (2, 4, 6, 8) only the assessment at two weeks (improvement of total symptom score) was considered by the physicians to be significantly different from placebo. Again, the only individual symptom where there was a positive response, according to the physician's assessment was sneezing at weeks 4 and 6.

Global physicians assessments for cetirizine 10 mg was not significantly better than placebo largely because 30% of these patients were considered to have failed treatment.

Another very important question in this study is whether patients had an adequate level of exposure to

perennial aeroallergens throughout this study. It doesn't seem that adequate measures were taken to insure that this would have happened. In the presence of a population that started with mild symptoms and without the assurance of adequate exposure to perennial aeroallergens there is very little room to show an effect by the drug that would not be different from that of placebo.

Request to Sponsor for additional information:

After looking at individual center entry dates it was clear that some of these centers had patients that had been entered in the study at the end of April and continued through June, differentially exposing these patients to seasonal aeroallergens. In the presence of a mixed positive drug effect in the patients receiving 10 mg cetirizine, without a clear support of a positive response in individual symptoms other than sneezing, we wanted to ascertain that what we were seeing was a clear positive drug effect on perennial allergic rhinitis of adequate duration, and not the effect that this drug may have in alleviating seasonal symptoms. To look at the possible influence that this could have in the results, we asked the Sponsor on September 15, 1992 on a telephone conversation to provide us with:

1. Efficacy analysis based only on the patients that received the study medication between Jan 1990 and April 1990.
2. In addition, we asked the Sponsor to provide us with individual figures per study center of patient's assessment by study week of individual symptoms and mean total symptom severity and to provide us with some of the analyses for this study in the format of the tables used for PAR-1 of:
 - a) Synopsis of repeated measure analyses of patient's mean daily rating of symptom severity. Table A.7 8 25802.
 - b) Summary of repeated measures analyses separately by study center-patients, mean daily total symptom severity. Table D.3 10 9393.
 - c) Summary of repeated measures analyses separately by study center-physicians' evaluation of total symptom severity. Table D.6 10 942

Final efficacy conclusions regarding whether the results of this study support the use of 10 mg of cetirizine qd in patients with PAR will be deferred until the information that has been requested from the Sponsor is received and evaluated.

Safety outcomes

Adverse event recorded by the investigator at one of the clinic visits (every 2 weeks) were limited primarily to headache, somnolence, fatigue and dry mouth. The incidence of headache was comparable to the placebo group. The three others were as follows:

	Placebo (N=80)	Cetirizine 5 mg (N=80)	Cetirizine 10 mg (N=79)
Somnolence	5.0%	10.0%	15.2%
Fatigue	3.8%	8.8%	6.3%
Dry mouth	3.8%	5.0%	7.6%

There is an increased incidence of severe somnolence in the cetirizine groups versus placebo (7/159 vs 0/80). A dose response is suggested as well.

There were 16¹ patients that discontinued the study due to adverse events or abnormal lab values. In the cetirizine group 7 had adverse experiences, 3 due to abnormal labs and 1 had an abnormal EKG. Four of the placebo patients discontinued the study due to adverse experiences and 1 due to abnormal labs.

In the cetirizine group 5/8 adv events were in the 5mg cetirizine group (mod.headache; mod. dyspnea which reappeared on rechallenge; severe tiredness, headaches, elevated BP that returned to nl after drug was d/c; severe drowsiness; sev. mood swings and depression) 3/8 adverse experiences were in the 10 mg group (slight ulceration corner of the mouth; mod to sev hair loss; dry mouth, hacky cough).

In the placebo group, 3 d/c the study due to adverse events (sev. headache, dizzy, numbness neck; mod. drowsiness; mod. allergic reaction-received ER treatment)

One patient that received placebo d/c the study due to an elevated SGOT at baseline that continued elevated at retest 6 days later (nl-60-67).

¹ There is a discrepancy in the above findings and the submission -in the summary, 15 pts. were reported to D/C study due to adverse events, however, in the Data Listing 5 pp 1259-1267, 16 pts are reported. Of these there are 3 patients in the 10 mg cetirizine group.

The other abn. labs were in the 5 mg cetirizine group with:

- 89-N-101 # 10 - 28 y/o male with isolated elevation of SGPT from normal value (30) to 62 (week 4), 101 (week 6) down to nl, 2 days post d/c drug (45).

- 89-N106 #149 - 46 y/o male pt with nl baseline SGOT and high SGPT (56); at end of week 4, SGPT (78) and SGOT (43), 4 days post d/c drug SGPT (58) and SGOT (39). May have been associated with increased alcohol use.

- 89-107 #187 - 57 y/o male with nl baseline total bilirubin, d/c drug at week 5 after she was found to have an isolated elevation of total and indirect bilirubin of 2.2 and 1.87 respectively. Repeat testing about one month later revealed the total bilirubin to be 1.7 units total and 1.49 indirect; further follow up not given.

The abnormal reported ECG was from a patient on the 5 mg cetirizine group, that was latter found to have mild mitral valve prolapse with mild mitral regurgitation -89-N-0103 #74.

Reviewer's comments on safety

It appears that perennial allergic rhinitic patients on cetirizine exhibit an increased incidence of somnolence than those on placebo. A dose response is also suggested.

Although minimal and incomplete safety evaluations (chem. and hem. labs) were done in this study, the incidence and significance of abnormal liver function tests with the use of this drug will be deferred for analysis until the integrated safety analysis for this drug is completed.

cc:

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APPENDIX 1. TABLE 1.

CETIRIZINE STUDY 89CE16-0448

2

A DOUBLE-BLIND PARALLEL MULTISITE STUDY OF THE SAFETY AND EFFICACY OF CETIRIZINE 5 MG QAM AND 10 MG QAM VERSUS PLACEBO IN THE TREATMENT OF PATIENTS WITH PERENNIAL ALLERGIC RHINITIS

I. INVESTIGATORS AND STUDY SITES

1. Grant 89-N-0101 Start Date: 26 January 90 Completion Date: 4 June 90 Harold Kaiser, M.D. Allergy Specialists 1149 Medical Arts Building Minneapolis, MN 55402	6. Grant 89-N-0106 Start Date: 7 February 90 Completion Date: 16 May 90 Phillip Lieberman, M.D. Allergy Associates 920 Madison Avenue - Suite 909 Memphis, TN 38103
2. Grant 89-N-0102 Start Date: 22 February 90 Completion Date: 16 June 90 William E. Pierson, M.D. Northwest Asthma & Allergy Center 4540 Sand Point Way N.E. Seattle, WA 98105-3914	7. Grant 89-N-0107 Start Date: 13 February 90 Completion Date: 23 April 90 Donald W. Aaronson, M.D. 9301 West Gold Road - Suite 301 Des Plaines, IL 60016
3. Grant 89-N-0103 Start Date: 30 January 90 Completion Date: 6 April 90 John J. Condem, M.D. AAIR 919 West Fall Road - Building B Rochester, NY 14618	8. Grant 89-N-0108 Start Date: 27 January 90 Completion Date: 21 April 90 J. Grossman, M.D. Albany Allergy & Asthma Services 62 Hackett Blvd. Albany, NY 12209 - 1718
4. Grant 89-N-0104 Start Date: 13 March 90 Completion Date: 12 June 90 Jordan Fink, M.D. 8700 West Wisconsin Avenue Milwaukee, WI 53226	9. Grant 89-N-0110 Start Date: 3 February 90 Completion Date: 13 April 90 Sami Bahna, M.D. Department of Allergy/Clinical Immunology Cleveland Clinic Foundation 9500 Euclid Avenue Cleveland, OH 44915 - 5035
5. Grant 89-N-0105 Start Date: 25 January 90 Completion Date: 26 April 90 Richard Green, M.D. 320 Fort Duquesne Blvd. Gateway Towers - Suite 380 Pittsburgh, PA 15222	

APPENDIX 1. TABLE 2

TABLE 6: MEAN(±SD) BASELINE AND DEMOGRAPHIC CHARACTERISTICS OF EVALUABLE PATIENTS (CONTINUED)

	TREATMENT GROUP			P-VALUE ¹
	PLACEBO (N= 76)	CETIR. 5 MG (N= 78)	CETIR. 10 MG (N= 76)	
SIGNS OF PERENNIAL ALLERGIC RHINITIS				
NASAL CONGESTION	2.16± 0.67	2.37± 0.61	2.16± 0.65	.061
ITCHING OF NOSE	1.42± 0.77	1.40± 0.90	1.43± 0.75	.934
SNEEZING	1.55± 0.68	1.55± 0.75	1.62± 0.78	.989
POST NASAL DRIP	2.00± 0.75	2.03± 0.76	1.96± 0.74	.793
ITCHING OF EYES	1.29± 0.83	1.27± 0.86	1.47± 0.72	.197
WATERING OF EYES	1.03± 0.77	0.97± 0.79	1.17± 0.81	.387
WATERY NASAL DISCHARGE	1.75± 0.71	1.77± 0.77	1.76± 0.71	.506
TOTAL SYMPTOM SEVERITY	9.04± 2.33	8.99± 2.55	9.42± 2.30	.621

1. P-VALUE ASSOCIATED WITH THE F-TEST OF TREATMENT EFFECT FROM A TWO-WAY ANOVA.

CETIRIZINE STUDY 89CE16-0448

Table 12A: Use of Rescue Medication by Study Week

Mean (STD) Dose of Pseudoephedrine
(All Study Patients)

Study Week	Treatment			p-value ¹
	Placebo	5mg Cet.	10mg Cet.	
1	25.9 (49.2)	21.9 (39.8)	11.5 (23.5)	0.084
2	29.5 (55.1)	19.6 (37.5)	18.7 (42.6)	0.341
3	34.8 (64.5)	29.5 (47.4)	18.6 (50.4)	0.052
4	29.6 (58.2)	29.7 (46.6)	14.2 (44.7)	0.051
5	26.1 (50.5)	27.8 (49.1)	13.8 (40.1)	0.056
6	27.9 (55.8)	27.6 (49.9)	12.9 (32.7)	0.052
7	29.1 (57.1)	23.0 (46.7)	16.6 (40.0)	0.180
8	27.8 (58.3)	25.2 (49.5)	18.7 (40.5)	0.418
Mean of Wk 1-8	28.8	25.5	15.6	

Percentage of Use of Pseudoephedrine

Study Week	Treatment			p-value ¹
	Placebo	5mg Cet.	10mg Cet.	
1	25/78 (35%)	36/79 (46%)	25/78 (32%)	0.162
2	29/74 (39%)	28/75 (37%)	27/76 (36%)	0.903
3	27/79 (39%)	35/74 (47%)	22/73 (30%)	0.084
4	29/70 (41%)	35/73 (48%)	19/73 (26%)	0.021
5	22/64 (34%)	29/67 (43%)	18/69 (26%)	0.109
6	26/62 (42%)	31/64 (48%)	20/69 (29%)	0.033
7	22/59 (37%)	25/61 (41%)	21/66 (32%)	0.427
8	19/57 (33%)	27/58 (47%)	23/65 (35%)	0.210
Mean of Wk 1-8	37.5%	44.6%	30.8%	

Mean (STD) Dose of Pseudoephedrine
(Patients who Used Pseudoephedrine)

Study Week	Treatment			p-value ¹
	Placebo	5mg Cet.	10mg Cet.	
1	74.8 (58.1)	48.1 (47.3)	35.9 (29.3)	0.109
2	75.3 (65.8)	52.6 (45.4)	52.6 (58.1)	0.371
3	90.2 (76.6)	62.4 (52.0)	61.6 (77.1)	0.424
4	71.5 (72.4)	62.0 (50.4)	54.4 (75.4)	0.479
5	76.1 (60.5)	64.3 (57.0)	52.8 (65.1)	0.378
6	66.5 (70.1)	56.9 (59.1)	44.6 (48.3)	0.242
7	77.9 (70.9)	56.1 (59.3)	52.1 (57.1)	0.587
8	83.4 (75.3)	54.1 (61.3)	53.0 (53.7)	0.369
Mean of Wk 1-8	77.0	57.1	50.9	

1: p-value associated with F-test of treatment effect in a two-way ANOVA
2: p-value associated with the Cochran-Mantel-Haenszel test of overall treatment effect, using centers as strata

Table 4: Distribution of Reasons for Premature Discontinuation

Table Entries are Numbers of Patients(Percentage of Patients)

Reason	Treatment			Total
	Placebo	5mg Cet.	10mg Cet.	
Intercurrent Illness	10(12.8%)	7(8.8%)	5(6.7%)	22(9.4%)
Adverse Experience	3(3.8%)	7(8.8%)	1(1.3%)	11(4.7%)
Other	1(1.3%)	3(3.8%)	1(1.3%)	5(2.1%)
Lost To Followup	0	1(1.3%)	3(0.4%)	4(1.7%)
Lack of Efficacy	2 (2.65)	1(1.3%)	1(1.3%)	4(1.7%)
Markedly Abnormal Labs	1(1.3%)	3(3.8%)	0	4(1.7%)
Protocol Violation/ Poor Compliance	2	0	1	3
Total	19(24.4%)	22(27.5%)	12(15.0%)	53(22.7%)

APPENDIX 1. TABLE 5

TABLE 7A: SUMMARY OF PATIENT DIARY DATA - MEAN(SD) SYMPTOM SEVERITY BY STUDY WEEK FOR EVALUABLE PATIENTS

TABLE ENTRIES ARE ADJUSTED MEAN SEVERITY
TREATMENT GROUP

PARAMETER	WEEK	CETIRIZINE			P-VALUE ¹
		PLACEBO	5 MG QAM	10 MG QAM	
NASAL CONGESTION	1	1.9	1.9	1.8	.54
	2	1.9	1.7	1.7	.14
	3	1.9	1.7	1.6	.08
	4	1.9	1.7	1.6	.12
	5	1.7	1.7	1.5	.54
	6	1.7	1.5	1.5	.10
	7	1.8	1.5	1.5	.06
	8	1.7	1.6	1.5	.59
	MEAN	1.8	1.6	1.6	.17
ITCHING OF THE NOSE	1	1.2	1.1	0.9	.12
	2	1.1	0.8	0.8	.09
	3	0.9	0.8	0.7	.11
	4	0.9	0.7	0.7	.21
	5	0.9	0.7	0.7	.23
	6	0.9	0.7	0.6	.16
	7	0.9	0.6	0.7	.06
	8	0.9	0.6	0.7	.23
	MEAN	0.9	0.7	0.7	.15
SNEEZING	1	1.1	0.9 [#]	0.7 [#]	<.01
	2	1.1	0.8 [#]	0.6 [#]	<.01
	3	1.0	0.8	0.6 [#]	<.01
	4	1.0	0.8	0.5 [#]	<.01
	5	0.8	0.7	0.6	.17
	6	0.9	0.7	0.6	.06
	7	1.0	0.7	0.6 [#]	.03
	8	0.9	0.8	0.6	.16
	MEAN	1.0	0.8	0.6 [#]	<.01
POST NASAL DRIP	1	1.7	1.7	1.6 [#]	.01
	2	1.6	1.4	1.3	.06
	3	1.6	1.5	1.3	.13
	4	1.4	1.4	1.3	.43
	5	1.4	1.3	1.2	.40
	6	1.4	1.3	1.2	.45
	7	1.4	1.3	1.1	.12
	8	1.4	1.2	1.1	.25
	MEAN	1.4	1.3	1.2	.27

¹ : P-VALUE ASSOCIATED WITH F-TEST OF TREATMENT EFFECT FROM ANCOVA.
: SIGNIFICANTLY DIFFERENT FROM PLACEBO MEAN CHANGE, P ≤ 0.05

CETIRIZINE STUDY 09CE16-0448

TABLE 7A: SUMMARY OF PATIENT DIARY DATA - MEAN(SD) SYMPTOM SEVERITY BY STUDY WEEK FOR EVALUABLE PATIENTS (CONTINUED)

TABLE ENTRIES ARE ADJUSTED MEAN SEVERITY
TREATMENT GROUP

PARAMETER	WEEK	CETIRIZINE			P-VALUE ¹
		PLACEBO	5 MG QAM	10 MG QAM	
ITCHING OF THE EYES	1	1.0	1.0	0.7 [#]	<.01
	2	0.9	0.8	0.6	.09
	3	0.6	0.7	0.6	.06
	4	0.8	0.7	0.6	.22
	5	0.8	0.6	0.6	.15
	6	0.7	0.6	0.6	.47
	7	0.8	0.7	0.6	.14
	8	0.8	0.6	0.6	.31
	MEAN	0.8	0.7	0.6	.18
WATERING OF THE EYES	1	0.6	0.7	0.5 [#]	<.01
	2	0.6	0.6	0.4	.11
	3	0.6	0.6	0.4	.12
	4	0.6	0.5	0.4	.19
	5	0.6	0.5	0.5	.34
	6	0.6	0.5	0.5	.56
	7	0.7	0.5	0.4	.24
	8	0.6	0.4	0.4	.51
	MEAN	0.6	0.5	0.4	.33
WATERY NASAL DISCHARGE	1	1.5	1.2 [#]	1.0 [#]	<.01
	2	1.3	1.0 [#]	1.0 [#]	.05
	3	1.2	0.9	1.0	.12
	4	1.2	0.9	0.9	.07
	5	1.1	0.8	1.0	.14
	6	1.2	0.9	1.0	.22
	7	1.1	0.9	0.9	.33
	8	1.1	0.9	0.9	.60
	MEAN	1.1	1.0	1.0	.31
TOTAL SYMPTOM SCORE	1	7.5	6.5	5.2 [#]	<.01
	2	6.6	5.6 [#]	4.9 [#]	<.01
	3	6.1	5.3	4.5 [#]	.02
	4	5.9	5.1	4.3 [#]	.02
	5	5.7	4.6	4.5	.09
	6	5.7	4.7	4.5	.13
	7	5.5	4.6	4.2 [#]	.06
	8	5.6	4.5	4.3	.15
	MEAN	5.9	5.0	4.5 [#]	.05

¹ : P-VALUE ASSOCIATED WITH F-TEST OF TREATMENT EFFECT FROM ANCOVA.
: SIGNIFICANTLY DIFFERENT FROM PLACEBO MEAN CHANGE, P ≤ 0.05

CETIRIZINE STUDY 09CE16-0448

APPENDIX I. TABLE 6

Table 7b Summary of Patient Diary Data
Analysis of Covariance Results by Study Week for Evaluable Patients

Parameter	Week	Baseline	Treatment	Weeks	p value for test of		10mg - PRO	5mg - PRO	5mg - 10mg
					Treatments by Center	Homogeneity of Slopes			
Nasal Congestion									
	1	<0.01	0.14	0.26	0.39	0.57			
	2	<0.01	0.14	0.67	0.83	0.19			
	3	<0.01	0.09	0.67	0.93	0.30			
	4	<0.01	0.12	0.10	0.14	0.04			
	5	<0.01	0.34	0.06	0.85	0.66			
	6	<0.01	0.18	0.07	0.01	0.67			
	7	<0.01	0.06	0.07	0.15	0.70			
	8	<0.01	0.59	0.04	0.16	0.41			
	Mean	<0.01	0.17	0.03	0.04	0.63			Treat-by-Week: p=0.82
Itching of the Nose									
	1	<0.01	0.12	0.19	0.37	0.33			
	2	<0.01	0.09	0.08	0.39	0.31			
	3	<0.01	0.11	0.08	0.32	<0.01			
	4	<0.01	0.21	0.16	0.37	0.08			
	5	<0.01	0.24	0.15	0.44	0.06			
	6	<0.01	0.11	0.25	0.75	0.35			
	7	<0.01	0.06	0.20	0.57	0.12			
	8	<0.01	0.23	0.48	0.25	0.20			
	Mean	<0.01	0.13	0.24	0.43	0.07			Treat-by-Week: p=0.97
Sneezing									
	1	<0.01	<0.01	0.02	0.23	0.45	0.01	<0.01	0.02
	2	<0.01	<0.01	0.02	0.27	0.41	<0.01	<0.01	0.14
	3	<0.01	<0.01	0.04	0.83	0.22	0.17	<0.01	0.07
	4	<0.01	<0.01	<0.01	0.62	0.45	0.08	<0.01	0.04
	5	<0.01	0.17	<0.01	0.41	0.39			
	6	<0.01	0.06	0.01	0.60	0.08			
	7	<0.01	0.03	0.11	0.66	0.43	0.11	0.01	0.47
	8	<0.01	0.16	0.18	0.51	0.12	0.19	<0.01	0.11
	Mean	<0.01	<0.01	0.02	0.68	0.36			Treat-by-Week: p=0.79
Post-Nasal Discharge									
	1	<0.01	0.01	0.24	0.36	0.42	0.96	<0.01	0.01
	2	<0.01	0.06	0.59	0.40	0.78			
	3	<0.01	0.13	0.24	0.74	0.65			
	4	<0.01	0.43	0.12	0.51	0.81			
	5	<0.01	0.40	0.01	0.25	0.91			
	6	<0.01	0.45	<0.01	0.05	0.79			
	7	<0.01	0.12	<0.01	0.06	0.13			
	8	<0.01	0.26	0.01	0.04	0.25			
	Mean	<0.01	0.27	<0.01	0.37	0.44			Treat-by-Week: p=0.99

Cetirizine Study: 89CLE10-0448

Itching of the Eyes									
	1	<0.01	<0.01	<0.01	0.46	0.58	0.83	<0.01	0.01
	2	<0.01	0.09	<0.01	0.12	0.30			
	3	<0.01	0.67	<0.01	0.56	0.03			
	4	<0.01	0.23	<0.01	0.53	0.10			
	5	<0.01	0.15	<0.01	0.96	0.06			
	6	<0.01	0.27	<0.01	0.84	0.27			
	7	<0.01	0.14	0.03	0.87	<0.01			
	8	<0.01	0.31	0.16	0.89	<0.01			
	Mean	<0.01	0.18	0.02	0.87	0.03			Treat-by-Week: p=0.91
Watering of the Eyes									
	1	<0.01	<0.01	<0.01	0.60	0.04	0.13	<0.01	0.10
	2	<0.01	0.21	<0.01	0.49	0.05			
	3	<0.01	0.12	<0.01	0.41	<0.01			
	4	<0.01	0.20	<0.01	0.74	<0.01			
	5	<0.01	0.30	<0.01	0.73	0.02			
	6	<0.01	0.36	0.02	0.81	0.03			
	7	<0.01	0.24	0.19	0.88	0.20			
	8	<0.01	0.51	0.19	0.50	0.60			
	Mean	<0.01	0.33	0.04	0.72	0.11			Treat-by-Week: p=0.87
Watery Nasal Discharge									
	1	<0.01	<0.01	<0.01	0.18	0.33	0.02	<0.01	0.05
	2	<0.01	0.05	0.01	0.43	0.85	0.02	0.04	0.79
	3	<0.01	0.12	0.01	0.54	0.96			
	4	<0.01	0.67	0.04	0.58	0.48			
	5	<0.01	0.14	0.01	0.17	0.78			
	6	<0.01	0.22	0.02	0.61	0.93			
	7	<0.01	0.33	0.11	0.76	0.97			
	8	<0.01	0.40	0.09	0.83	0.87			
	Mean	<0.01	0.31	0.04	0.75	0.98			Treat-by-Week: p=0.58
Total Symptom Score									
	1	<0.01	<0.01	<0.01	0.54	0.54	0.13	<0.01	<0.01
	2	<0.01	<0.01	<0.01	0.48	0.19	0.04	<0.01	0.28
	3	<0.01	0.02	<0.01	0.80	0.01	0.15	<0.01	0.15
	4	<0.01	0.02	<0.01	0.69	0.11	0.15	<0.01	0.19
	5	<0.01	0.09	<0.01	0.54	0.42			
	6	<0.01	0.13	<0.01	0.60	0.47			
	7	<0.01	0.04	0.01	0.51	0.34	0.09	<0.01	0.58
	8	<0.01	0.15	0.02	0.40	0.62			
	Mean	<0.01	0.15	<0.01	0.66	0.47	0.14	<0.01	0.45
									Treat-by-Week: p=0.93

APPENDIX 1. TABLE 7

Table 8b: Summary of Investigator Assessments
Analysis of Covariance Results by Study Week for Evaluable Patients

Parameter	Week	Baseline	Treatment	Center	p-value for test of					
					Treatment -bv-Center	Homogeneity of Slopes	5mg v. PBO	10mg v. PBO	5mg v. 10mg	
Nasal Congestion										
	2	<0.01	0.09	0.11	0.34	0.09				
	4	<0.01	0.15	0.10	0.26	0.24				
	6	<0.01	0.77	0.03	0.04	0.49				
	8	<0.01	0.59	0.03	0.33	0.04				
	Mean	<0.01	0.49	<0.01	0.06	0.21				Treat-by-Week: p=0.74
Itching of the Nose										
	2	<0.01	0.17	0.01	0.84	0.59				
	4	<0.01	0.34	<0.01	0.68	0.66				
	6	<0.01	0.13	0.03	0.41	0.24				
	8	<0.01	0.69	<0.01	0.17	0.80				
	Mean	<0.01	0.48	<0.01	0.36	0.30				Treat-by-Week: p=0.85
Sneezing										
	2	<0.01	0.06	<0.01	0.51	0.94				
	4	<0.01	<0.01	<0.01	0.89	0.78	0.71	<0.01	<0.01	
	6	<0.01	0.02	<0.01	0.86	0.35	0.52	<0.01	0.04	
	8	<0.01	0.22	<0.01	0.54	0.19				
	Mean	<0.01	0.01	<0.01	0.67	0.48	0.87	<0.01	0.02	Treat-by-Week: p=0.27
Post-Nasal Discharge										
	2	<0.01	0.20	0.17	0.18	0.10				
	4	<0.01	0.25	<0.01	0.80	0.73				
	6	<0.01	0.22	<0.01	0.07	0.66				
	8	<0.01	0.68	0.03	0.20	0.93				
	Mean	<0.01	0.52	<0.01	0.09	0.69				Treat-by-Week: p=0.91
Itching of the Eyes										
	2	<0.01	0.14	<0.01	0.33	0.61				
	4	<0.01	0.83	<0.01	0.30	0.46				
	6	<0.01	0.37	<0.01	>0.99	0.31				
	8	<0.01	0.43	0.05	0.39	0.14				
	Mean	<0.01	0.54	<0.01	0.55	0.35				Treat-by-Week: p=0.83
Watering of the Eyes										
	2	<0.01	0.13	<0.01	0.16	0.03				
	4	<0.01	0.42	<0.01	0.95	0.03				
	6	<0.01	0.31	0.04	0.92	0.09				
	8	<0.01	0.44	0.22	0.66	0.08				
	Mean	<0.01	0.28	<0.01	0.92	0.03				Treat-by-Week: p=0.96
Watery Nasal Discharge										
	2	<0.01	0.01	<0.01	0.86	0.79	0.09	<0.01	0.22	
	4	<0.01	0.60	<0.01	0.33	0.59				
	6	<0.01	0.25	<0.01	0.77	0.42				
	8	<0.01	0.68	<0.01	0.71	0.84				
	Mean	<0.01	0.57	<0.01	0.68	0.83				Treat-by-Week: p=0.53

APPENDIX 1. TABLE 8

TABLE 11: SUMMARY OF INVESTIGATOR GLOBAL EVALUATIONS FOR EVALUABLE PATIENTS

EVALUATION	PLACEBO	CETIR. 5 MG	CETIR. 10 MG
NO IMPROVEMENT	31 (45%)	14 (19%)	21 (30%)
SLIGHT IMPROVEMENT	19 (28%)	29 (39%)	16 (23%)
DEFINITE IMPROVEMENT	9 (13%)	21 (28%)	15 (21%)
HIGHLY EFFECTIVE	6 (9%)	8 (11%)	16 (23%)
COMPLETE DISAPPEARANCE	4 (6%)	3 (4%)	3 (4%)
TOTAL	69	75	71

CMH TEST¹ P = 0.008

PAIRWISE COMPARISON OF TREATMENT:

PLACEBO VS. 5 MG : P = 0.010

PLACEBO VS. 10 MG: P = 0.133

5 MG VS. 10 MG: P = 0.077

1. COCHRAN-MANTEL-HAENZEL TEST USING CENTER AS STRATA.

CETIRIZINE STUDY 89CE16-0448

JL ac

MEDICAL OFFICER'S REVIEW OF ORIGINAL SUBMISSION

SPONSOR - Pfizer Pharmaceuticals
235 East 42nd Street
New York, New York 10017

DRUG - Cetirizine HCl
2-(2-(4-(4-chlorophenyl)phenylmethyl)-1-piperazinyl)ethoxy)
acetic acid, dihydrochloride

RELATED DRUGS - Hydroxyzine

PHARMACOLOGIC CATEGORY - antihistamine (selective H₁ receptor antagonist)

DOSAGE FORM - 5, 10, and 20mg tablets

ROUTE OF ADMINISTRATION - Once-daily oral

PROPOSED INDICATIONS - Seasonal Allergic Rhinitis
Perennial Allergic Rhinitis
Chronic Idiopathic Urticaria

DATE OF SUBMISSION - June 30, 1988

GENERAL COMMENT

Cetirizine is the principal human metabolite of hydroxyzine. It has been synthesized chemically, and is said to show selective antagonism to H₁-receptors.

The sponsor's rationale for developing this compound as an anti-allergic agent for human use includes the following statements:

1- Hydroxyzine (NDA 10-392, HFD-120) is recognized as one of the "classical antihistamines" and has been in use for more than 30 years. It is also recognized as a highly effective antipruritic, but its appreciable sedative effect has limited its use.

2 - Cetirizine is a relatively highly ionized molecule at physiologic pH, and therefore thought to penetrate the blood-brain barrier poorly.

3 - Human pharmacokinetic studies show rapid and uniform absorption of cetirizine after oral administration. C_{max} is reached approximately one hour after a single 10mg oral dose. Plasma half-life is 7-9 hours, and histamine-induced skin wheals are effectively suppressed for 24 hours after a single dose. Approximately 60% of the drug is excreted unchanged in the urine.

Cetirizine is the subject of IND**CLINICAL BACKGROUND -**

Cetirizine hydrochloride 10mg tablets have been approved for marketing in Belgium (registered 1987) and France (registered 1988) under the trade name Zyrtec, registered to the multistate application has been approved (April 1988) for 6 countries (UK, Netherlands, Denmark, Ireland, Italy, Greece). Marketing has been approved by four of these six countries by the local authorities, and applications for marketing approval are pending in 3 other European countries. Note: the formulation of the tablet in these countries is different from the US tablet.

Cetirizine has not been removed from the market or withdrawn from clinical investigation in any country.

The doses studied clinically were based on the response seen in the initial model of H1-blocking activity studied in man - the inhibition of histamine-induced wheal and flare in the skin. These studies indicated some activity with a 2.5mg dose, definitive activity at 5mg and apparently maximal activity at 10 to 20mg. Significant activity was still apparent 24 hours after dosing in this model.

EXTENT OF EXPOSURE

Table 1 shows the extent of exposure to cetirizine in studies conducted by Pfizer in the NDA program under U.S. IND. Clinical efficacy and safety studies ranged from one week to six months in length. Pharmacokinetic studies, except for a single 10-day study, were single-dose (four studies) or single-dose crossovers (five studies). Clinical pharmacology studies were either single-dose (one study), single-dose crossover (three studies) or three days in length (one study).

Table 1. Exposure to Cetirizine in U.S. NDA Program

Type of Study	Number of Subjects	Mean Number Days	Mean Dose (mg)
Clinical Efficacy and Safety	1,568*	41.7	12.5
Pharmacokinetic	175	4.1	11.9
Clinical Pharmacology	83	2.0	13.6
Totals	1,826 subjects	35.8 days	12.5 mg

*Of these, 44 patients were not unique, having been studied in two separate multicenter studies in two different years.

ADVERSE EXPERIENCES

In the thirteen clinical trials included in this NDA, adverse experiences were taken from spontaneous comments by the patients. No leading questions were asked, and the patient diary did not have a category for adverse effects.

A total of 1369 patients were treated with cetirizine and 821 received placebo in placebo-controlled clinical trials. At least one adverse experience was reported by 46.8% of cetirizine patients and 39.3% of the placebo patients.

The only frequently reported events which occurred at a higher rate with cetirizine than placebo were somnolence* and fatigue (23.7% vs. 10.9%) and dry mouth (6.6% vs. 2.4%). The incidence of somnolence and fatigue showed a stepwise response to dose.

Table 2. Frequently Reported Adverse Experiences in Placebo-Controlled U.S. Clinical Trials (Percent Incidence)

Adverse Experience	Cetirizine (N=1369)	Placebo (N=821)
Somnolence + Fatigue	23.7%	10.9%
Headache	15.9	18.3
Dry Mouth	6.6	2.4
Nausea/Vomiting	3.3	5.2
Dizziness	2.6	2.2

Table 3. Incidence of Commonly Observed Adverse Experiences Not Associated With Equivalent Incidence In Placebo-Treated Patients

Adverse Experience	Placebo (N = 671)	Cetirizine 5 mg (N = 258)	10 mg (N = 636)	20 mg (N = 272)
Somnolence+Fatigue	11.1%	16.3%	23.7%	30.9%
Dry Mouth	1.5	4.7	7.4	7.7

Table 4. Frequently Reported Adverse Experiences in European Trials of Cetirizine (Percent Incidence)

Adverse Experience	Cetirizine (N=915)	Placebo (N=721)
Drowsiness, Tiredness, Etc.	8.8%	6.9%
Nausea, Cramps, Other G.I.	2.7	2.8
Headache	2.5	3.4
Dry Mouth or Nose	1.9	1.2

* The definition of somnolence included all terms grouped under the WHO preferred term of somnolence except lethargy.

PHARMACOKINETIC AND PHARMACODYNAMIC DATA

The correlation of cetirizine blood levels with clinical activity has not been studied systematically.

C_{max} in 14 healthy volunteers reached 384 (S.D.103) ng/ml at a T_{max} of about one hour after a single oral dose of 10mg (Appendix A, pp 11-14). The C_{max} for 16 geriatric subjects (age 65 and over) in the same study was 460 (S.D.59). This was significantly related to creatinine clearance in the elderly group (p=0.01). C_{max} was slightly higher after fasting administration than after food, but AUC remained the same. About 20% of the compound is metabolized.

The major elimination pathway is renal - approximately 60% of the daily dose is excreted unchanged in the urine.

Non-renal clearance accounts for about 20% of total body clearance of cetirizine.

Once-daily dosing for 10 days with 10mg showed an accumulation index of 1.14, a fluctuation index of 2.8, a mean C_{min} (24 hr) of 30.4 ng/ml, and an average steady-state concentration of 104 ng/ml. Apparent steady-state was reached the second day.

Increasing the dose to 10mg q12h for 10 days increased the C_{max} to about 455ng/ml, and the 12 h C_{min} to 240 ng/ml. Steady-state was reached on the third day with this regimen. Terminal elimination half-life was 7-9 hours.

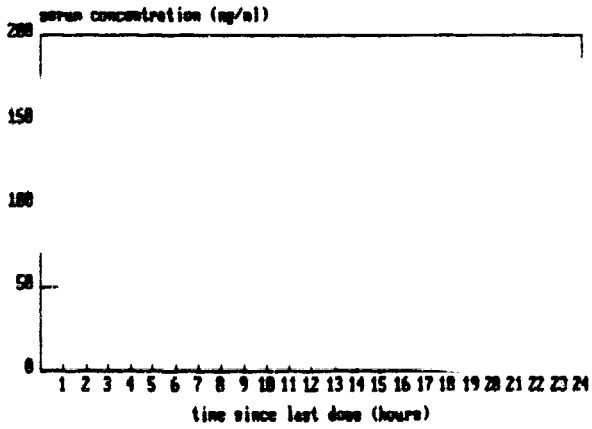
Linear dose-proportionality was seen for the 5, 10, and 20mg doses of cetirizine studied.

Blood levels of cetirizine were obtained at a single site (same investigator) in two clinical studies - SAR-1 and PAR-1, and in 59 patients in PRU-1. Blood levels were drawn in URT-2, but were not analyzed due to mishandling of samples.

In PRU-1, levels were drawn after one week and after three weeks of 10mg cetirizine qam. No evidence of accumulation was seen from week 1 to week 3 (see Appendix A, page 7).

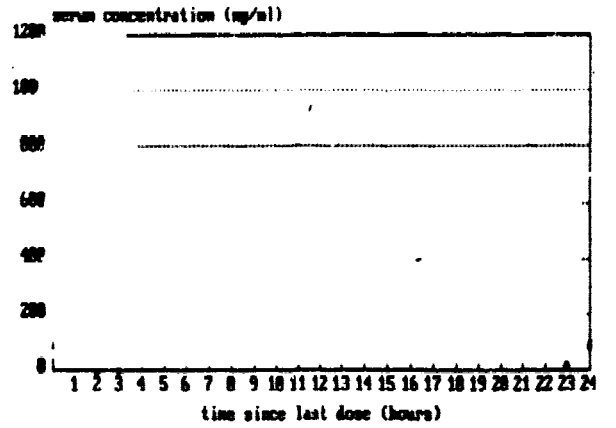
Sampling times in SAR-1 and PAR-1 were not standardized (Appendix A, p.8-10) - and the data are limited. They are represented in the following graphs:

CETIRIZINE SERUM LEVELS AFTER 5 MG



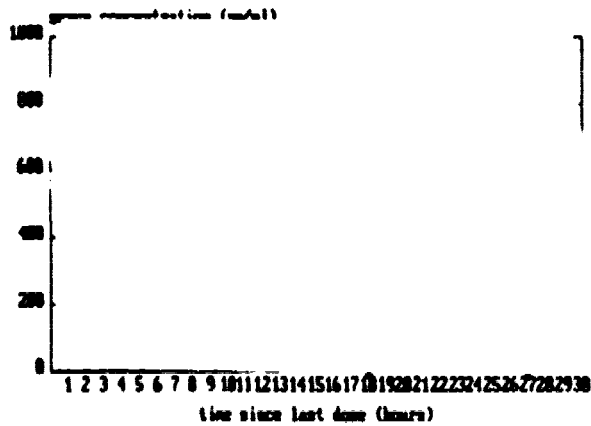
data from SAR-1 (04-N-0054)

CETIRIZINE SERUM LEVELS AFTER 10 MG



SAR-1(04-N-0054) and PAR-1(04-N-0053)

CETIRIZINE SERUM LEVELS AFTER 20 MG



SAR-1 (04-N-0054) and PAR-1 (04-N-0053)

CLINICAL STUDIES -**Controlled Studies**

This submission includes 12 controlled studies.

Five of these are multicenter trials in seasonal allergic rhinitis -including 774 cetirizine patients, 382 placebo patients and 226 patients receiving positive control agents (p.1 Appendix A).

Three are multicenter trials in perennial allergic rhinitis - including approximately 260 cetirizine patients, 200 placebo patients and 130 patients receiving positive control agents.

Two multicenter studies were done with chronic urticaria - including 172 cetirizine patients, 122 placebo patients and 69 patients receiving positive control agents.

Two multicenter studies involved patients with idiopathic pruritus. Included were 157 cetirizine patients, and 113 placebo patients.

In the cetirizine group, a total of 36 patients (out of 1363) had laboratory abnormalities considered "possibly related to drug therapy" (Appendix A. p 22,23). Six patients had elevations in both SGPT and SGOT (one accompanied by a slight elevation in alkaline phosphatase). The remaining 30 patients had elevations in a single liver function test. No follow-up tests were done in 16 of these patients. In seven patients, the abnormality returned towards normal while the patient continued to receive cetirizine and in 13 the abnormalities returned to normal after therapy had stopped. Treatment was discontinued because of a laboratory abnormality in six patients (3 cetirizine, 1 chlorpheniramine, 1 diphenhydramine and 1 placebo).

All three cetirizine patients who were discontinued had abnormal test results already present at baseline. No clinically significant changes were found in the mean values for liver function tests in cetirizine patients. A statistically significant change (1.77 U) in the mean SGOT value was found for the cetirizine 20mg group only. The mean change in the 10mg group (0.68 U) showed a trend toward significance. There were statistically significant increases in mean SGPT values in both the 10 and 20mg cetirizine groups (1.22 and 2.95 U, respectively). There were no significant changes in mean total bilirubin levels in any treatment group. None of these small but statistically significant changes were clinically relevant.

A - Seasonal Allergic Rhinitis

CLAIM: Cetirizine is indicated for the relief of symptoms associated with seasonal allergic rhinitis (hay fever). Symptoms treated effectively include sneezing, rhinorrhea, nasal pruritus, ocular pruritus, tearing and redness of the eyes.

The principal efficacy parameter in these studies was the self-rating of symptoms by patients in a daily diary. Patients rated their symptoms in the evening, except in SAR-2 and SAR-3, where symptoms were rated both upon arising and at bedtime. The symptoms rated included sneezing, rhinorrhea, ocular and nasal pruritus, tearing, and nasal congestion. Redness of the eyes was rated in SAR-1, but was dropped in subsequent studies, and itching of the mouth was rated in SAR-1 and 2, and subsequently dropped due to the infrequent reports of these symptoms. Total Symptom Score was reported as the the mean of 5, 6, or 7 symptoms evaluated in the respective studies. Nasal congestion was prospectively excluded from the Total Symptom Score and analyzed separately. The reason for this was that nasal congestion is known to be little affected by classical antihistamines, although it is a major symptom of allergic rhinitis. All symptoms were rated on a standard 4-point scale: 0=none; 1=mild; 2=moderate; 3=severe.

Investigators filled out rating scales at all visits and patients kept a daily diary. Investigators were also asked to make a global evaluation at the last visit. All patients were asked a general question at each visit about adverse reactions. Laboratory testing of blood and urine was performed before and after therapy in all studies and at interim visits in several studies.

Rescue medication was not permitted in any seasonal rhinitis trial. Patients with continuing intolerable rhinitis symptoms were instead discontinued from the trial.

The demographic distribution for all efficacy evaluable patients (p.2, Appendix A) in the seasonal allergic rhinitis studies shows that in SAR-1, 2 and 3, because of a restriction on entering women of child-bearing potential, there were more males than females and the average age of female patients was greater than that of males. In SAR-4 and 5 women of child-bearing potential practicing effective means of birth control were eligible for enrollment, and in these studies sex and age distributions were balanced. Age distributions varied little among studies, although adolescents were excluded from SAR-1 and 2.

SAR-1

This was a one-week, nine-center, double-blind, parallel, placebo-controlled dose response study in patients with documented (verified either by RAST or skin testing) ragweed, grass, or other regional weed pollen allergy. Doses of cetirizine used were 5mg, 10mg, or

20 mg once a day. Dosing was in the morning, and daily diary evaluations were recorded in the evening - giving a rating approximately 12 hours after medication. Patients had to have an acute seasonal exacerbation with a minimum symptom score (excluding nasal congestion) of 6. All patients who received three or more doses of cetirizine were rated for efficacy. Of a total of 419 patients entered, 412 patients were considered evaluable for efficacy.

The principal investigators were:

84-N-0049	Jerome Miller, M.D., Philadelphia, PA	59 patients
	entry dates: 8/20/84 through 9/25/84	
84-N-0050	Joseph M.Zeterberg, M.D., Cape Coral, FL	21 patients
	entry dates: 9/17/84 through 11/30/84	
84-N-0051	John T.Connell, M.D., Englewood, NJ	32 patients
	entry dates: 8/29/84 through 9/7/84	
84-N-0054	Philip T.Leese, M.D., Kansas City, MO	29 patients
	entry dates: 8/30/84 through 10/8/84	
84-N-0055	Robert Dockhorn, M.D., Prairie Village, KS	120 patients
	entry dates: 8/17/84 through 10/11/84	
84-N-0059	Stephen Wasserman, M.D., San Diego, CA	43 patients
	entry dates: 10/3/84 through 11/15/84	
84-N-0060	Elwood Buchman, M.D., Cincinnati, OH	49 patients
	entry dates: 8/17/84 through 9/19/84	
84-N-0062	Constantine J.Falliers, M.D., Denver, CO	40 patients
	entry dates: 8/20/84 through 9/4/84	
84-N-0063	Milan L.Brandon, M.D., San Diego, CA	26 patients
	entry dates: 8/27/84 through 11/27/84	

Of the seven patients excluded from efficacy, three were completely lost to follow-up, two withdrew for adverse experiences, one did not take study drug and one was lost to follow-up after a mid-week phone contact. The four patients excluded from the safety analyses were the three patients completely lost to follow-up and the one patient who did not take study medication.

Medication used was in capsule form - i.e. not the to be marketed formulation of cetirizine.

In both investigator and patient ratings, all three cetirizine doses were superior to placebo in relieving overall allergic rhinitis discomfort (Total Symptom Score).

The mean severity rating(TSS) over the entire treatment period analyzed by Repeated Measures Analysis(p.3 Appendix A) shows that cetirizine was significantly better than placebo in relieving sneezing, rhinorrhea, nasal pruritus, ocular pruritus, tearing, redness of the eyes and total symptom severity at all three dose levels. In addition, the 10 and 20mg doses relieved nasal congestion significantly more than placebo or 5mg, although the clinical significance of this is doubtful. The 20mg dose also was significantly better in improving nasal and palatal pruritus, and in relieving tearing.

In addition, the sponsor analyzed the individual responses as percent change from baseline to final, in Total Symptom Score, as rated by the investigator. This is presented in Table 7.

Table 7

% of Evaluable Patients with
Specified % Change, by Quartiles

Treatment Regimen		Less than 25%	25-49%	50-74%	Greater Than or =75%	Total N Eval.
Cet	5 mg QAM	21%	25%	18%	37%	(97)
Cet	10 mg QAM	17	11	24	48	(100)
Cet	20 mg QAM	12	16	22	49	(98)
Placebo		37	13	31	19	(98)

Global efficacy ratings (Appendix A, p.4) showed all three doses of cetirizine to be significantly better than placebo, but not different from one another.

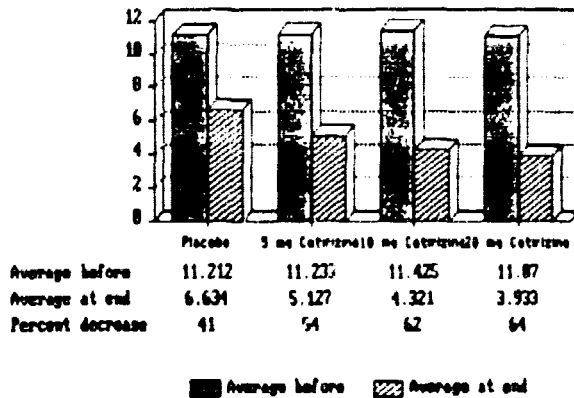
A total of 10 patients (Appendix A, p.15) discontinued treatment with cetirizine because of adverse reactions. Reported adverse experiences were generally mild to moderate in severity, were of short duration and resolved spontaneously. The incidence of adverse experiences for placebo, cetirizine 5 mg, 10 mg and 20 mg was 28, 29, 52 and 48%, respectively. Headache, somnolence, dry mouth and fatigue were the most common adverse experiences. The incidence of somnolence was 6% in the placebo group, 9% with cetirizine 5 mg, 23% with cetirizine 10 mg, and 25% with cetirizine 20 mg. There were no serious or unexpected adverse experiences reported in any treatment group and the number of patients discontinuing the study due to an adverse effect was similar (2 to 4 per group) among the four groups. Cetirizine caused no change in hematopoietic or renal function and was associated with only slight, clinically insignificant increases of SGOT and SGPT in a small percentage of patients (Appendix A, p 22,23).

No. of Withdrawals for Lack of Efficacy/Total No. Evaluable
Total Daily Cetirizine Dose

Placebo	5 mg	10 mg	20 mg
4/102	2/101	1/106	2/103

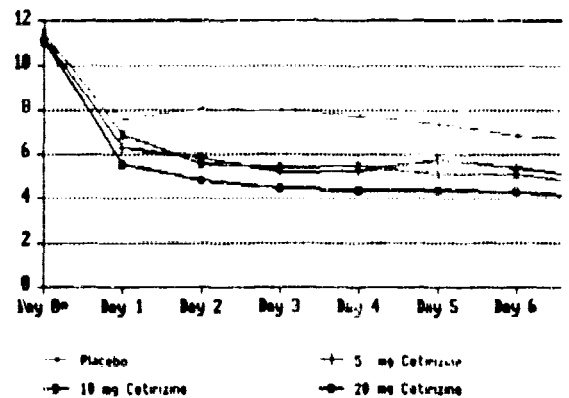
The overall efficacy on a daily basis is represented in the following graphs:

TOTAL SEVERITY
Investigator Rating



SAR-1

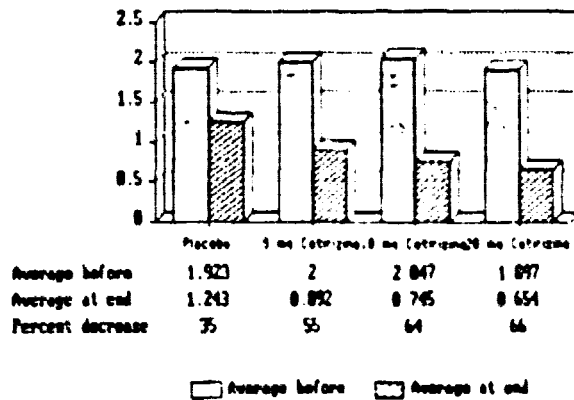
TOTAL SEVERITY
Patient Diary



* Taken from Investigator Rating

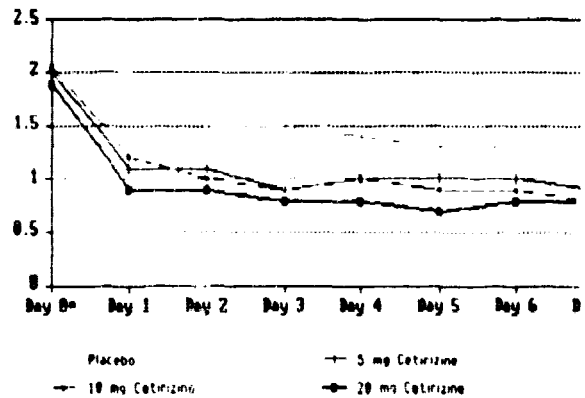
Taking each of the symptoms claimed to be effectively treated in turn,

SNEEZING
Investigator Rating



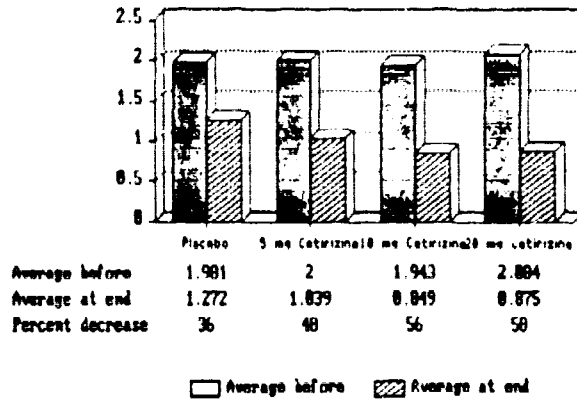
SAR-1

SNEEZING
Patient Diary



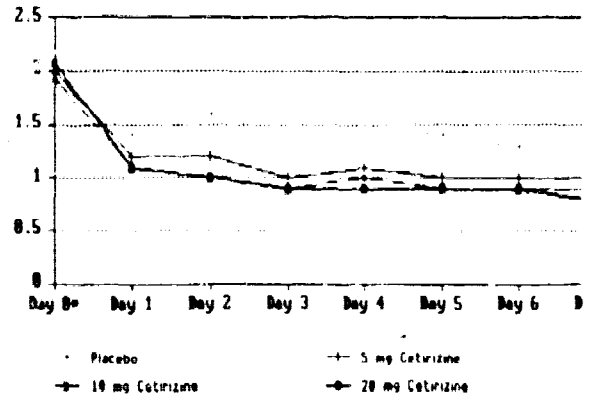
* Taken from Investigator Rating

RHINORRHEA Investigator Rating



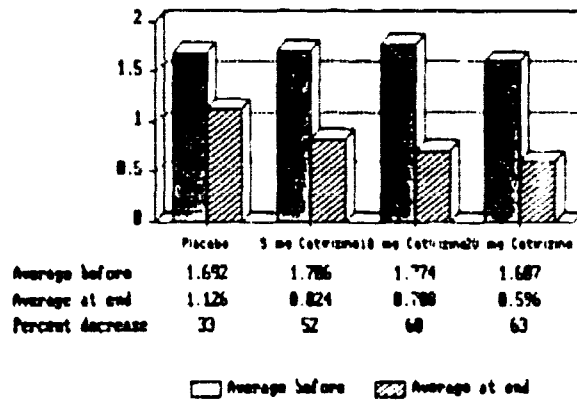
SAR-1

RHINORRHEA Patient Diary



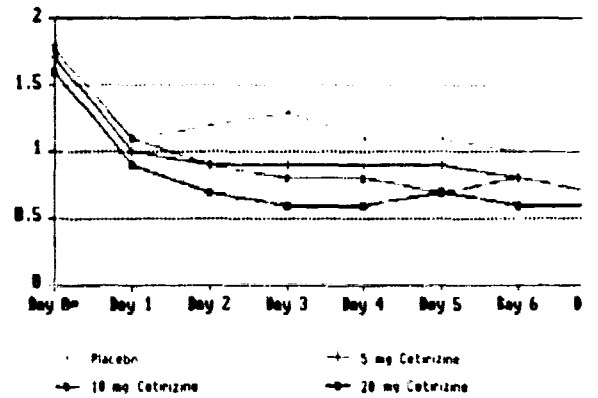
* Taken from Investigator Rating

NASAL PRURITUS Investigator Rating



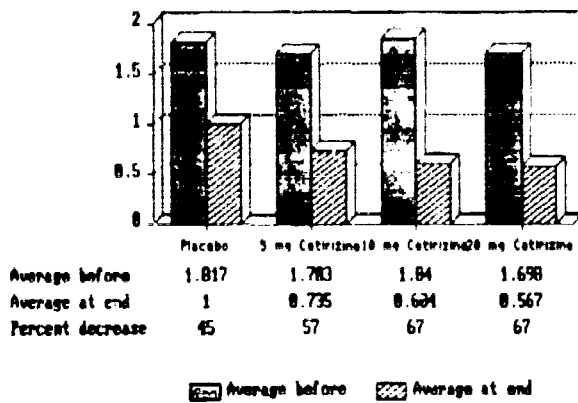
SAR-1

NASAL PRURITUS Patient Diary



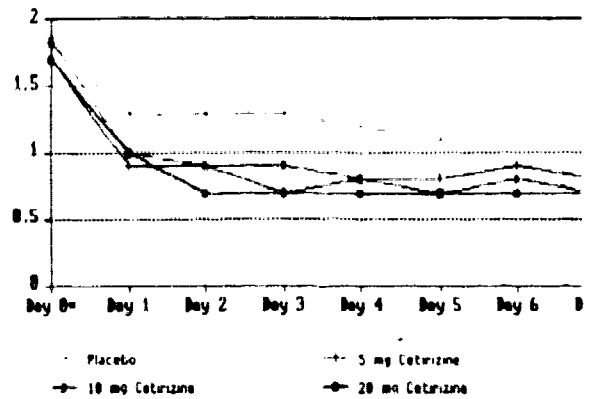
* Taken from Investigator Rating

OCULAR PRURITUS Investigator Rating



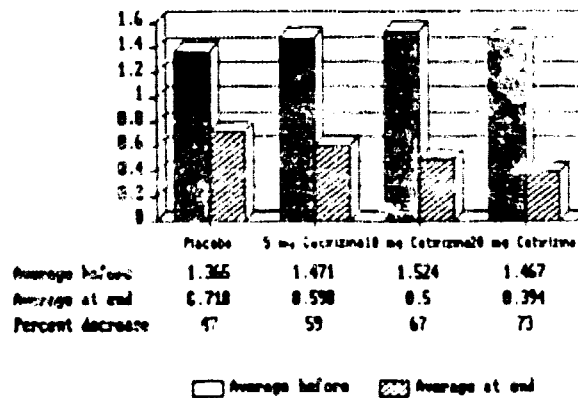
SAR-1

OCULAR PRURITUS Patient Diary



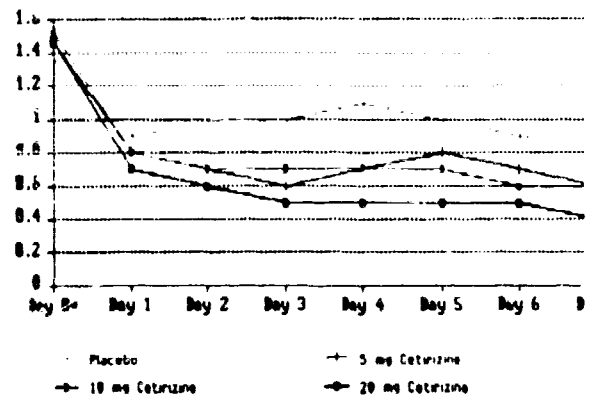
* Taken from Investigator Rating

WATERING EYES Investigator Rating



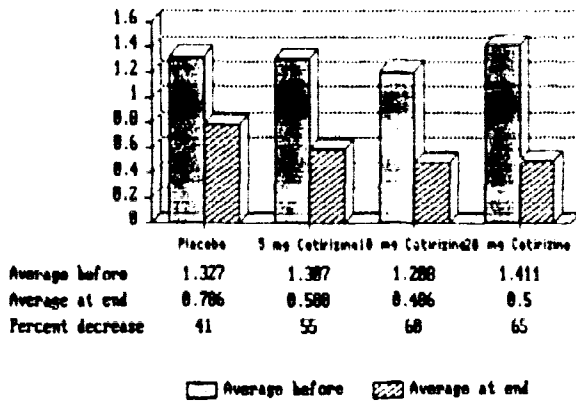
SAR-1

WATERING EYES Patient Diary



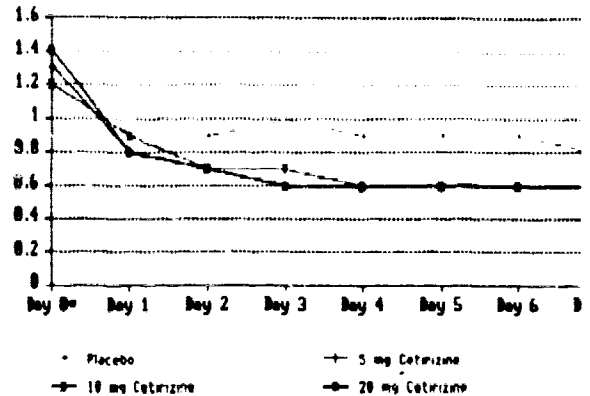
* Taken from Investigator Rating

REDNESS OF EYES Investigator Rating



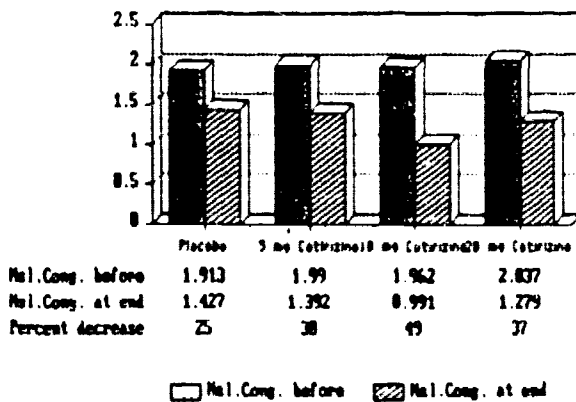
SNR-1

REDNESS OF EYES Patient Diary



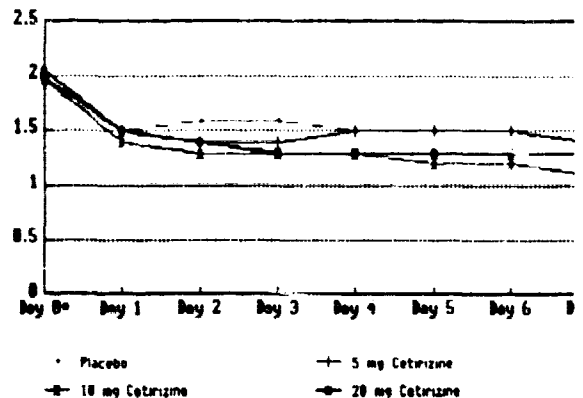
• Taken from Investigator Ratings

NASAL CONGESTION Investigator Rating



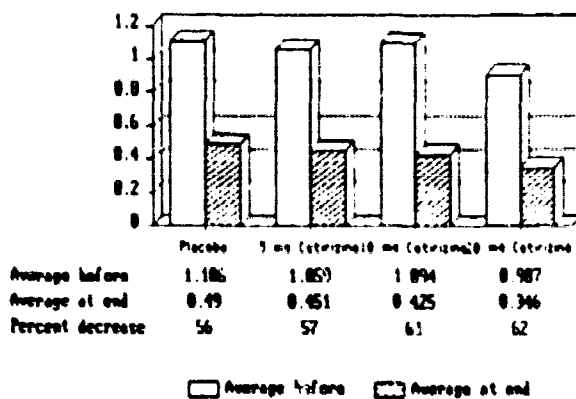
SNR-1

NASAL CONGESTION Patient Diary



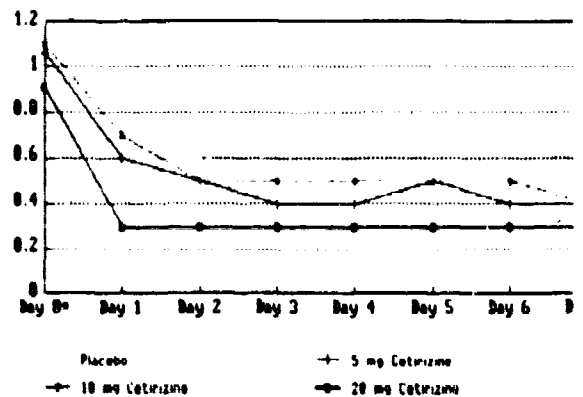
• Taken from Investigator Ratings

Itching Roof of Mouth Investigator Rating



SNR-1

Itching Roof of Mouth Patient Diary



• Taken from Investigator Ratings

For the majority of allergic rhinitis symptoms, the lowest cetirizine dose (5mg) appears to give significant relief. Doubling or quadrupling the dose does indeed give some further relief, but at the cost of a significant increase in the reported incidence of somnolence.

Pollen counts were not required in the protocol for this study, and the nine sites were widely separated geographically. A close look at the sites and the patient entry dates shows that all locations (varying from San Diego to Kansas City, Cincinnati, Denver, Philadelphia, New Jersey, and Cape Coral, Fla) would be expected to have had significant pollen counts for the stated grasses or weeds at the times under consideration. At our request, the sponsor was able to obtain pollen counts for five of the nine sites during the appropriate times - and these show significant counts of either ragweed or grasses as specified in the protocol. Due to the non-uniform methods of sampling and varying units of measurement, it is not possible to pool these data for analysis. In addition, a site by site analysis done by the company did not show any significant variation.

SAR-2

This study is a multicenter (3 sites), two-week, double-blind, parallel, placebo-controlled trial of the safety and efficacy of different dosing regimens of cetirizine in the treatment of seasonal allergic rhinitis. The dose was 10 mg per 24 hours - either as 10mg QAM, 10mg QHS, or 5mg BID. The cetirizine was administered as capsules, not the to-be-marketed dosage form. Entry requirements included a minimum symptom score of 8 (excluding nasal congestion), and all patients who received 6 or more doses (three days, as dosing was bid) were rated for efficacy. Grass pollen allergy was documented by RAST or skin testing. Patients with perennial allergic rhinitis could be entered if they had an acute seasonal exacerbation.

Of the 204 patients entered into this study, 198 were evaluable for efficacy and 200 were evaluable for safety. Four patients were excluded from both safety and efficacy analyses. Of these, three patients were lost to follow-up after the initial visit and one patient did not take study drug. Two additional patients were excluded from all efficacy analyses: one because of the presence of an upper respiratory infection and another because of a protocol violation.

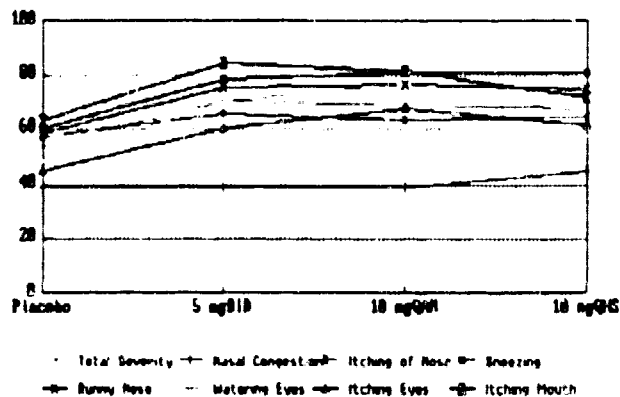
Patients were randomly allocated to one of four treatment groups: cetirizine 5mg BID, cetirizine 10mg QAM, cetirizine 10mg QHS or placebo. Of the 198 efficacy evaluable patients, 51, 48, 49 and 50 were treated with placebo, cetirizine 10mg QAM, cetirizine 10mg QHS and cetirizine 5mg BID, respectively. Patients rated symptoms on arising in the morning, and at bedtime - thus giving a measure of efficacy at 12 and 24 hours after medication. Symptom severity was rated on a four-point scale by both the investigator and the patients. The investigator evaluated the symptoms prior to treatment and at the end of the first and second week of treatment. A global assessment of the therapeutic efficacy of the study drug was made by the investigator at the end of the study.

The principal investigators were:

85-N-0045	Steven Wasserman - San Diego, CA	88 patients
	patients entered 5/21/85 through 6/7/85	
85-N-0046	David Tinkleman - Atlanta, Georgia	72 patients
	patients entered 5/9/85 through 6/28/85	
85-N-0051	Donald Aaronson - Des Plaines, Iowa	44 patients
	patients entered 6/3/85 through 6/29/85	

Looking at the efficacy as percentage decrease in symptoms from baseline to the end of the study shows no significant difference in any of the parameters between the three cetirizine regimens.

EFFICACY IN SAR-2 PERCENT DECREASE IN SYMPTOMS



INVESTIGATOR RATINGS

For the first week, the patient's rating showed a single daily dose of 10mg given QAM or QHS to be significantly superior to placebo in relieving sneezing, rhinorrhea, nasal pruritus, ocular pruritus and tearing. The 5mg BID dose was significantly effective for the first three symptoms noted above, but not for the latter two. Total symptom scores were significantly lower than placebo for all cetirizine regimens, which did not differ from one another. During the second week, placebo scores improved daily, so that by day 13 there was essentially no difference between cetirizine and placebo. The mean severity rating over the entire treatment period (Repeated Measures Analysis) showed all three cetirizine regimens to be significantly better than placebo - see Appendix A, p.3.

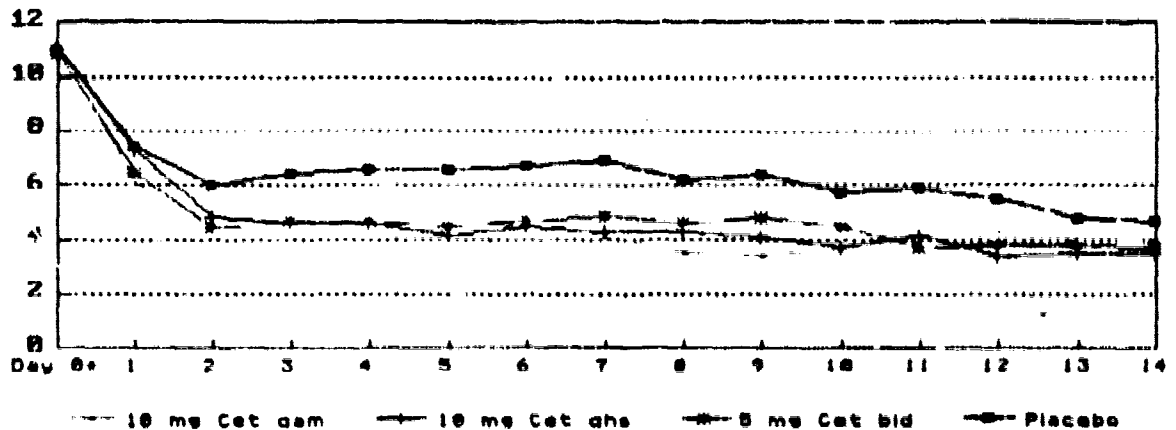
The investigator's ratings and global assessment generally supported the results of the patient's evaluations. The incidence of adverse experiences was not significantly different among the cetirizine groups.

NDA 19835

6 OF 11



TOTAL SEVERITY SAR-2 Patient Diary



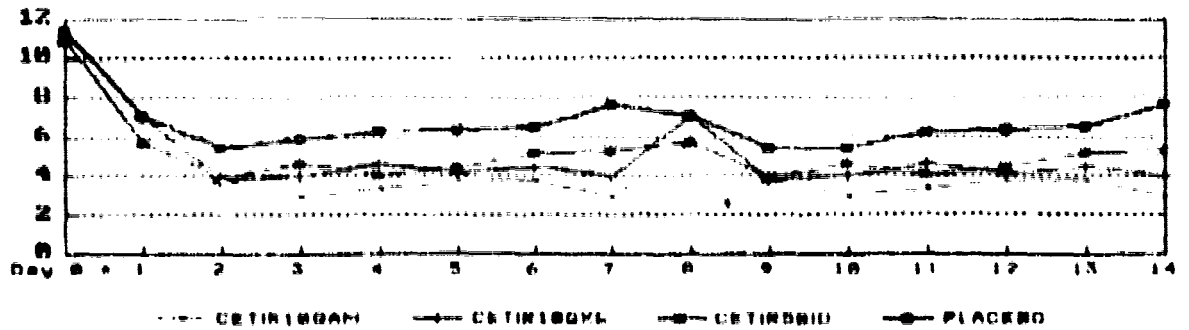
Investigator Rating

Total Symptom Score plotted with AM and PM evaluations (Appendix A, p.24) show the same picture, with the 10mg HS dose having a smoother curve, although there is no statistical difference between the various cetirizine regimens.

This study supports the efficacy claim for cetirizine 10mg on a once-daily basis. Efficacy as measured at 12 and 24 hours post-dosing was comparable and significantly better than placebo. In addition, it demonstrates that dividing the dose does not increase efficacy or improve toleration. The dose can be given in the morning or at night with equal efficacy.

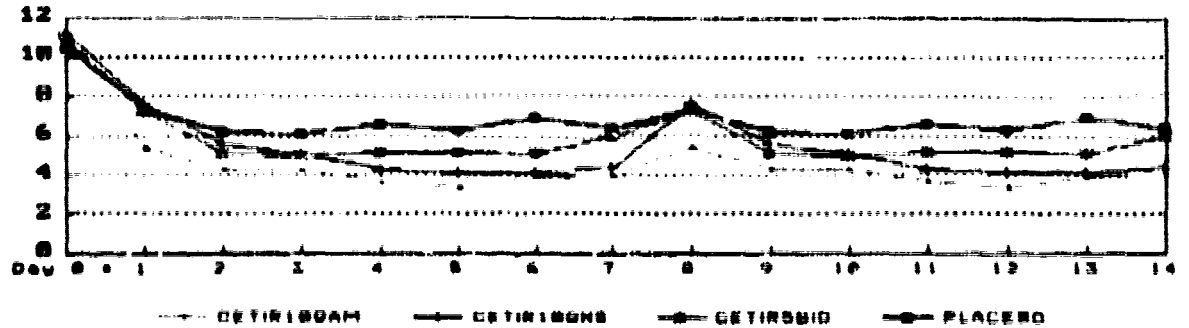
Pollen counts were not required in the protocol, however, the sponsor was able to obtain these at our request for all three sites. Looking at the entry dates at the three sites in terms of the pollen counts obtained - it appears that only site 45 had high counts throughout the entire study period. The improvement in placebo scores towards the end of the study may be due to a decrease in the prevalent pollen count at two of the three sites - and a consequent spontaneous improvement of symptoms. Separating the sites for efficacy evaluation shows a distinct effect from cetirizine over placebo throughout the two-week period at site 45, but not at the other two.

WK 1: TOTAL SEVERITY 85N0045 N-22/22/22/22



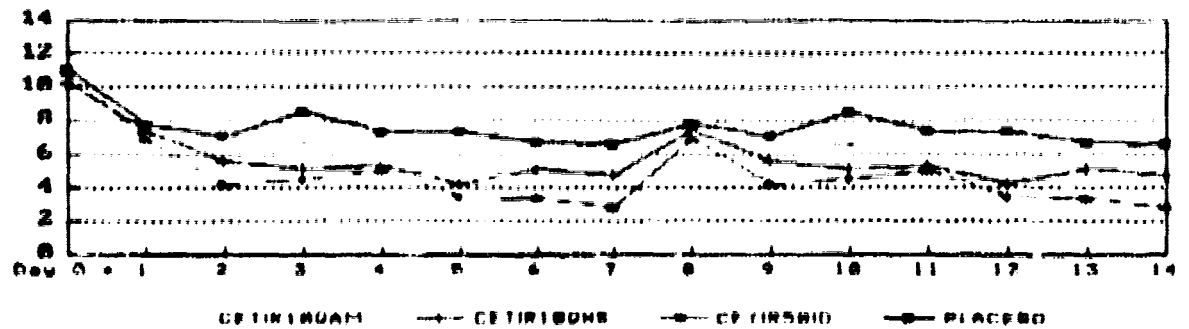
SAN DIEGO, CA
Investigator Rating

WK 1: TOTAL SEVERITY 85N0046 N-18/19/17/18



ATLANTA, GA
Investigator Rating

WK 1: TOTAL SEVERITY 85N0051 N-10/10/12/12



CHICAGO, IL
Investigator Rating

SAR-3

This was a multi-center (5 sites), two-week, double-blind, parallel, placebo and positive-controlled study. Four groups were studied, 5mg cetirizine QAM, 10mg cetirizine QHS, chlorpheniramine SR 8mg BID, and placebo. All patients had documented grass pollen allergy with an acute seasonal exacerbation. Entry requirements included a minimum total symptom score of 10 (including nasal congestion). All patients on treatment for a minimum of 3 days were included in the efficacy analysis. The severity of six symptoms of seasonal allergic rhinitis was rated on a four-point scale by both the investigators and patients. Patients rated symptom severity twice each day during the study - again giving 12 hour and 24 hour post-dosing evaluations. The investigators evaluated efficacy parameters prior to therapy and at the end of the first and second weeks. A global assessment of the therapeutic efficacy of the study drug was made by each patient at the end of the trial.

Out of a total of 314 patients entered, 303 patients were evaluable for efficacy. Four patients were excluded from the safety evaluation, three of these were lost to follow-up, and one did not take the study medication. Of the other seven patients excluded from the efficacy analysis, 6 were discontinued early for ADR's (mainly somnolence), and one developed an upper respiratory infection.

The incidence of somnolence was 10.4% for placebo, 23.4% with chlorpheniramine SR 8mg BID, 16.9% with 5mg cetirizine, and 21.5% for 10mg cetirizine.

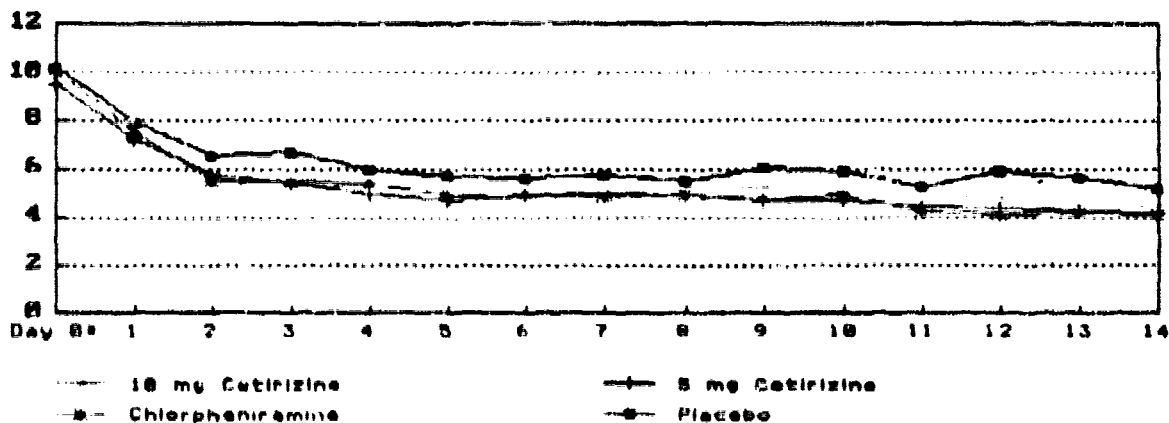
The dosage form used was capsules - not the to-be-marketed formulation.

The principal investigators were:

85-N-0065	Herbert Mansmann, Jr., M.D. Philadelphia, PA	78 patients
	entry dates: 8/26/85 - 9/25/85	
85-N-0066	David Tinkelman, M.D. Atlanta, GA	80 patients
	entry dates: 8/26/85 - 10/9/85	
85-N-0067	Guy Settignano, M.D. Providence, RI	27 patients
	entry dates: 9/6/85 - 9/21/85	
85-N-0068	Don Q. Mitchell, M.D. Jackson, MS	66 patients
	entry dates: 8/28/85 - 10/9/85	
85-N-0069	Harold B. Kaiser, M.D. Minneapolis, MN	63 patients
	entry dates: 8/22/85 - 9/17/85	

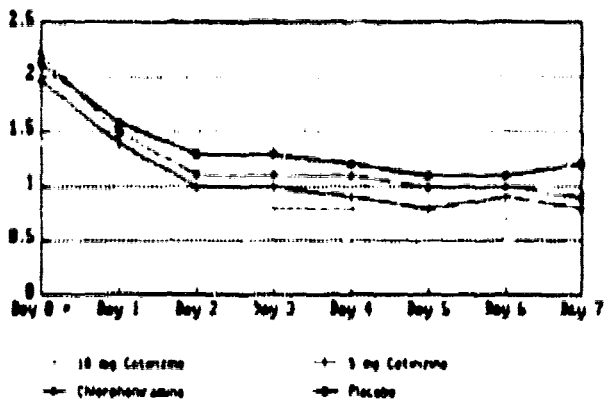
Statistically (Appendix A, p.3), all three active regimens were significantly ($p < .05$) superior to placebo in total symptom score and in controlling sneezing in the patient's assessment, and cetirizine 5mg QAM and chlorpheniramine were significantly more effective than placebo in relieving nasal pruritus. The clinical significance is questionable - as demonstrated by the following graphs:

Total Severity SAR-3 Patient Rating



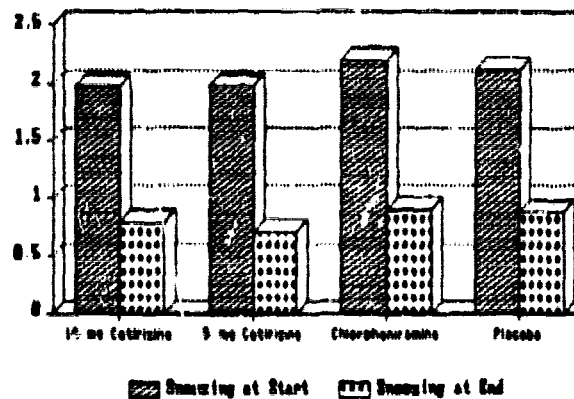
investigator Rating

Sneezing - Week 1 SAR-3



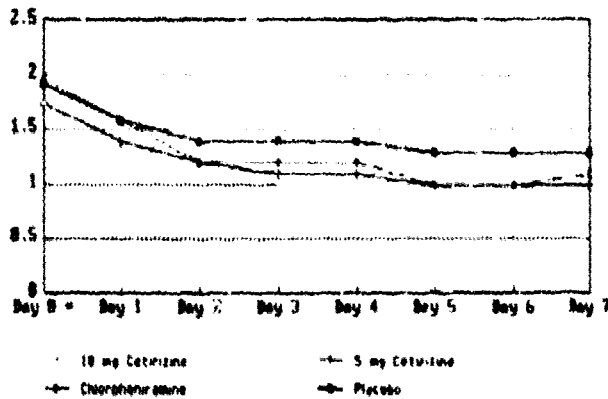
Patient Rating (investigator score)

Sneezing in SAR-3 Average Before and After



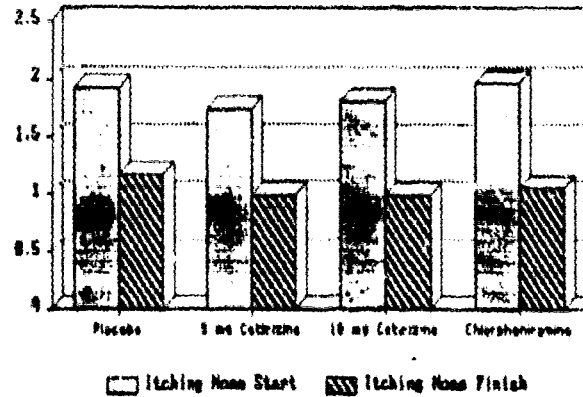
investigator Rating

**Itching Nose - Week 1
SAR-3**



Patient Rating (investigator score)

**Itching Nose in SAR-3
Average at Start and Finish**



Investigator Rating

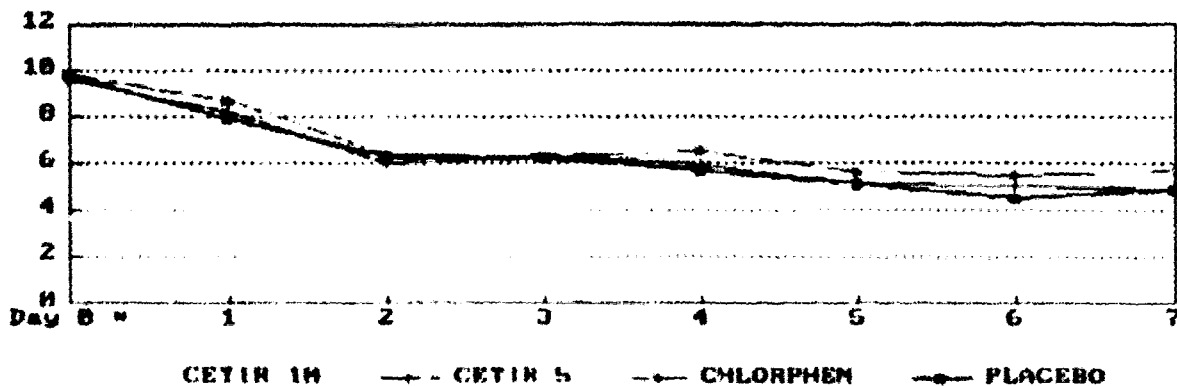
Other symptom ratings in the patient's assessment were numerically superior for the active drug groups compared with placebo, but the differences were not statistically significant. The TSS plotted for AM and PM evaluations (Appendix A, p.25) appeared to support once-daily dosing for cetirizine.

The investigator's symptom ratings and medication efficacy evaluation did not significantly distinguish between placebo and any active medication.

This study failed to show a clinically significant difference between the positive control and the placebo, suggesting a basic problem with the study.

Looking at the pollen counts at the various centers, it is apparent that only center 68 (Jackson, Mississippi) had high counts throughout the study period. A look at the efficacy for this center shows the following.

**WK1: TOTAL SEVERITY
85N0068
N=16/16/17/16**



Investigator Rating

Even at this site, there is no discernible differentiation between placebo effect and either drug - confirming the problem with the execution of the study. This study thus cannot be considered "adequate and well-controlled" - efficacy data are meaningless, but the safety data add to the overall data-base.

-SAR-4

This was a four-week, multi-center (5 sites), double-blind, parallel, placebo-controlled comparison of cetirizine 5mg QAM and terfenadine 60mg BID. Of a total of 235 patients entered, 231 patients were evaluable for efficacy. Of the four patients excluded from efficacy, one was lost to follow-up, one did not take medication, and two patients took study drug for less than three days. The two patients excluded from the safety analyses were the patients lost to follow-up and the patient who did not take any medication. Entry requirements included documented grass pollen allergy, with a minimum total symptom score of 10 (including nasal congestion). Patients were randomly assigned to one of three treatment groups: cetirizine 5mg QAM, terfenadine 60mg BID or placebo. The investigator rated the severity of six rhinitis symptoms prior to treatment and at the end of the second and fourth weeks. Patients rated symptom severity daily in a diary. Cetirizine was taken in the morning, and evaluations were done just prior to dosing - providing a measure of efficacy 24 hours after medication. At the end of treatment, the investigator and patient made a global assessment of the therapeutic effect of study drug.

The dosage form was cetirizine capsules, not the to-be-marketed formulation.

The principal investigators were:

86-N-0047 Stephen Wasserman, M.D. San Diego, CA entry dates: 5/29/86 - 7/15/86	60 patients
86-N-0048 Leonard Altman, M.D. Seattle, WA entry dates: 6/20/86 - 7/24/86	50 patients
86-N-0049 Ned Whitcomb, M.D. Carmichael, CA entry dates: 5/22/86 - 6/5/86	50 patients

86-N-0050 Richard Lockey, M.D.

54 patients

Tampa, FL

entry dates: 6/11/86 - 6/29/86

86-N-0074 Phillip Lieberman, M.D.

21 patients

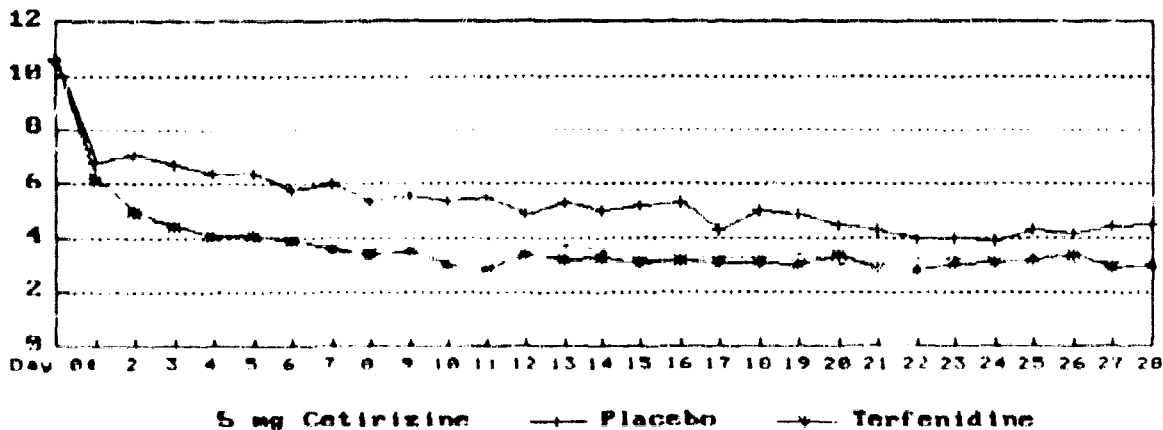
Memphis, TN

entry dates: 5/27/86 - 6/13/86

The mean severity rating over the entire 4-week treatment period (Appendix A, p.3) showed 5mg cetirizine to be significantly better than placebo - and comparable to terfenadine 60mg bid - for sneezing, rhinorrhea, nasal and ocular pruritus, and total symptom severity. Tearing was numerically improved, but not statistically significant. In the by-week analysis, cetirizine 5mg provided significant improvement in total symptom severity, itching of the nose, sneezing, watery nasal discharge, and itching of eyes during weeks 1, 2 and 3. Terfenadine was also significantly better than placebo in relieving total symptom severity during weeks 1, 2 and 3 and provided significant relief of itching of the nose (weeks 1-3), sneezing (weeks 1-4), watery nasal discharge (weeks 2-3) and watering of eyes (week 1) at various times during the treatment period. Although both cetirizine and terfenadine maintained lower total symptom severity scores than placebo during week 4, the placebo effect was great enough that the differences between active treatment and placebo were not statistically significant.

Results from the investigator ratings were consistent with patient ratings showing that both cetirizine 5mg and terfenadine significantly improved total symptom severity and alleviated itching of the nose, sneezing, watery nasal discharge and itching of eyes during the four-week treatment period.

TOTAL SEVERITY SAR-4 Patient Diary



Investigator Rating

The placebo effect improved throughout the 4 week study period. By week 4, there was no longer a significant difference between any of the groups. Pollen counts at the various sites showed that only sites 49 and 50 had consistently high counts throughout the study period. Separating the efficacy curves for the five sites however show no apparent correlation with the pollen counts. The pollen counts were not sampled by any one method, making potential correlations tenuous at any rate.

Adverse effects centered mainly on reported sedation. The cetirizine group reported a 13% incidence of somnolence, while both the placebo group and the terfenadine group reported a 5% incidence.

Overall, this study supports the efficacy of 5mg cetirizine daily for the symptomatic relief of seasonal allergic rhinitis. The efficacy appears comparable to that of 60mg terfenadine bid. The incidence of somnolence in the cetirizine group was more than double that seen with placebo or terfenadine.

SAR-5

This was a four-week, multicenter (4 centers), double-blind, parallel, placebo-controlled comparison of cetirizine 10mg QAM and terfenadine 60mg BID. Two hundred and ten (210) patients with documented ragweed pollen allergy and an acute seasonal exacerbation were entered in this study. Entry requirements included a minimum total symptom score of 10 (including nasal congestion).

Patients were randomly assigned to one of three treatment groups: cetirizine 10mg QAM, terfenadine 60mg BID or placebo. The dosage form of cetirizine was capsules, not the to-be-marketed preparation.

Symptoms were assessed by both the investigator and patients using a four-point scale. Patients rated the severity of six symptoms once daily (just prior to the AM dose). The investigator rated the symptom severity prior to treatment and at the end of the second and fourth weeks. At the end of treatment, the investigator made a global assessment of the therapeutic effect of study drug using a 4-point scale.

Two hundred and five (205) patients were evaluable for efficacy and 208 were evaluable for safety. The two patients who were not evaluable for safety and efficacy withdrew before taking study medication. Of the 3 other patients excluded from all efficacy analyses, two were non-compliant, and one had a concurrent illness which led to exclusion of the patient's efficacy data.

A significant treatment by center interaction was found at one site(86-N-0051). Since the results at this location differed markedly from the other three sites, the sponsor separated all 54 patients at that site from all efficacy but not safety analyses in the final analysis .

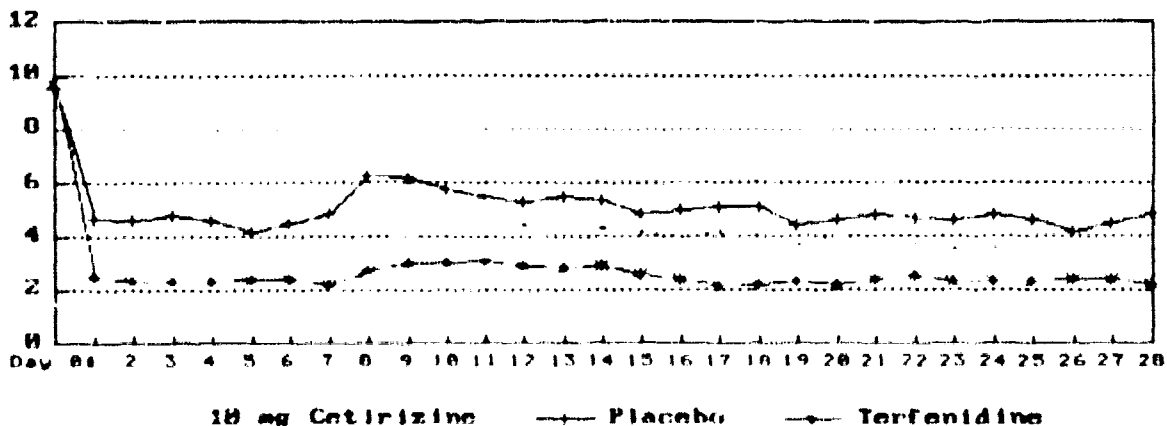
The principal investigators were:

86-N-0051	Constantine J.Falliers, M.D. Denver, Colorado entry dates: 8/15/86 - 8/25/86	54 patients
86-N-0052	Jay Grossman, M.D. Albany, New York entry dates: 8/18/86 - 9/9/86	54 patients
86-N-0053	Jerome Miller, M.D. Bala Cynwyd, Pennsylvania entry dates: 8/18/86 - 9/18/86	54 patients
86-N-0054	Howard Schwartz, M.D. Cleveland, Ohio entry dates: 8/25/86 - 9/5/86	48 patients

Cetirizine and terfenidine were more effective than placebo for most symptoms, although the differences did not reach statistical significance.

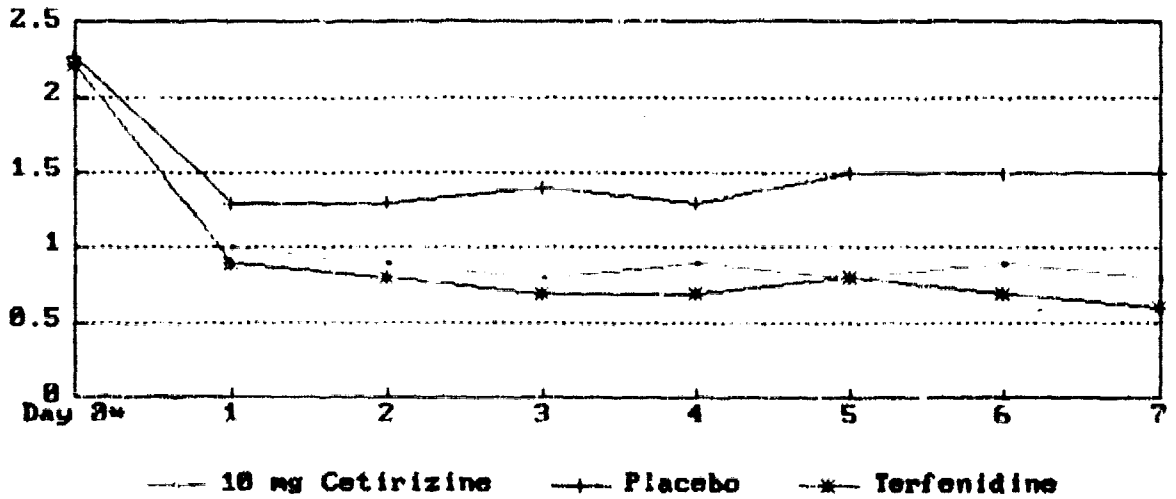
In the patient's efficacy assessment, both active treatments were significantly superior to placebo in controlling sneezing. Numerical superiority to placebo was seen for total symptom score and for several other symptoms, although the differences did not reach statistical significance. Cetirizine and terfenadine did not significantly differ from one another in any patient rating.

TOTAL SEVERITY SAR-5 Patient Diary



Investigator Rating

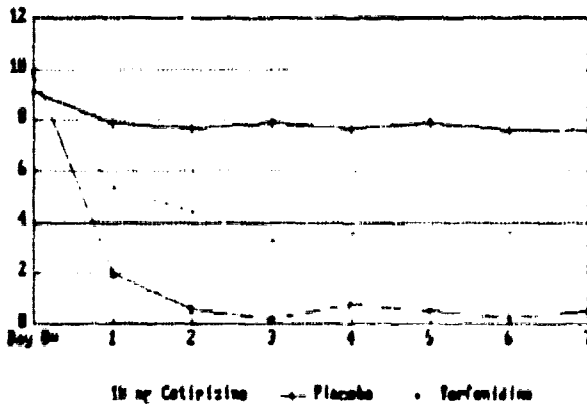
SNEEZING in SAR-5 Patient Rating



*from Investigator's Rating

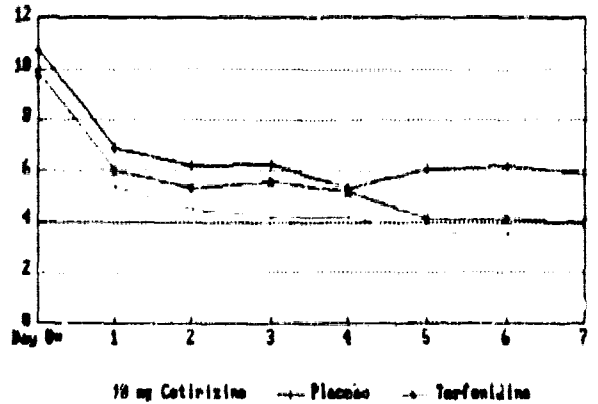
Taking the four sites individually, the patient diary ratings for the first week show the following for total symptom severity and sneezing:

**TOTAL SEVERITY, patient diary
SAR-5, 86N0051**



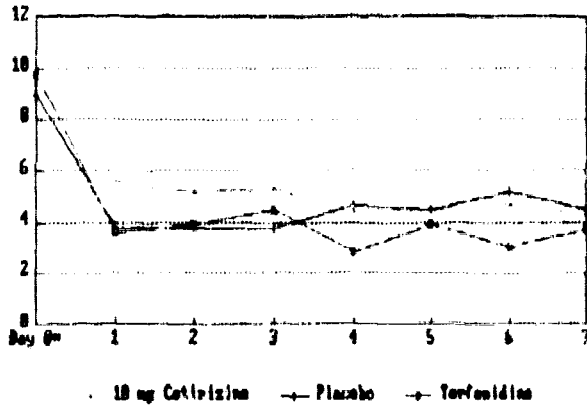
*Investigator Rated

**TOTAL SEVERITY, patient diary
SAR-5, 80N0052**



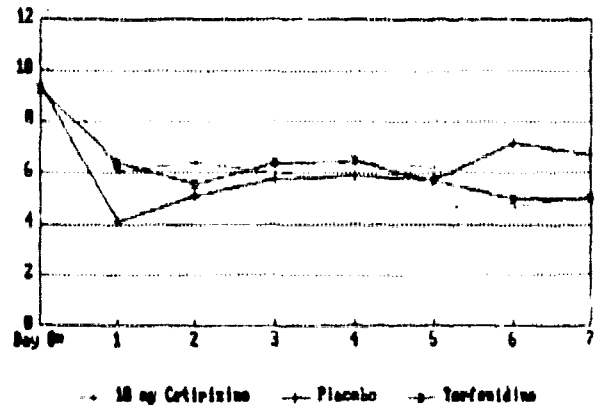
*Investigator Rated

TOTAL SEVERITY, patient diary
SAR-5, 86N0053



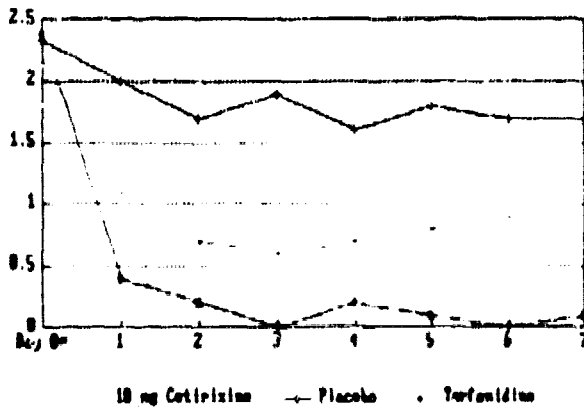
Investigator Rating

TOTAL SEVERITY, patient diary
SAR-5, 86N0054



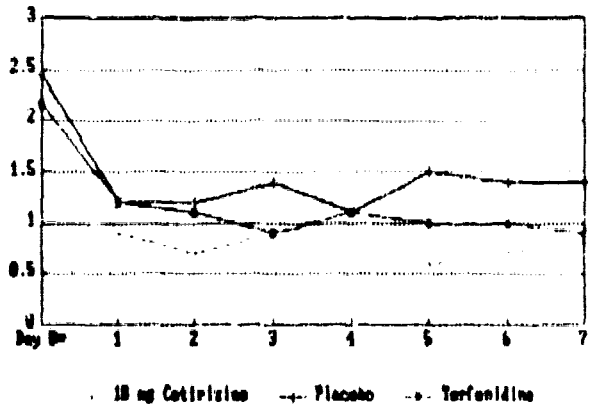
Investigator Rating

SNEEZING, patient diary
SAR-5, 86N0051



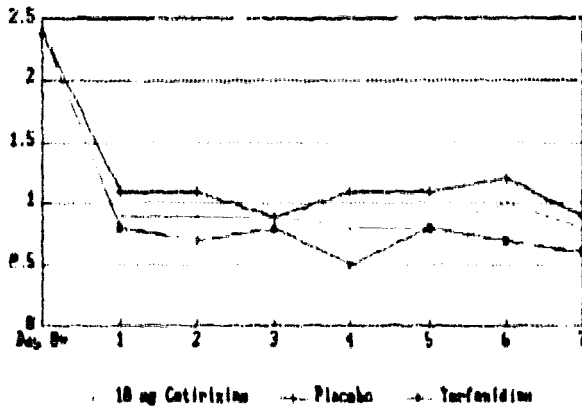
Investigator Rating

SNEEZING, patient diary
SAR-5, 86N0052



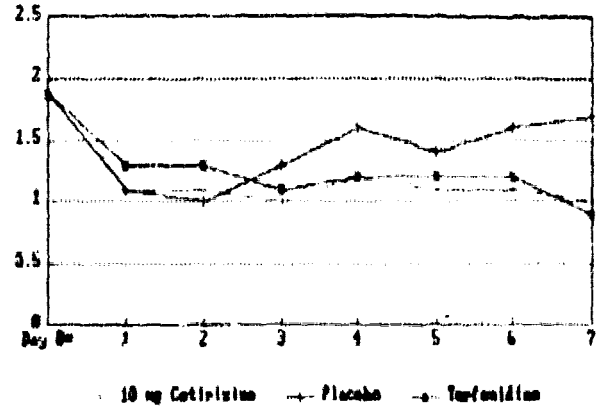
Investigator Rating

SNEEZING, patient diary
SAR-5, 86N0053



Investigator Rating

SNEEZING, patient diary
SAR-5, 86N0054

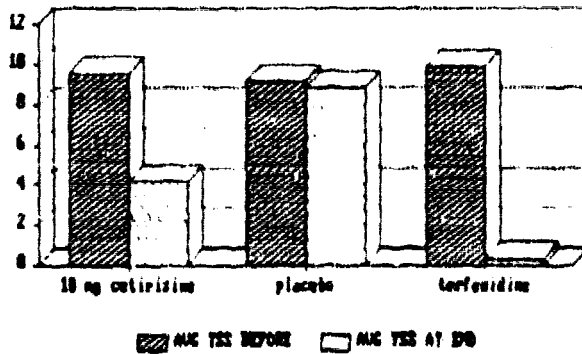


Investigator Rating

In the investigators' global assessment of therapeutic activity, there were no significant differences among the 3 treatment groups. Fewer patients in the active treatment groups dropped out of the study due to inadequate response compared with the placebo group, although the differences were not statistically significant.

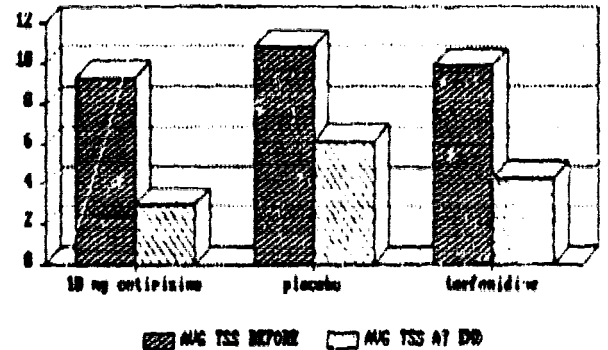
Looking at the individual sites again, a pattern similar to that in the patient diaries is seen:

TOTAL SEVERITY
SAR-5, 86N-0051
Investigator rating



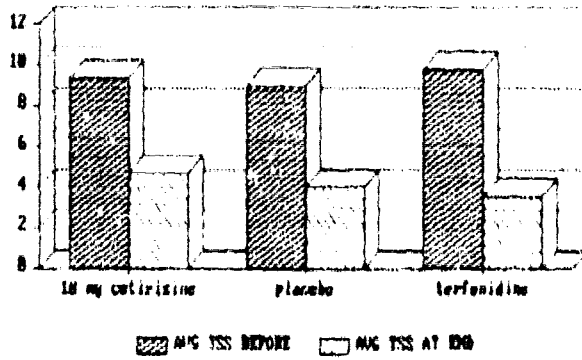
TSS-total symptom score

TOTAL SEVERITY
SAR-5, 86N-0052
Investigator rating



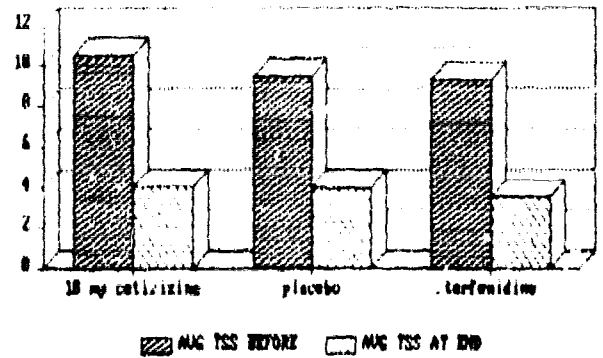
TSS-total symptom score

TOTAL SEVERITY
SAR-5, 86N-0053
investigator rating



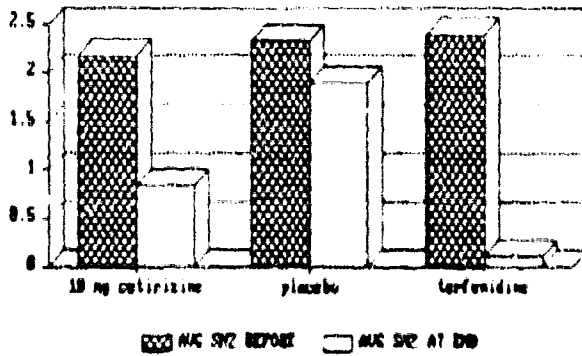
TSS: total symptom score

TOTAL SEVERITY
SAR-5, 86N-0054
investigator rating

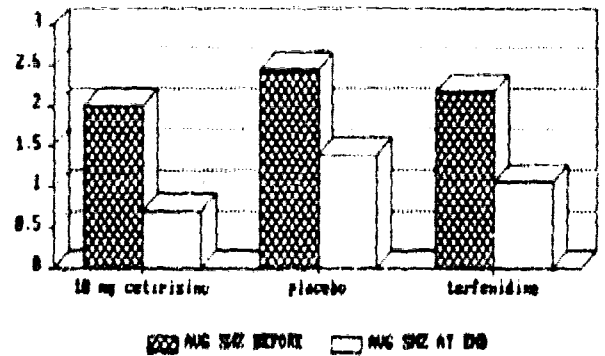


TSS: total symptom score

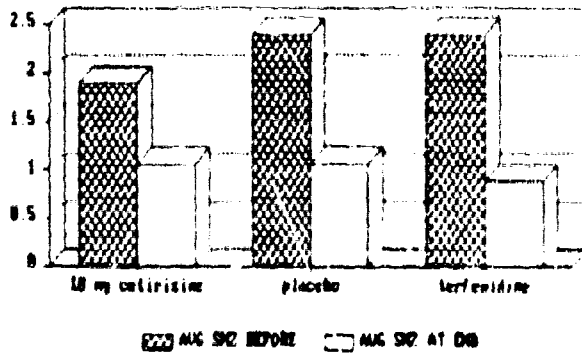
SNEEZING
SAR-5, 86N-0051
investigator rating



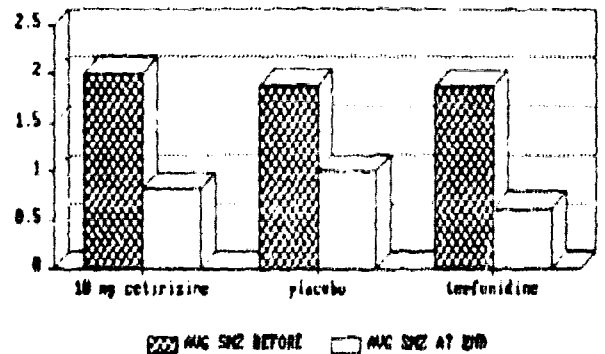
SNEEZING
SAR-5, 86N-0052
investigator rating



SNEEZING
SAR-5, 86N-0053
investigator rating



SNEEZING
SAR-5, 86N-0054
investigator rating



efficacy.

Headache was the most common adverse experience in all three treatment groups, followed by somnolence. The incidence of somnolence in the cetirizine group was 10% compared with 4% in both the terfenadine and placebo groups.

This study as a whole indicates that cetirizine 10mg QAM is safe and marginally effective in alleviating the symptoms of seasonal allergic rhinitis and is comparable to terfenadine 60mg BID. Somnolence in the cetirizine group again was over twice that reported in the placebo and the terfenadine groups. Looking at the one site able to differentiate between the placebo and the positive control, cetirizine appears definitely effective for the symptomatic relief of seasonal allergic rhinitis - although the miraculous results obtained with terfenadine here put a question mark on the study.

In summary, the five placebo-controlled seasonal allergic rhinitis studies presented here show:

- A - 5mg cetirizine once-daily provides good symptomatic relief of seasonal allergic rhinitis as presented in this NDA.
- B - Once-daily dosing appears justified on the basis of evaluations at 12 hrs (SAR 1, 2 and 3) and 24 hrs (SAR 2, 3, 4 and 5) after dosing. SAR 2 and 3 had evaluations done at both 12 and 24 hours post-dosing, and there was very little difference between the two. In addition, preclinical studies showed that inhibition of histamine-induced wheal-and-flare response in the skin is still evident at 24 hours.
- C - Increasing the dose to 10 or 20mg improves the efficacy for some parameters slightly, but at a cost of significantly more reported somnolence.
- D - 5mg cetirizine once daily appears comparable in efficacy to 60mg terfenadine bid or 8mg chlorpheniramine S.R. bid.
- E - The incidence of reported somnolence at a dose of 5mg once daily is statistically comparable to placebo and terfenadine, although it is consistently larger numerically. The incidence of somnolence increases in a dose-related manner, and is significantly greater than that seen with placebo or terfenadine when the dose of cetirizine exceeds 5mg daily.

- F - No unusual or unexpected adverse reactions were reported. The ADR's were primarily confined to somnolence and headache, were not serious, and did not require active treatment.
- G - The number of patients who did not complete treatment for any reason was 33/1382. The distribution was comparable in all groups.
- H - A graphic summary of the five studies in terms of location, season, and incidence of somnolence is presented on the next few pages.

SEASONAL ALLERGIC RHINITIS GEOGRAPHIC LOCATIONS AND DATES

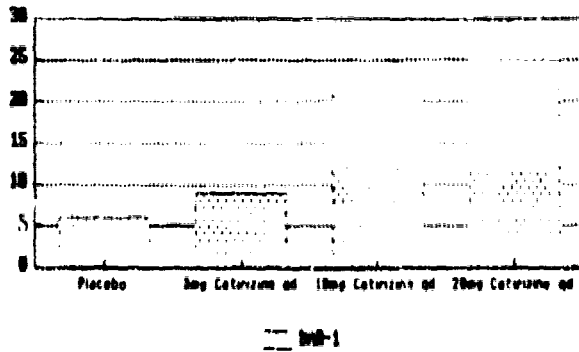
SAR-1	AUGUST THROUGH DECEMBER 1984	N=419
	PA, FL, NJ, MO, KS, CA, OH, CO, CA	
SAR-2	APRIL THROUGH AUGUST 1985	N=204
	CA, GA, IA	
SAR-3	AUGUST THROUGH OCTOBER 1985	N=314
	PA, GA, RI, MB, MN	
SAR-4	MAY THROUGH AUGUST 1986	N=235
	CA, WA, CA, FL, TN	
SAR-5	AUGUST THROUGH OCTOBER 1986	N=210
	CO, NY, PA, OH	

SEASONAL ALLERGIC RHINITIS EFFICACY

	# sites	N	duration	control	placebo	efficacy
SAR-1	9	419	1 week		yes	yes
SAR-2	3	204	2 weeks		yes	yes
SAR-3	5	314	2 weeks	chlorphen iramine	yes	???
SAR-4	5	235	4 weeks	terfenidine	yes	yes
SAR-5	4	210	4 weeks	terfenidine	yes	1 site only

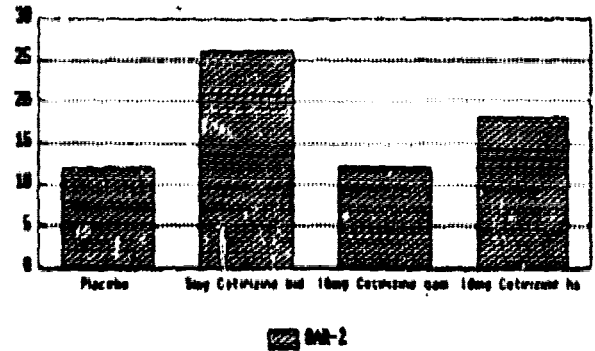
Efficacy

SAR-1
PERCENT SOMNOLENCE REPORTED
N=415



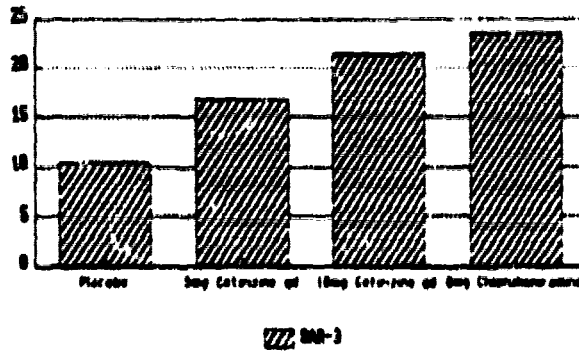
14 patients excluded, 3 were lost to follow-up, one did not take medication

SAR-2
PERCENT SOMNOLENCE REPORTED
N=200



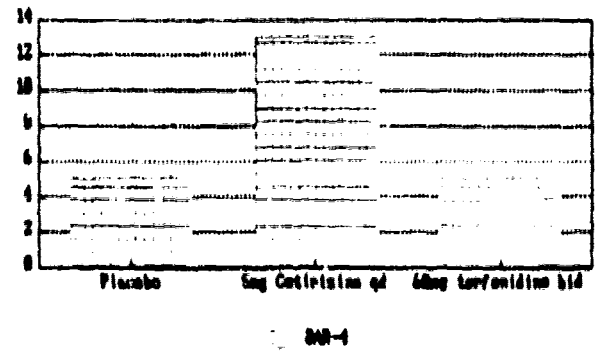
14 patients excluded, 3 lost to follow-up, one did not take medication

SAR-3
PERCENT SOMNOLENCE REPORTED
N=310



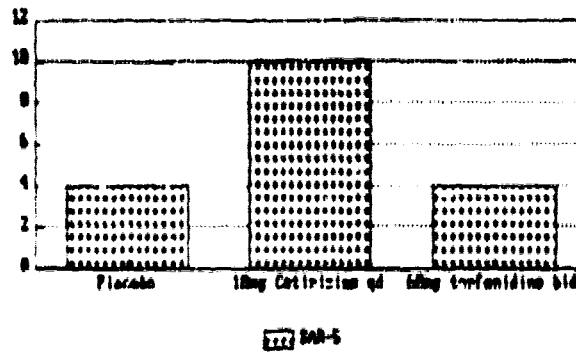
14 patients excluded, 3 lost to follow-up, one did not take medication

SAR-4
PERCENT SOMNOLENCE REPORTED
N=233



12 patients excluded, one lost to follow-up, one did not take medication

SAR-5
PERCENT SOMNOLENCE REPORTED
N=208

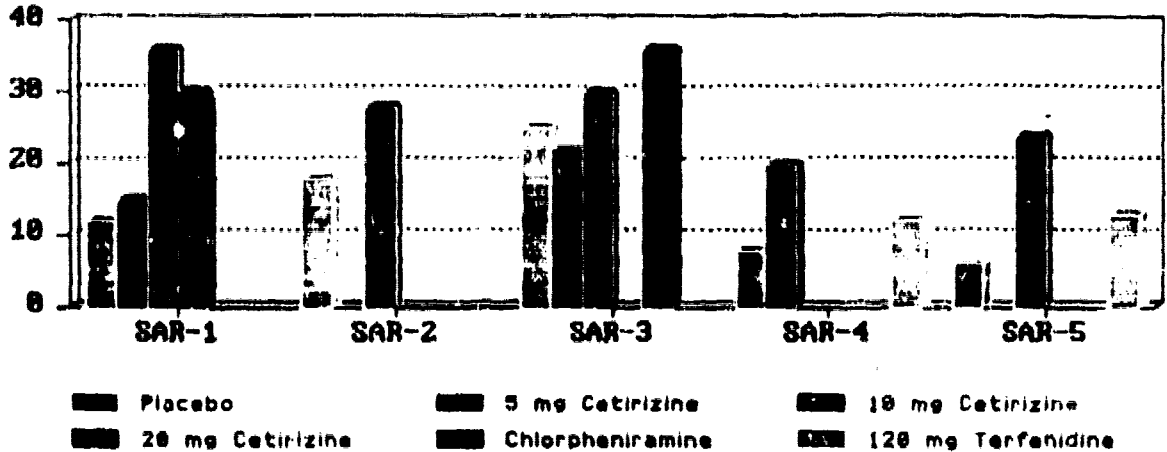


12 patients excluded, did not take medication

Finally, the incidence of "sedative type" ADR's in the five seasonal allergic rhinitis studies can be compared in the following graph (reports of somnolence, dizziness, fatigue, ataxia, stupor, confusion and impaired concentration were combined as related symptoms).

ADR's IN SAR 1-5

Somnolence and related symptoms Percent reported



B - Perennial Allergic Rhinitis

daily dosage

CLAIM: Cetirizine is indicated for the relief of symptoms associated with perennial allergic rhinitis. Symptoms treated effectively include post-nasal discharge, sneezing, rhinorrhea, nasal pruritus, tearing and ocular pruritus.

In support of the perennial claim, three double-blind, parallel, placebo-controlled multicenter studies are submitted. Cetirizine 5-20 mg/day was administered to patients with perennial allergic rhinitis for periods of four to six weeks. One of the four-week trials (PAR-3) had an eight-week open-label extension. In each study, seven symptoms of rhinitis were rated, using a four-point scale (0=none, 1=mild, 2=moderate, 3=severe), once-daily during the study by the patients (weekly during the open-label phase of PAR-3) and at baseline and at study visits by the investigator, who also rated the overall effectiveness of the medication in each patient at the final study visit (and at the end of the double-blind phase of PAR-3). The patient's daily evaluations were considered the principal efficacy parameter.

Pseudoephedrine was allowed as rescue medication, and was recorded and analyzed. Use of topical nasal decongestants however was not recorded, and was not excluded.

A total of 629 patients were randomized to study medication. Of these, 17 were excluded from the efficacy analysis for various (non-efficacy related) reasons. The remaining 612 patients (97.3% of those entered) were evaluated for efficacy, including 20 who discontinued double-blind study participation due to lack of response.

PAR-1

This was a four-week, randomized, six-center, double-blind, placebo-controlled study of cetirizine 10 and 20mg QAM, in patients with documented (verified by skin testing) perennial allergic rhinitis. A minimum symptom score of 8 (including nasal congestion) was required for entry, and the perennial nature of the allergy was characterized by a lack of amelioration or worsening of symptoms during November through March. Of a total of 220 patients who entered the study, 215 were evaluable for efficacy (143 on cetirizine and 72 on placebo) and 216 were evaluated for safety. Of the five patients excluded, two patients had been entered twice (at different sites - Kansas City, MO and Prairie Village, KS). One of these patients was excluded once for safety and once for efficacy analyses (he had started on 20mg cetirizine on 2/14/85 at KS, then entered into the placebo group at MO on 2/20/85, but was D/C'd after 2 visits), the second patient was excluded once for safety analyses and twice for efficacy analyses (he was entered into the placebo group at both sites, and completed the course at both places, overlapping two weeks). Of the two additional patients excluded from both safety and efficacy analyses, 1 patient withdrew from the study because of concurrent illness and 1 was lost to follow-up.

Medication used was in capsule form, not the to-be-marketed tablet form.

The study was performed from January 1985 through April 1985.

The principal investigators were:

84-N-0053	Philip T. Leese, M.D. Kansas City, MO Start Date 1-23-85	28 patients Stop Date 4-14-85
84-N-0056	Robert J. Dockhorn Prairie Village, KS Start Date 1-31-85	48 patients Stop Date 4-02-85
84-N-0061	Elwood Buchman, M.D. Cincinnati, OH Start Date 1-25-85	32 patients Stop Date 4-04-85
84-N-0064	Herbert C. Mansmann, Jr., M.D. Philadelphia, PA Start Date 1-28-85	43 patients Stop Date 3-29-85

84-N-0064	Herbert C. Mansmann, Jr., M.D. Philadelphia, PA Start Date 1-28-85	43 patients Stop Date 3-29-85
84-N-0065	Bernard A. Berman, M.D. Brookline, MA 02146 Start Date 2-22-85	35 patients Stop Date 4-30-85
84-N-0114	Elliott Middleton, Jr., M.D. Buffalo, NY Start Date 3-08-85	34 patients Stop Date 4-16-85

Serum levels of drug were monitored at the week 1 and week 4 visits in all 27 patients enrolled at site 84-N-0053 (note - this is the same site where blood levels were monitored in SAR-1). Of these 27 patients, 19 received cetirizine (Appendix A, p.9-10).

All patients who received at least three doses of study medication were evaluated for efficacy.

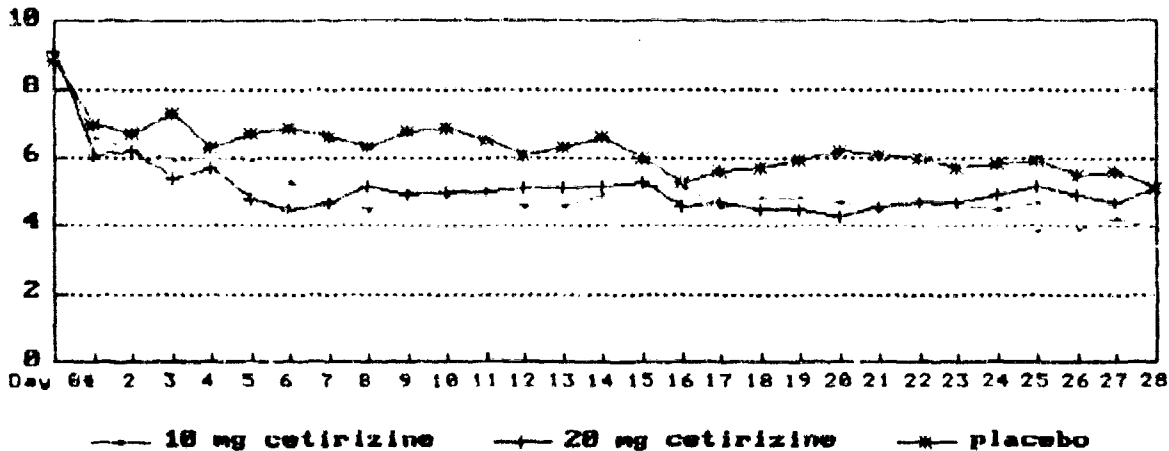
The results of the mean daily patient assessment (by repeated measures analysis) showed both cetirizine 10mg and 20mg QAM to be significantly (Appendix A, p.16) superior to placebo in relieving post-nasal discharge and sneezing, and reducing the severity of total symptomatology. The 20mg dose was also significantly better than placebo in the relief of rhinorrhea. The mean total severity on a weekly basis showed a significant difference compared to placebo only for week 2 and 3 with both cetirizine doses, and for week 1 with 20mg cetirizine. Evaluations were recorded in the evening, approximately 12 hours post dose.

Pseudoephedrine was allowed as rescue medication, and its use was tabulated (Appendix A, p.18). There was a statistically significant difference between the placebo and the active drug groups. The total amount used was so small that clinical significance is doubtful. In addition, use of topical nasal decongestants was neither interdicted or recorded - making the numbers meaningless from the start.

Looking at the individual centers, only one center showed a significant difference compared to placebo, both in the patients' and the physicians' evaluation (Appendix A, p.17,18). This center, 84N-0056, in Prairie Village, KS, contributed the largest number of patients (46/215) to the study. It also is the study with the highest score in the placebo group. Without this group, the differences with placebo do not reach statistical significance, although the trend is in the same direction (see statistical review). In addition, there was no evidence of a dose-response effect - if anything, the reverse was true. Especially in the physicians' evaluation - 10mg cetirizine scored better than 20mg in four of the six centers (Appendix A, p.18).

Investigator Global Efficacy Rating
in PAR-1

**TOTAL SEVERITY PAR-1
Patient Diary**



*from investigator rating

In the investigator global assessment of efficacy, both doses of cetirizine were significantly better than placebo, with no significant difference between them. "Good" to "excellent" ratings were achieved in 49% and 54% of cetirizine 10mg and 20mg groups, respectively, compared to 24% on placebo.

Number of Patients (%)

Treatment	Failure	Pair	Good	Excellent
Cet 10mg QAM* N=72	17 (23.6)	20 (27.8)	22 (30.5)	13 (18.1)
Cet 20mg QAM* N=68	14 (20.6)	17 (25.0)	24 (35.3)	13 (19.1)
Placebo N=70	25 (35.7)	28 (40.0)	10 (14.3)	7 (10.0)

Rating scale: failure=no improvement/worse; fair=slight/insufficient improvement; good=definite improvement; excellent=highly effective/complete disappearance of signs and symptoms.

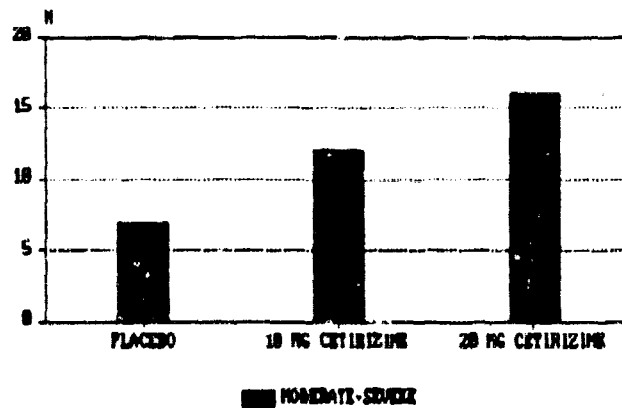
* Treatment effect significantly superior to placebo (p less than or equal to 0.05).

Adverse effects were limited primarily to headache, somnolence, fatigue, dry mouth and dizziness. The incidence of headache was comparable with the placebo group. The three others were as follows:

	Placebo (N=73)	10 mg Cetirizine (N=72)	20 mg Cetirizine (N=71)
Somnolence	16.4%	15.3%	22.5%
Fatigue	2.7%	11.1%	14.1%
Dizziness	2.7%	6.9%	1.4%
Combined	21.8%	33.3%	38 %

Looking at the combined number of patients reporting moderate or severe somnolence, fatigue and dizziness graphically, one gets the following picture:

PAR-1
SOMNOLENCE, FATIGUE and DIZZINESS



number of patients reporting

There clearly is an increased incidence of moderate or severe somnolence, fatigue and dizziness in the cetirizine groups over the placebo. A dose response is suggested as well.

This study supports the claim that cetirizine provides overall symptomatic relief in patients with perennial allergic rhinitis - but only for a short time (2 to 3 weeks). The particular symptoms relieved most are sneezing and postnasal discharge. The 10mg dose appears to provide adequate relief, with little further improvement on increasing the dose to 20mg. The combined incidence of somnolence, fatigue and dizziness is greater with cetirizine than with placebo, and suggests a dose response.

PAR-2

This is a six-week, randomized, five-center, double-blind, placebo and positive-controlled study with three parallel treatment groups: cetirizine 5mg QAM/10mg QHS, chlorpheniramine 8mg BID, or placebo BID.

One hundred and eighty-two (182) patients with documented (by RAST or skin testing) perennial allergic rhinitis were entered into the study; 172 were evaluable for efficacy and 179 were evaluable for safety. Of the 3 patients excluded from both safety and efficacy analyses, 2 did not take study medication and 1 was lost to follow-up. Of the 7 additional patients excluded from all efficacy analyses, 2 withdrew early because of abnormal baseline lab values, 2 because of adverse experiences, 1 for a sinus infection, 1 for an upper respiratory infection, and 1 patient discontinued due to both an upper respiratory infection and an adverse experience. Symptom severity was rated on a four-point scale by both the investigator and patients. A minimum symptom score of 10 (including nasal congestion) was required for entry. Patients rated seven symptoms daily (in the evening) during the six-week study. Investigators evaluated the same parameters at baseline and at the end of the first, third, and sixth weeks. A global assessment of the therapeutic efficacy of the study drug was made by the investigator at the end of the study using a four-point scale.

Medication used was in capsule form, not the to-be-marketed tablet form.

The study was performed from 2/15/86 through 6/2/86.

The principal investigators were:

85-N-0145	Harold B.Kaiser, M.D. Minneapolis, MN Start Date 2/17/86	37 patients Stop Date 4/23/86
85-N-0146	Michael S.Rowe, M.D. Detroit, MI Start Date 3/10/86	30 patients Stop Date 5/02/86
85-N-0148	Edwin A.Bronsky, M.D. Murray, UT 84107 Start Date 2/19/86	42 patients Stop Date 5/27/86
85-N-0149	Salmon Goldberg, M.D. Northbrook, IL Start Date 2/15/86	48 patients Stop Date 4/30/86
85-N-0150	Jay Grossman, M.D. Albany, NY Start Date 2/25/86	25 patients Stop Date 6/02/86

During the first week of the trial, both cetirizine and chlorpheniramine were significantly superior to placebo in reducing the severity of sneezing, runny nose, and overall symptom severity.

In contrast to week 1 results, cetirizine and chlorpheniramine were not significantly better than placebo in alleviating any symptoms (except sneezing in chlorpheniramine patients at week 2, and sneezing in patients taking either active treatment at week 6) or total symptom severity during weeks 2 to 6. Results from the investigator ratings were similar to patient ratings.

At the end of week 3, cetirizine and chlorpheniramine reduced the severity of some of the symptoms compared with placebo but none of the differences were statistically significant. At the end of week 6, both active treatments significantly alleviated sneezing and chlorpheniramine significantly reduced itching of the nose and total symptom severity compared with placebo. A global assessment of therapeutic efficacy was made at the end of the study. The results showed that 38% of the cetirizine group and 42% of the chlorpheniramine group had responses to therapy that were judged either "good" or "excellent" but the differences were not statistically different from the 24% "good" or "excellent" placebo responders. The consumption of the rescue decongestant, pseudoephedrine, in the two active groups was not significantly different from placebo - and is meaningless in any case, being that topical decongestants were not prohibited or recorded.

Headache and somnolence were the most common adverse experiences among the three treatment groups. The frequency of headache was 12% in the cetirizine group, 20% in the chlorpheniramine group and 24% in the placebo group. Somnolence occurred in 12% of the patients treated with cetirizine, 20% of those treated with chlorpheniramine, and 7% of the patients who received placebo.

Neither cetirizine or the positive control was significantly better than placebo after one week.

This study can be said to show that cetirizine provided significant symptomatic relief of perennial allergic rhinitis for one week only, and was comparable to chlorpheniramine in that regard. The incidence of somnolence with cetirizine was greater than with placebo, but less than with chlorpheniramine.

PAR-3

This multicenter, randomized, parallel study consisted of a four-week, double-blind, placebo-controlled phase with dose-titration, followed by an eight-week open phase during which dosage was stable. Cetirizine dose was 5-10mg qam, diphenhydramine was 25-50mg tid. The severity of seven signs and symptoms and overall symptomatology was

evaluated nightly for four weeks and weekly thereafter by patients, using a four-point scale. Investigators performed a similar evaluation and global assessment of efficacy, using a similar scale, at baseline, weeks 4, 8 and 12, as well as an assessment of the degree of sedation. They recorded rescue decongestant use and adverse experiences.

227 patients with documented (by RAST or skin testing) perennial allergic rhinitis were entered into the study: 225 were evaluable for efficacy - 74 were on cetirizine, 75 on diphenhydramine and 76 on placebo. A minimum symptom score of 8 (including nasal congestion) was required for entry. There were no significant differences in demographics or symptom severity, at baseline, among the three treatment groups.

Medication used was in capsule form, not the to-be-marketed tablet form.

The principal investigators were:

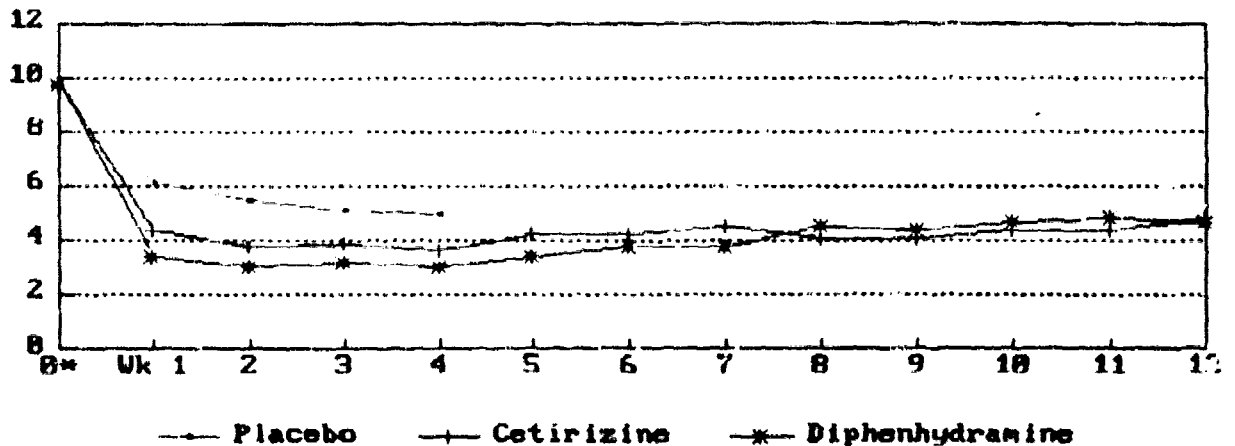
86-N-0152	J.Grossman, M.D. Albany, N.Y. Start Date 2/09/87	42 patients Stop Date 4/07/87
86-N-0153	M.Coleman, M.D. Stamford, CT Start Date 2/10/87	37 patients Stop Date 4/16/87
86-N-0154	J.J.Condemi, M.D. Rochester, N.Y. Start Date 1/27/87	34 patients Stop Date 3/10/87
86-N-0155	J.Fink, M.D. Milwaukee, WI Start Date 2/02/87	34 patients Stop Date 7/09/87
86-N-0156	R.Morris, M.D. Minneapolis, MN Start Date 1/26/87	41 patients Stop Date 3/23/87
86-N-0157	H.Schwartz, M.D. Cleveland, OH Start Date 3/09/87	39 patients Stop Date 4/24/87

The results of patient symptom severity ratings indicate that over the first four weeks of therapy (double-blind phase), both active drugs were significantly better than placebo (Appendix A, pp 19-20) in relieving sneezing, runny nose, watering and itching eyes and itching nose, and in reducing total symptom severity. Diphenhydramine also provided significant relief of post-nasal discharge compared to placebo. The active drugs were similar except during the first week of therapy (prior to titration to the higher dosage) when diphenhydramine was significantly better than cetirizine in relieving sneezing and runny nose, and reducing total symptom severity. A significantly higher

proportion of patients on cetirizine (37%) and diphenhydramine (51%) remained on the lower dosage as compared to placebo (18%).

Looking at the patients' mean total severity ratings on a weekly basis over the entire treatment period - an interesting picture emerges:

PAR-3, Total Symptom Severity Pt's Mean Daily Rating (excluding nasal congestion)



* from Investigator Rating

The placebo group was discontinued after the double-blind phase.

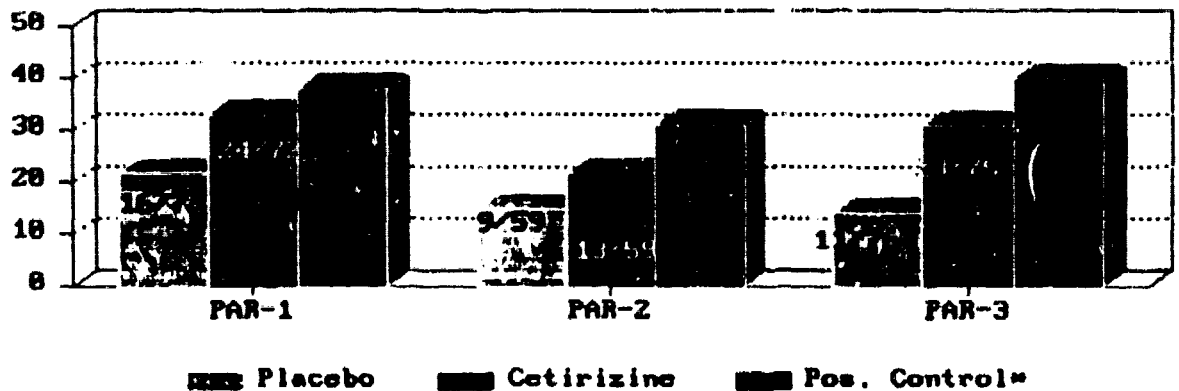
Looking at the graph, one can make several observations -

- 1 - Cetirizine and diphenhydramine appear to be comparable in producing overall symptomatic relief.
- 2 - The effect was greatest in the first four weeks, and gradually diminished over the following eight weeks.
- 3 - Placebo produced definite symptomatic relief as well, although statistically significantly less than the "active" drugs during the four weeks of the double-blind period. It would have been interesting to see what happened if placebo had been continued into the next eight weeks.
- 4 - The effect from the "active" drugs during the last eight weeks appears very close to the placebo effect in the first four weeks.

In their global assessment of efficacy investigators found both active drugs to be significantly superior to placebo during the double-blind phase, with no statistically significant difference between them. Fifty-nine percent and 56% of cetirizine and diphenhydramine-treated patients, respectively, showed "good" to "excellent" overall efficacy compared to 21% on placebo. This is consistent with the lower rate of drop-outs due to lack of efficacy with cetirizine (2.7%) than with placebo (5.3%), as shown in Table 6.

Adverse effects were similar to previous studies, and consisted primarily of sedation and related symptoms as well as headache. The incidence of ADR's in the three perennial allergic rhinitis studies can be compared in the following graph (reports of somnolence, dizziness, fatigue, ataxia, stupor, confusion and impaired concentration were combined as related symptoms).

ADR'S IN PAR 1,2+3 Somnolence and related symptoms Percent reported



*Diphenhydramine (PAR-3)
Chlorpheniramine (PAR-2)
20 mg Cetirizine (PAR-1)

This study shows that cetirizine 10mg daily was comparable to diphenhydramine 75-150mg daily in providing symptomatic relief of perennial allergic rhinitis. Both active drugs showed a gradual decline in efficacy during the eight week open phase - efficacy appearing similar to the placebo effect in the double-blind phase.

Taken together, the three placebo-controlled perennial allergic rhinitis studies show that:

- 1 - 10mg cetirizine once-daily provides overall symptomatic relief in perennial allergic rhinitis for up to four weeks.
- 2 - Dosing was QAM in PAR-1 and PAR-3, and evaluations were recorded in the evening. The once-daily dosage regimen is not fully justified on this basis. PAR-2 used a BID dosing schedule, with once-daily evaluations. Here efficacy was demonstrated only for week 1.
- 3 - 10mg cetirizine QD appears comparable to 8mg chlorpheniramine BID and to 25-50mg diphenhydramine TID. The once-daily evaluation was done in the evening, thus evaluating the efficacy of cetirizine approximately 12 hrs post-dose.
- 4 - The incidence of somnolence and related symptoms is consistently larger compared to placebo, but somewhat less than that seen with chlorpheniramine and diphenhydramine.

C - Chronic Urticaria

CLAIM: Cetirizine is indicated for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria. It reduces the frequency, size, number and duration of hives and markedly reduces the associated pruritus.

In support of this claim, two double-blind, placebo-controlled multicenter studies are submitted, including 175 cetirizine patients, 125 placebo patients and 75 receiving the positive control agent, hydroxyzine. The principal parameters evaluated were the frequency, size and duration of urticarial lesions, the number of episodes and the severity of the associated pruritus as reported by the patients. Supportive parameters of efficacy included the investigator's global efficacy ratings and the analysis of patients discontinued due to lack of efficacy. These parameters were assessed in a daily diary by the patients and at baseline and at the study visits by the investigators, who also rated the overall effectiveness of the medication in each patient at the final study visit. Cetirizine 5-20mg once daily was administered for four weeks, in patients with chronic idiopathic urticaria of at least six weeks duration.

A total of 372 patients were randomized to study medication. Of these, 5 patients were lost to follow-up, 1 never took study medication and 6 others were withdrawn for various reasons (other than lack of efficacy) before the third day of therapy. The remaining 360 patients (96.8% of those entered) were evaluated for efficacy, including 53 who were discontinued due to lack of response.

URT-1

This is a four-week, six-center, double-blind, parallel, placebo-controlled fixed-dose study of cetirizine 10 and 20mg QHS One hundred and fifty-three (153) patients diagnosed as having chronic idiopathic urticaria, including patients who were considered to be "atopic", were entered in the study. Of these, 149 patients were evaluable for efficacy and 150 were evaluable for safety. Three patients (one from each treatment group) were excluded from all safety and efficacy analyses because of the following reasons: lost to follow-up, withdrawal of consent and did not take study drug. The fourth patient excluded from all efficacy analyses (placebo) withdrew early because of an abnormal laboratory value at baseline. Patients received either cetirizine 10mg capsules QHS, cetirizine 20mg capsules QHS or placebo QHS for a period of four weeks. Evaluations were filled out just prior to taking the next dose in the evening - providing a measure of efficacy 24 hours post-dosing. Of the 149 efficacy evaluable patients, 49, 49 and 51 were treated with placebo, cetirizine 10mg and cetirizine 20mg, respectively. Medication used was in capsule form, not the to-be-marketed tablet form.

The study was performed between August 1985 and March 1987.

The principal investigators were:

85-N-0039 Richard F. Lockey, M.D. Tampa, FL Start Date 12-16-85	34 patients Stop Date 02-03-87
85-N-0040 E.W. Rosenberg, M.D. Memphis, TN Start Date 01-28-86	13 patients Stop Date 12-03-86
84-N-0041 Robert J. Dockhorn, M.D. Prairie Village, KS Start Date 08-22-85	36 patients Stop Date 03-25-87
85-N-0042 Sheldon L. Spector, M.D. Los Angeles, CA Start Date 10-10-85	25 patients Stop Date 11-26-86
85-N-0043 Zach H. Haddad, M.D. Los Angeles, CA Start Date 10-11-85	34 patients Stop Date 12-18-86
85-N-0044 Nicholas A. Soter, M.D. New York, NY Start Date 03-20-86	11 patients Stop Date 12-02-86

In the patient's ratings, both cetirizine doses were significantly superior to placebo in improving all symptom parameters: total number of lesions, number of episodes, size of lesions, duration of lesions and pruritus. The onset of activity was rapid, being apparent at the earliest measuring point following the first dose of medication, the day 2 diary evaluation. Statistical significance for both cetirizine doses vs placebo was achieved for number of episodes and pruritus by day 2, and for the other three parameters by day 3. The efficacy of cetirizine was maintained for the entire 4-week treatment period, although a continually increasing response across the 4 weeks was noted in the placebo group. The two doses of cetirizine were equivalent to one another.

The investigator's symptom ratings and global evaluation also support the efficacy of cetirizine in this indication. Sixty-nine and 61% of the cetirizine 10mg and 20mg patients, respectively, had good or excellent responses which was significantly superior to the 33% in the placebo group. Additionally, 31% of placebo patients discontinued therapy due to lack of efficacy, compared with 6% and 10% in the cetirizine 10 and 20 mg groups, respectively. Both cetirizine vs placebo comparisons were statistically significant.

Somnolence, headache and dry mouth were the most common adverse experiences reported. The incidence of somnolence in the cetirizine 10mg (14%) and cetirizine 20mg group (19%) was significantly higher than in the placebo group (2%). A higher incidence of dry mouth was also reported in the cetirizine 10mg (10%) and 20mg (8%) compared with placebo-treated patients (2%). The incidence of headache was similar among the three treatment groups. No serious or unexpected ADR's were reported. Only one patient (cetirizine 10 mg) discontinued the study due to an adverse experience (insomnia).

URT-2

This was a four-week, fourteen-center, double-blind, parallel, placebo-controlled, dose-titration, parallel study of cetirizine vs hydroxyzine in chronic idiopathic urticaria. Titration, if required, was done on day 4 and at the end of week 1, followed by three weeks of maintenance. Cetirizine dosing began at 5mg QAM with an intermediate step at 10mg QAM and a maximum of 20mg QAM. Hydroxyzine began at 25mg QHS with an intermediate step at 25mg BID and a maximum of 25mg TID. Evaluations were recorded in the evening - measuring efficacy for cetirizine at approximately 12 hours after the last dose. Of a total of 219 patients entered, 211 were efficacy evaluable, and 215 patients were evaluable for safety. Four patients were excluded from both the efficacy and safety analyses because they were lost to follow-up. An additional 4 patients were excluded only from the efficacy analysis, 3 because they took study drug for less than 3 days, and one because the patient withdrew consent after taking only one dose of study medication.

Medication used was in capsule form, not the to-be-marketed tablet.

The principal investigators were:

86-N-0075	Debra Breneman, M.D. Cincinnati, OH	24 patients
86-N-0077	Suzanne Bruce, M.D. Houston, TX	21 patients
86-N-0078	Michael Tharp, M.D. Dallas, TX	23 patients
86-N-0079	Peter Boggs, M.D. Shreveport, LA	20 patients
86-N-0080	Donald Aaronson, M.D. Des Plaines, IL	6 patients
86-N-0081	Gerald Klein, M.D. Vista, CA	19 patients
86-N-0082	James Kalivas, M.D. Kansas City, KS	18 patients
86-N-0084	Herbert Mansmann, M.D. Philadelphia, PA	5 patients
86-N-0085	Harold B. Kaiser, M.D. Minneapolis, MN	17 patients
86-N-0086	Michael Bigby, M.D. Boston, MA	4 patients
86-N-0087	Edwin Bronsky, M.D. Murray, UT	24 patients
86-N-0088	Salmon Goldberg Northbrook, IL	24 patients
86-N-0089	Eugenia Hawrylko, M.D. Brooklyn, NY	11 patients
86-N-0090	John G. Leonardy, M.D. Atlanta, GA	3 patients

In the patient's assessment, both active regimens were significantly superior to placebo in improving four out of five parameters: total number of lesions, number of episodes, size of lesions, and degree of pruritus. Significant improvement was not seen in the average duration of lesions. Cetirizine and hydroxyzine were comparable in efficacy.

Both cetirizine and hydroxyzine were rated by the investigators as significantly more effective than placebo on a global basis. A rating of definite improvement or better was achieved by 72% and 75% of patients in the cetirizine and hydroxyzine groups, respectively, compared to 42% of the placebo patients. In addition, significantly more patients discontinued placebo therapy (25%) due to lack of efficacy than cetirizine (10%) or hydroxyzine (7%) patients. Pairwise comparisons of incidence of terminations due to inadequate response were significant for placebo compared with cetirizine ($p=.021$) and with hydroxyzine ($p=.002$).

In the daily analysis of mean patient symptom ratings, patients taking cetirizine and hydroxyzine demonstrated significant reductions in symptoms compared with placebo patients by day 2.

Cetirizine 5 mg provided adequate relief of symptoms in 33% of patients, indicated by the fact that these did not titrate above the minimum dose. Significantly greater percentages of patients remained at the minimum dose in the cetirizine (33%) and hydroxyzine (39%) groups ($p=.05$ and $.008$, respectively) compared with placebo (19%). No serious or unexpected adverse reactions were reported. Headache and somnolence were the most common adverse experiences. Headache occurred in 23.2% of patients taking cetirizine, 15.3% of patients taking hydroxyzine, and 16.2% of placebo patients. Somnolence was reported by 21.7% of cetirizine patients, 36.1% of hydroxyzine patients, and 13.5% of placebo patients. This difference was significant ($p=.001$) in the hydroxyzine group (but not in the cetirizine group) compared with placebo. The investigator's global assessment of sedation also showed significantly greater sedation in the hydroxyzine group compared with placebo ($p=.001$). Cetirizine was considered less sedating than hydroxyzine by the investigators, but more sedating than placebo ($p=.013$). Five patients left the study due to the occurrence of an adverse experience, one each in the cetirizine and placebo groups, and three in the hydroxyzine group. No changes in laboratory tests considered possibly due to study medication were recorded in patients taking cetirizine or hydroxyzine.

**Incidence of Adverse Experiences in U.S. Clinical Trial of
Cetirizine vs. Hydroxyzine (URT-2)**

	Cetirizine (N=69)	Hydroxyzine (N=72)	Placebo (N=74)
Total Number of Patients Reporting at Least One Adverse Experience	32 (43.2%)	3 (62.3%)	39 (4.2%)
Number of Patients Discontinued Due to Adverse Experiences	1 (1.4%)	3 (4.2%)	1 (1.4%)
Number of Patients Reporting Somnolence	15 (21.7%)	26 (36.1%)	10 (13.5%)
Number of Patients Reporting Dry Mouth	2 (2.9%)	8 (11.1%)	5 (6.8%)
Number of Patients Reporting Fatigue	4 (5.8%)	4 (5.6%)	2 (2.7%)

The two multicenter studies URT-1 and URT-2 provide definitive evidence for the efficacy of cetirizine, given as a single daily dose of 5 to 20 mg for the treatment of chronic idiopathic urticaria. Efficacy was evaluated 24 hours post-dose in URT-1, and 12 hours post-dose in URT-2. With the exception of the duration of lesions score for URT-2, cetirizine was significantly more effective than placebo for all measures. URT-1 showed that 10 and 20mg doses of cetirizine were equally effective, with no increased benefit from the higher dose. URT-2 demonstrated that a titrated regimen of 5 to 20mg/day of cetirizine was as effective as the positive control, hydroxyzine 25-75mg/day. 33% of patients had adequate relief with a 5mg daily dose of cetirizine, 27% required a 10mg dose, and 39% went on to 20mg daily.

Placebo therapy was not associated with a high response rate, with almost one-half of the placebo patients in each trial achieving no relief in the investigator's global assessment. By contrast, only about 15% of cetirizine patients failed to show any improvement. Combining the trials, 27% of placebo patients were withdrawn early due to lack of efficacy. This was significantly more than in the cetirizine (9%) or hydroxyzine (7%) group.

D - Idiopathic Pruritus

Two multicenter studies in idiopathic pruritus are presented in this submission, including 160 cetirizine patients and 110 receiving placebo. Idiopathic or "dry skin" pruritus was chosen as a model for the anti-pruritic efficacy of cetirizine in a non-allergic condition. As this condition is common in an older population, a secondary objective was to obtain safety data in this age group. Studies were conducted during the winter season when low indoor humidity is believed to be a major predisposing factor.

PRU-1

This was a double-blind, randomized, parallel, multicenter, placebo-controlled study of 129 elderly patients with idiopathic pruritus. Patients with documented symptoms of idiopathic pruritus that were not sufficiently relieved by treatment with an emollient of hydrophilic ointment and the use of only "Dove" soap for 1 week entered the study. Of the 129 patients, 126 were evaluable for efficacy and 128 were evaluable for safety. One patient (cetirizine) did not take study drug and was excluded from both safety and efficacy analyses. Two patients (placebo) were excluded from all efficacy analyses because of early withdrawal due to an inadequate response and an adverse experience, respectively. Patients were treated with either cetirizine 10mg capsules QHS or placebo QHS for a period of 3 weeks. Of the 126 efficacy evaluable patients, 63 were treated with placebo and 63 received cetirizine. Patients rated the severity of their pruritus daily using a four point rating scale. Investigators rated the severity of pruritus (using the same rating scale as the patients) and the degree of relief at the end of each week of treatment. They also provided a global evaluation (4 point scale) of the efficacy of treatment at the end of the trial.

The principal investigators were:

- 85-N-0135 James T.Gourzis, M.D., PhD
Cincinnati, OH
- 85-N-0137 Debra Brennan, M.D.
Cincinnati, OH
- 85-N-0138 Martin S.Finkelstein, M.D.
New York, NY
- 85-N-0139 James Kalivas, M.D.
Kansas City, KS
- 85-N-0140 Calvin Treger, M.D.
Seattle, WA
- 85-N-0142 Gary Cole, M.D.
Long Beach, CA

There were no significant differences between the two treatments according to the patient ratings of the severity of pruritus averaged over the entire treatment period or in the weekly analyses. There were no differences between groups with respect to the investigators' global evaluations regarding the effectiveness of therapy.

Somnolence and headache were the most common adverse experiences in the two treatment groups. The incidence of somnolence in the placebo and cetirizine groups was 9.2% and 19.0%, respectively. This difference was not statistically significant ($p=0.108$). Headache was reported in 12.3% and 14.1% of the placebo and cetirizine treatment groups, respectively. One patient in the placebo treatment group died suddenly of causes unrelated to this study. No other serious or unexpected adverse experiences occurred. One cetirizine and 2 placebo patients discontinued study medication due to an adverse experience.

This study supports the safety of cetirizine 10mg daily for up to three weeks in elderly patients (60- 85 years of age) with idiopathic pruritus. No significant improvement was demonstrated as compared to placebo, and no claim is made for efficacy in this condition.

PRU-2

In the second multi-center study, cetirizine 10 and 20mg tablets were evaluated in a double-blind, parallel, placebo-controlled study of 142 patients with idiopathic pruritus. All 142 patients entered into the study were evaluable for efficacy and safety. Patients with documented symptoms of idiopathic pruritus, that were not sufficiently relieved after one week of placebo therapy in addition to their usual non-pharmacologic treatment measures (i.e., emollients, soaps, etc.), had either cetirizine 10mg (48 patients) or 20mg (46 patients) or placebo (48 patients) QAM added to their therapeutic regimen for a period of 2 weeks. Patients made twice-daily ratings of the severity of pruritus using a four-point scale and also provided a global evaluation of the efficacy of treatment at the end of the trial on a 10 cm visual analog scale. Investigators rated the severity of pruritus and the degree of relief also using four-point scales at the initiation and at the end of week 2 of treatment.

The principal investigators were:

86-N-0197 David R. Bickers, M.D.
South Euclid, OH

86-N-0198 James T. Gourzis, M.D.
Cincinnati, OH

86-N-0199 James Kalivas, M.D.
Kansas City, KS

86-N-0200 Robert Loss, M.D.
Rochester, N.Y.

86-N-0201 Roland Medansky, M.D.
Chicago, IL

86-N-0202 Tom Russel, M.D.
Milwaukee, WI

In the patients' evaluation, there were no statistically significant differences between the two active treatments and placebo with respect to severity of pruritus averaged over the entire treatment period or during weeks 1 or 2 (by-week analyses).

There were also no differences among the three treatment groups with respect to the investigators' evaluations of the effectiveness of therapy.

Somnolence, dry mouth and headache were the most common adverse experiences in all three treatment groups. The incidences of somnolence, dry mouth and headache in the placebo group were 4.2%, 0%, and 0%, respectively. In the cetirizine groups, the respective incidences of these adverse experiences were 12.5%, 10.4% and 6.3% in the 10 mg QAM group and 28.3%, 10.9% and 4.3% in the 20 mg QAM group.

The results of this study indicate that cetirizine 10 or 20mg is safe but ineffective in the treatment of idiopathic pruritus.

UNCONTROLLED STUDIES

One six month, uncontrolled study is included in this submission.

One hundred and ninety-nine patients entered the study at four sites, 168 with documented symptoms of perennial rhinitis, and 31 with documented symptoms of chronic idiopathic urticaria. All 199 patients were included in the safety analysis and the descriptive efficacy analysis. All patients commenced the study taking cetirizine 5mg QAM, and could be titrated to 10mg and further to 20mg if adequate relief of symptoms was not obtained after at least 4 days at a given dose. The dose could be decreased during the study if an intolerable adverse reaction occurred.

The principal investigators were:

86-N-0042 James P.Kemp, M.D.
San Diego, CA

86-N-0043 Don Q.Mitchell, M.D.
Jackson, MS

86-N-0044 Robert J. Dockhorn, M.D.
Prairie Village, KS

86-N-0045 Macy I. Levine, M.D.
Pittsburgh, PA

Of the 199 patients enrolled in the study, 22(11%) were maintained on 5mg/day, 42(21%) on 10mg/day, and 108(63%) on 20mg/day. Nine patients did not achieve a satisfactory maintenance dose.

Headache was the most common adverse experience, occurring in 33.7% of all patients, and in 29.9% and 34.6% of patients in the 5-10 mg/day or 20mg/day subgroups, respectively. Among all patients other frequently-reported adverse experiences were somnolence (12.6% incidence), fatigue (12.1%), dry mouth (10.1%) and dizziness (5.5%). Headache occurred with an incidence of 22.6% during week 1-4, declined to 9.8% during week 4-8, and ranged from 8.3% to 11.0% during the rest of the study. Somnolence exhibited a progressive decline, with an incidence of 10.1% during the first month, 5.2% during the second month, and 2.8% at the final interval. Fatigue was an exception to the general pattern, declining following a week 1-4 incidence of 10.1% to 5.7% during week 4-8, then rising to 7.7% at the final 2 intervals. Dry mouth and dizziness exhibited sustained declines greater than 75% after the first month.

Four patients withdrew from treatment early due to adverse experiences; two due to weight gain, one due to drowsiness, and one with a complex of symptoms including worsening of asthma, blurred vision and depression. One hundred eighty-one patients (91%) remained in the trial for longer than 20 weeks.

Dosage reduction was instituted in 15 patients in the study: 9 due to drowsiness/tiredness, 2 due to dry eyes, and one due to weight gain/appetite increase. Three patients did not have any adverse experiences responsible for the reduction in dose, and the reduction was either due to investigator error, or the reason for the reduction could not be determined from review of the case. In all cases in which an adverse experience was related to the dose change, the adverse experience either resolved or decreased in intensity following the dosage reduction.

A trend in body weight increase was observed during the study. A total of 4% of the patients reported weight gain. The mean measured gain in weight at 20 weeks was 2.8%, with no further gain at 26 weeks. Weight gain was greatest among adolescent males. For the patients older than eighteen years, significant changes from baseline and percent changes from baseline were recorded for both sexes separately and combined at all study visits, with the exception of males at week 2. Mean percent increases at week 26 were 2.6% and 2.5% for males and females, respectively. There was no significant difference between sexes in the week 26 weight gain in the eighteen or older subgroup. There were

no apparent sex-related differences. Two patients (1.0%) dropped out due to weight gain, one of whom was an obese woman with a history of large weight fluctuations.

There were nine abnormal laboratory values considered "possibly due to study medication," 7 in SGPT, one in SGOT, and one was in total bilirubin. All elevations were mild, and were not considered clinically significant by the investigators. A small upward trend in calcium values was suggested by the scatterplots of pre- and post-therapy clinical laboratory values. These elevations were all within the normal range, and do not appear to be clinically relevant. No changes of clinical importance were observed in the scatterplots or the analysis of mean changes from baseline for other laboratory tests.

This study supports the safety of cetirizine 5-20 mg/day for periods up to six months in patients with conditions such as allergic rhinitis, chronic idiopathic urticaria, and idiopathic pruritus.

REVIEWER'S COMMENTS:

Twelve of the thirteen clinical studies included in this NDA were done using a capsule rather than the to-be-marketed formulation. Bioequivalence therefore is of utmost importance. Consultation with our biopharmacology reviewer so far suggest that bioequivalence has been satisfactorily demonstrated - but I am awaiting the final review.

The clinical studies submitted demonstrate the efficacy of cetirizine for symptomatic relief in seasonal allergic rhinitis. The dosage recommendation of 5 to 10mg once daily is adequately supported.

The efficacy in perennial allergic rhinitis at a dose of 10mg once daily appears comparable to the positive controls used. Evaluations were only done at 12 hours post-dosing, thus making the once-daily recommendation questionable. The efficacy appears to diminish after four weeks.

The indication for symptomatic relief of chronic idiopathic urticaria is well-demonstrated. A dosage regimen of 5-20 mg once-daily is adequately demonstrated, with evaluations done at 24 hours post-dosing in the first study, and at 12 hours post-dosing in the second study.

Safety evaluations to date have not demonstrated any serious or unexpected adverse drug reactions. Sedation, somnolence and fatigue, as well as headache are the most commonly reported ADR's. Occasional elevations of liver enzymes are seen, these tend to revert back to normal with continued drug therapy, and do not appear to be of clinical significance.

The annotated package insert should be modified as follows:

On page 3, the third paragraph should delete the sentence "This results in high bioavailability with low inter- or intrasubject variation in blood levels."

The last paragraph of page 3, the sentence referring to elderly patients should leave out ",but only" as follows - "The clearance of cetirizine is reduced in elderly patients in proportion to the decrease in creatinine clearance"

On p.4, under Perennial Allergic Rhinitis, a sentence should be added: Activity appears to diminish after 4 weeks.

The last sentence on p.4 should be changed to: Significant dose-related somnolence/fatigue is reported in clinical trials. The overall combined incidence of somnolence and fatigue (spontaneously reported) varies from 16 to 31%. Patients should be warned about engaging in activities requiring mental alertness, such as driving a car or operating potentially dangerous machinery.

Renée K. Landesman, M.D.
29 January 1990

cc: Orig NDA 19-835
HFD-155 | Div File
HFD-155 | Ledit
HFD-155 | Delgado
HFD-155 | Himmel

This review summarizes efficacy studies SAE-1-5 NAE 1-3 & UET 1-2. Dr Landesman review requires further safety analysis.

An integrated Safety summary will ^{be} prepared by the Sponsor prior to approval. No significant safety issues identified in these studies - cardiac effects are seen in subsequent studies which require further evaluation. Cetirizine shows efficacy in SAE & urticaria. See further review of Perennial allergic rhinitis by Dr Delgado.
C. Bunker 2/9/94

Appendix A
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Table 1. Adequate and Well-Controlled Studies for the Indication: Seasonal Allergic Rhinitis*

NDA Report No.	Duration of Treatment (Weeks)	Cetirizine Regimen(s)	Positive Control Regimen	Efficacy Results
SAR-1	1	5 mg QAM 10 mg QAM 20 mg QAM	None	Positive for All Active Regimens
SAR-2	2	10 mg QAM 10 mg QHS 5 mg BID	None	Positive for All Active Regimens
SAR-3	2	5 mg QAM 10 mg QHS	Chlorpheniramine 8 mg S.R. BID	Partially Positive for All Active Regimens
SAR-4	4	5 mg QAM	Terfenadine 60 mg BID	Positive for Both Active Regimens
SAR-5	4	10 mg QAM	Terfenadine 60 mg BID	Marginally Positive for Both Active Regimens

* All Studies Utilized a Randomized, Double-Blind, Placebo-Controlled, Parallel Design.

Table 2. Summary of Patient Enrollment and Efficacy Evaluability in Seasonal Allergic Rhinitis Studies

NDA Report No.	No. of Study Sites	Total Number of Patients Entered				Number of Efficacy Evaluable Patients			
		Cetirizine	Active Control	Placebo	Total	Cetirizine	Active Control	Placebo	Total
SAR-1	9	315	0	104	419	310	0	102	412
SAR-2	3	152	0	52	204	147	0	51	198
SAR-3	3	138	78	78	314	132	75	76	303
SAR-4	3	79	78	78	235	79	78	74	231
SAR-5	4	70	70	70	210	69	67	69	205*
Total	26	774	226	382	1382	737	220	372	1349

* Includes 54 patients in Study No. 84-N-0031. This site was excluded from the multicenter analysis because of an extreme center's treatment effect.

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Table 3. Demographic Characteristics of Patients Evaluable for Efficacy in Seasonal Allergic Rhinitis Studies

NDA Study No.	Treatment	Total No. Patients	Age (Years)		Body Weight (Pounds)	
			Mean	Range	Mean	Range
SAR-1	Cetirizine 5 mg QAM					
	Male	75	34	18 - 76	166	109 - 270
	Female	26	44	24 - 63	138	100 - 190
	Cetirizine 10 mg QAM					
	Male	60	35	18 - 54	178	130 - 244
	Female	46	44	26 - 71	154	110 - 335
	Cetirizine 20 mg QAM					
	Male	77	34	19 - 72	177	102 - 270
	Female	26	46	30 - 68	148	103 - 235
	Placebo					
Male	68	37	21 - 80	170	120 - 250	
Female	34	45	27 - 74	159	84 - 210	
SAR-2	Cetirizine 10 mg QAM					
	Male	24	34	19 - 62	178	125 - 263
	Female	24	43	28 - 69	143	99 - 201
	Cetirizine 10 mg QHS					
	Male	30	37	18 - 79	172	120 - 240
	Female	19	47	29 - 65	148	120 - 190
	Cetirizine 5 mg BID					
	Male	31	42	18 - 73	181	130 - 278
	Female	19	41	27 - 58	162	102 - 270
	Placebo					
Male	28	33	18 - 59	172	145 - 215	
Female	23	48	27 - 71	137	95 - 210	
SAR-3	Cetirizine 5 mg QAM					
	Male	60	27	12 - 53	157	93 - 210
	Female	13	47	34 - 81	154	119 - 220
	Cetirizine 10 mg QHS					
	Male	67	29	12 - 53	174	90 - 263
	Female	12	42	30 - 56	140	111 - 175
	Chlorpheniramine S.R. 8 mg BID					
	Male	62	28	12 - 65	167	77 - 340
	Female	13	47	27 - 69	137	113 - 180
	Placebo					
Male	63	35	13 - 71	169	103 - 238	
Female	13	46	30 - 67	139	101 - 177	
SAR-4	Cetirizine 5 mg QAM					
	Male	39	33	13 - 66	171	80 - 230
	Female	40	34	19 - 68	143	110 - 202
	Terfenadine 60 mg BID					
	Male	34	31	14 - 60	176	129 - 250
	Female	44	31	14 - 67	142	89 - 238
	Placebo					
	Male	53	32	12 - 59	183	117 - 260
Female	41	34	13 - 64	143	87 - 235	
SAR-5	Cetirizine 10 mg QAM					
	Male	38	38	14 - 74	178	113 - 275
	Female	31	37	19 - 70	134	100 - 290
	Terfenadine 60 mg BID					
	Male	29	32	12 - 63	169	80 - 220
	Female	38	37	16 - 58	146	103 - 220
	Placebo					
	Male	32	32	12 - 65	172	81 - 325
Female	37	35	14 - 61	143	108 - 243	

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Table 6. Summary of Effectiveness of Cetirizine Against Symptoms of Seasonal Allergic Rhinitis as Rated by Patients

NDA Report No. (Duration)	Treatment Regimen	Mean Severity Rating over Entire Treatment Period (Symptom Measures Analyzed)								Total Symptom Severity
		Sneezing	Rhinorrhea	Nasal Pruritus	Ocular Pruritus	Tearing	Redness of Eyes	Palatal Pruritus	Nasal Congestion	
SAR-1 (1 week)	Cet 5 mg QAM	* 1.00	* 1.09	* 0.89	* 0.82	* 0.68	* 0.66	0.66	1.44	* 5.50
	Cet 10 mg QAM	* 0.95	* 0.96	* 0.83	* 0.82	* 0.68	* 0.65	0.90	* 1.75 ^a	* 5.39
	Cet 20 mg QAM	* 0.81 ^b	* 0.95	* 0.69 ^b	* 0.71	* 0.53 ^b	* 0.62	* 0.79 ^b	* 1.34	* 4.37 ^b
	Placebo	1.58	1.42	1.16	1.21	0.97	0.92	0.94	1.31	7.60
SAR-2 (2 weeks)	Cet 10 mg QAM	* 0.71	* 0.99	* 0.87	* 0.71	* 0.52	0	0.29	1.41	* 4.14
	Cet 10 mg QHS	* 0.56	* 0.89	* 0.77	* 0.76	* 0.54	0	0.39	1.35	* 3.90
	Cet 5 mg BID	* 0.64	* 0.81	* 0.81	0.94	0.75	0	0.42	1.31	* 4.36
	Placebo	1.18	1.29	1.23	1.14	0.82	0	0.50	1.53	6.11
SAR-3 (2 weeks)	Cet 5 mg QAM	* 0.82	1.16	* 0.97	0.96	0.79	0	0	1.67	* 4.71
	Cet 10 mg QHS	* 0.85	1.15	1.07	1.04	0.82	0	0	1.67	* 4.93
	Chlorphen. 8 mg SR BID	* 0.96	1.16	* 1.07	0.92	0.79	0	0	1.71	* 4.89
	Placebo	1.20	1.38	1.34	1.21	0.94	0	0	1.79	6.09
SAR-4 (4 weeks)	Cet 5 mg QAM	* 0.83	* 0.81	* 0.79	* 0.78	0.54	0	0	1.33	* 3.76
	Terfenadine 60 mg QID	* 0.82	* 0.89	* 0.84	* 0.63	0.60	0	0	1.36	* 3.64
	Placebo	1.15	1.15	1.21	0.99	0.61	0	0	1.55	5.12
SAR-5 (4 weeks)	Cet 10 mg QAM	* 0.85	1.03	0.88	0.87	0.66	0	0	1.46	4.30
	Terfenadine 60 mg BID	* 0.84	1.01	0.84	0.71	0.57	0	0	1.57	3.98
	Placebo	1.22	1.13	1.07	0.99	0.79	0	0	1.58	5.00

NOTES: Severity Ratings: 0=None; 1=Mild; 2=Moderate; 3=Severe
Total Symptom Severity Score Excludes Nasal Congestion
* P less than 0.05 vs Placebo
0 Not Measured
^a P less than 0.05 vs Cetirizine 5 mg QAM
^b P less than 0.05 vs Cetirizine 10 mg QAM

Table 5. Summary of Global Efficacy Ratings (a) in Seasonal Allergic Rhinitis Studies

NDA Report No.	Treatment Regimen	Total No. of Patients Rated	Global Assessment: Number (%)			
			Failure	Fair	Good	Excellent
SAR-1 (b)	Cet 5 mg QAM *	99	27 (27%)		72 (73%)	
	Cet 10 mg QAM *	106	22 (21)		84 (79)	
	Cet 20 mg QAM *	103	25 (24)		78 (76)	
	Placebo	102	48 (47)		54 (53)	
SAR-2	Cet 10 mg QAM	47	11 (23)	10 (21)	18 (38)	8 (17)
	Cet 10 mg QHS *	47	6 (13)	10 (21)	19 (40)	12 (26)
	Cet 5 mg BID	48	11 (23)	10 (21)	15 (31)	12 (25)
	Placebo	51	19 (37)	10 (20)	16 (27)	8 (16)
SAR-3	Cet 5 mg QAM	73	22 (30)	26 (36)	20 (27)	5 (7)
	Cet 10 mg QHS	78	17 (22)	38 (49)	22 (28)	1 (1)
	Chlorphen. 8 mg SR BID	73	13 (18)	33 (45)	23 (32)	4 (6)
	Placebo	74	23 (31)	30 (41)	21 (28)	0 (0)
SAR-4	Cet 5 mg QAM *	79	16 (20)	21 (27)	27 (34)	15 (19)
	Terfenadine 60 mg BID *	78	15 (19)	25 (32)	26 (33)	12 (15)
	Placebo	71	21 (30)	25 (35)	20 (28)	5 (7)
SAR-5	Cet 10 mg QAM	48	10 (21)	24 (50)	12 (25)	2 (4)
	Terfenadine 60 mg BID	49	12 (25)	13 (27)	20 (41)	4 (8)
	Placebo	51	20 (39)	12 (24)	11 (22)	8 (16)

* P less than 0.05 vs Placebo

(a) In SAR-1, 2, 4 and 5 global efficacy was rated by the investigator; in SAR-3 it was rated by the patient in the presence of the investigator.

(b) In SAR-1 global efficacy was rated as either effective or not effective.

Table 6. Summary of Patient Withdrawal from Seasonal Allergic Rhinitis Studies Due to Lack of Efficacy (Cetirizine and Placebo Cases Only)

No. of Withdrawals for Lack of Efficacy/Total No. Evaluable

NDA Report No.	Placebo	Total Daily Cetirizine Dose		
		5 mg	10 mg	20 mg
SAR-1	4/102	2/101	1/106	2/103
SAR-2	2/51	--	1/147	--
SAR-3	4/76	1/73	2/79	--
SAR-4	2/74	4/79	--	--
SAR-5	10/51	--	3/51	--
Totals*	22/354 (6.2%)	7/253 (2.8%)	7/383 (1.8%)	2/103 (1.9%)

* The likelihood ratio Chi-Square statistic indicates an overall value of p less than 0.001. P values for pairwise comparisons were:

cetirizine 5 mg/day vs. placebo p = 0.010

cetirizine 10 mg/day vs. placebo p = 0.043

cetirizine 20 mg/day vs. placebo p = 0.055

No drug vs. drug comparisons were significant.

Table 7. Summary of Individual Response Analyses (% Change, Baseline to Final, in Total Symptom Score as Rated by Investigator)

NDA Report No.	Treatment Regimen	% of Evaluable Patients with Specified % Change, by Quartiles				Total N Eval.
		Less than 25%	25-49%	50-74%	Greater Than or = 75%	
SAR-1	Cet 5 mg QAM	21%	25%	18%	37%	(97)
	Cet 10 mg QAM	17	11	20	48	(100)
	Cet 20 mg QAM	12	16	22	49	(98)
	Placebo	37	13	31	19	(98)
SAR-2	Cet 10 mg QAM	11	9	22	38	(43)
	Cet 10 mg QHS	7	9	21	63	(43)
	Cet 5 mg BID	12	7	13	66	(41)
	Placebo	20	12	24	40	(42)
SAR-3	Cet 5 mg QAM	18	21	21	41	(68)
	Cet 10 mg QHS	23	17	20	39	(69)
	Chlorphen. 8 mg SR BID	26	11	29	35	(66)
	Placebo	29	10	26	31	(70)
SAR-4	Cet 5 mg QAM	13	13	23	46	(68)
	Terfenadine 60 mg BID	9	10	33	42	(66)
	Placebo	20	26	23	30	(61)
SAR-5	Cet 10 mg QAM	12	17	26	45	(42)
	Terfenadine 60 mg BID	20	17	21	38	(42)
	Placebo	30	16	16	39	(44)
TOTALS	Cet 5 mg QAM*	17.6%	20.6%	21.5%	40.3%	(233)
	Cet 10 mg (all)*	13.0%	12.4%	21.8%	51.2%	(340)
	Cet 20 mg QAM*	12%	16%	22%	49%	(98)
	Terfenadine 60 mg BID*	14.8%	14.8%	29.6%	40.7%	(108)
	Placebo	28.9%	16.2%	25.0%	29.5%	(315)

* Response distributions (Mantel-Haenszel Test) for active drugs were all significantly different from placebo (P less than 0.05). Response distributions for active drugs were not significantly different from one another, with the exception of cetirizine 5 mg QAM vs. cetirizine 10 mg (all) (p=0.01).

Note: As this was a retrospective analysis, statistical tests were not performed on individual studies.

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Pharmachoice LLC Monitoring of Celecoxib Plasma Concentrations (ng/ml) at the End of Week 1 and Week 3

Analysis Group		Sampling Time After Last Dose									
		Week 1					Week 3				
		0-9 hr	8-17 hr	15-23 hr	15-23 hr	18-21	0-9 hr	8-17 hr	15-23 hr	15-23 hr	18-21
Total	Mean	264.0	160.3	134.0	174.6	121.0	-	190.3	171.0	153.3	143.6
	N	1	13	26	11	2	0	10	20	8	6
	Min	264.0	73.2	31.2	88.6	110.0	-	31.8	74.6	60.6	72.6
	Max	264.0	286.0	283.0	296.0	131.0	-	320.0	290.0	236.0	202.0
	Std	-	82.2	68.7	66.9	12.6	-	72.2	68.6	60.0	22.2
Females	Mean	264.0	281.7	171.0	179.1	110.0	-	228.1	173.3	182.7	97.2
	N	1	6	12	6	1	0	8	10	3	2
	Min	264.0	69.9	31.2	88.6	110.0	-	136.0	126.0	164.0	96.4
	Max	264.0	320.0	283.0	296.0	110.0	-	320.0	207.0	236.0	98.1
	Std	-	88.0	69.7	82.1	-	-	32.0	26.7	38.2	1.2
Males	Mean	-	161.9	166.9	164.1	132.0	-	160.0	169.7	101.2	169.8
	N	0	9	14	5	1	0	10	10	5	6
	Min	-	23.2	33.6	128.0	132.0	-	31.8	74.6	60.6	72.6
	Max	-	286.0	239.0	264.0	132.0	-	320.0	290.0	136.0	202.0
	Std	-	82.4	52.0	56.7	-	-	79.3	66.9	60.7	110.6
Under 65 yrs	Mean	-	177.1	132.2	133.0	121.0	-	220.0	187.9	113.8	139.6
	N	0	6	10	6	2	0	5	8	6	6
	Min	-	102.0	31.2	107.0	110.0	-	136.0	133.0	60.6	72.6
	Max	-	267.0	272.0	296.0	132.0	-	320.0	290.0	164.0	202.0
	Std	-	76.9	68.7	80.3	12.6	-	71.8	50.3	52.0	108.9
65 yrs or older	Mean	264.0	152.7	161.7	162.3	-	-	178.0	153.1	153.1	138.7
	N	1	9	16	7	0	0	13	12	6	2
	Min	264.0	73.2	73.0	88.6	-	-	31.8	74.6	78.3	96.4
	Max	264.0	286.0	283.0	296.0	-	-	320.0	290.0	236.0	220.0
	Std	-	92.2	57.3	60.6	-	-	76.0	72.2	62.3	87.6

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CSA036/014/1

SAR-1

Pharmacokinetic Monitoring of Carbamazepine Serum Levels

Carbamazepine Dose	Patient Number	Sex	Age	Concentration (ng/ml)	Time Elapsed Since Last Dose (Hours)	Concomitant Medication

3 mg

10 mg

20 mg

PAR-1

Pharmacokinetic Monitoring of Cetirizine Serum Levels

Cetirizine Dose	Patient Number	Sex	Age	End of Week	Concentration (ng/ml)	Time Elapsed Since Last Dose (Hours)	Concomitant Medication

-48

*The patient discontinued taking study medication after the dose on Day 4.

PAR-1

Pharmacokinetic Monitoring of Cetirizine Serum Levels

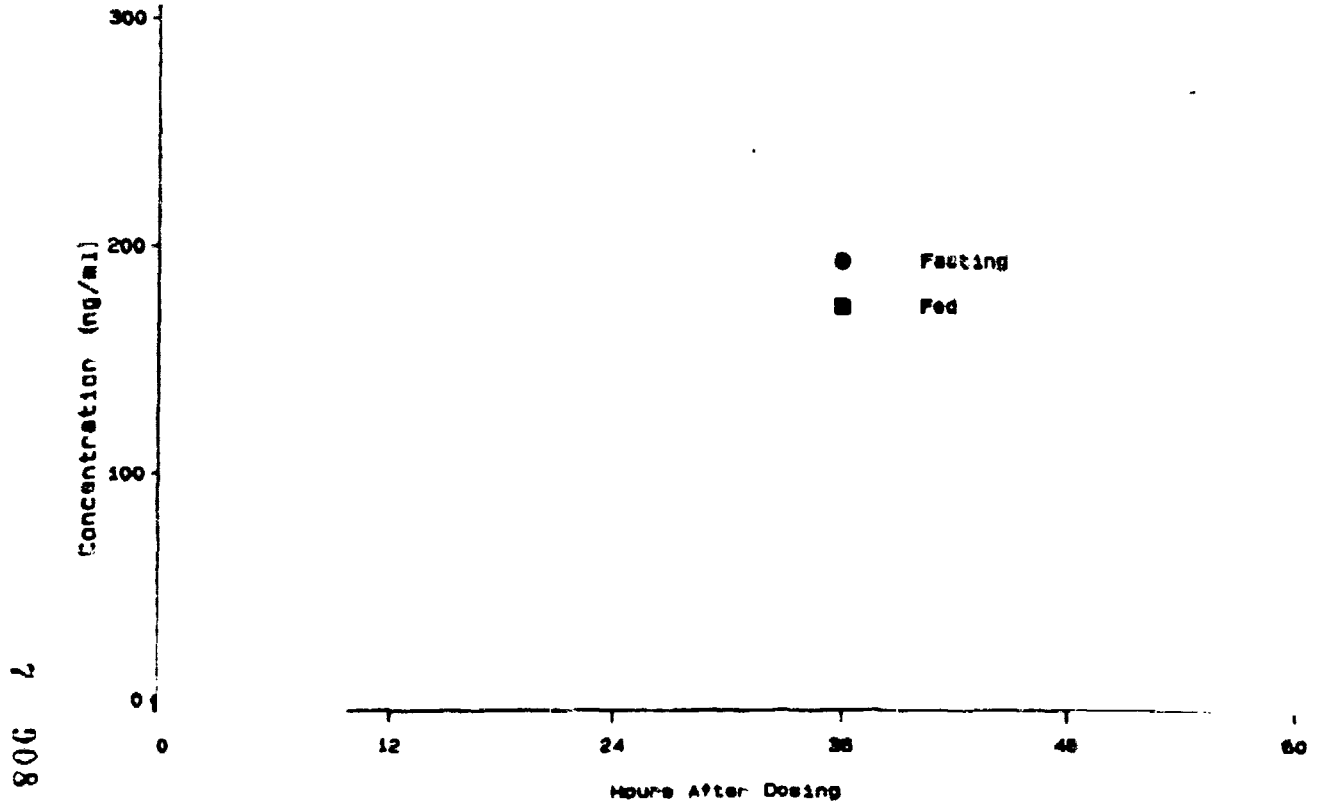
Cetirizine Dose	Patient Number	Sex	Age	End of Week	Concentration (ng/ml)	Time Elapsed Since Last Dose (Hours)	Concomitant Medication

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- * Cetirizine serum level was not obtained at end of Week 1.
- ** Sample was drawn on Day 11. The patient discontinued from the study at this time.

PAR-1

Cetirizine Study 86-N-0105
Mean Cetirizine Concentration From 0 TO 60 Hours

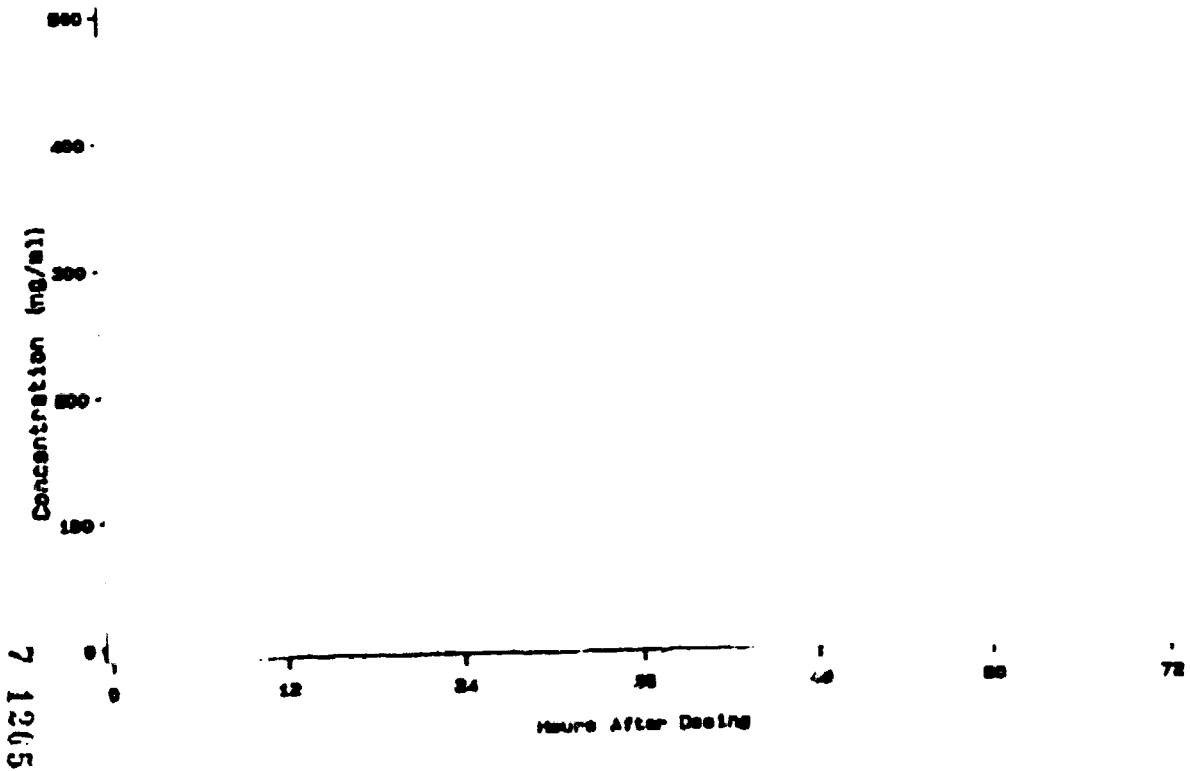


N=24

Cmax 289 (46)

Tmax 1.0 (0.5)

FIGURE 1
Ceftriaxone Study 85-N-0073
Mean Ceftriaxone Concentration From 0 TO 72 Hours



7 1265

Table 2. Mean (±S.D.) Cetirizine Concentrations in Adult and Geriatric Volunteers After Oral Administration of 10 mg Cetirizine

Time (hr)	Serum Cetirizine Levels (ng/ml of free base equivalents)		ANOVA P-value
	Adult Subjects (N=14)	Geriatric Subjects (N=16)	

Table 3. Mean ($\pm$ S.D.) Pharmacokinetic Parameters in Adult and Geriatric Subjects After Oral Administration of 10mg Cetirizine

Parameter	Age Group		ANOVA P-value
	Adult Subjects (N=14)	Geriatric Subjects (N=16)	
AUC (72 hr) (hr·ng/ml)	3317 (903)	5593 (1773)	0.01
AUC (hr·ng/ml)	3318 (903)	5653 (1824)	0.01
C _{max} (ng/ml)	384 (103)	460 (59)	0.02
T _{max} (hr)	1.0 (0.5)	0.9 (0.3)	0.55
T _{1/2} (hr)	7.4 (1.6)	11.0 (3.0)	0.01
TBC/F (ml/min)	46 (14)	28 (10)	0.01
TBC/i (ml/min/kg)	0.64 (0.17)	0.42 (0.14)	0.01
CL _R (ml/min)	24 (8)	13 (7)	0.01
V _d /F (l)	28 (5)	26 (6)	0.22
V _d /F (l/kg)	0.39 (0.05)	0.38 (0.06)	0.61

Results of linear regression analyses of the pharmacokinetic parameters with respect to age, creatinine clearance (CCr) and serum creatinine (SCr) are presented in Table 4 and Figures 2-15. AUC, C_{max}, T_{1/2}, TBC/F, CL_R and CCr were significantly correlated with age while T_{max} and V_d were not. AUC, C_{max}, T_{1/2}, TBC/F and CL_R were also significantly correlated with renal function (CCr) while T_{1/2} and serum creatinine (SCr) were not. Additionally, T_{1/2} was significantly correlated with serum creatinine. Linear regression on age and creatinine clearance showed these variables to be closely related (p=0.0001, R²=0.61). However, when analyzing the effect of both age and CCr on AUC, the results showed that, given a subject's age, CCr adds significantly to the regression (p=0.01), whereas given CCr, age does not add significantly (p=0.40). This indicates that the age effect on pharmacokinetic parameters observed in this study was attributed mainly to the decreased renal function of the elderly group.

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PFLER CLINICAL RESEARCH

APPENDIX C. LISTING OF PATIENTS WHO DISCONTINUED TREATMENT WITH CETIRIZINE
DUE TO ADVERSE EXPERIENCES - U. S. STUDIES

STUDY NO.	GRANT	PATIENT NO.	SEX	AGE	DOSE	ADVERSE EXPERIENCE

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PAR-1

TABLE A.7
SYNOPSIS OF REPEATED MEASURES ANALYSES OF PATIENTS' MEAN DAILY RATING OF SYMPTOM SEVERITY

	ADJUSTED MEAN SEVERITY ^{1,2}			RELEVANT P-VALUES ³			Initial + Treat.
	Placebo	Cetr. 10 mg	Cetr. 20 mg	Treat.	Center	Week	
		Treat.	Treat.		Treat.		
NASAL CONGESTION	1.39	1.61	1.83	.161	.890	.877	.062
POST-NASAL DISCHARGE	1.37	1.12**	1.11**	.041	.911	.231	.972
SNEEZING	0.97	0.79**	0.72**	.026	.858	.936	.795
RUNNY NOSE	1.12	0.96	0.86**	.033	.835	.813	.388
ITCHING NOSE	0.89	0.72	0.70	.088	.426	.517	.317
WATERING EYES	0.72	0.56	0.66	.205	.699	.761	.169
ITCHING EYES	0.84	0.70	0.70	.255	.601	.612	.508
ITCHING MOUTH	0.38	0.36	0.29	.259	.176	.625	.014
TOTAL SEVERITY ⁴	6.33	5.11**	4.97**	.012	.751	.442	.696

¹ Number of cases included in analysis: Placebo, 60; Cetr. 10 mg, 68; Cetr. 20 mg, 68. Number of cases varies slightly among symptoms due to scattered missing data.

² Symptom severity (Mean Daily Rating) averaged over weeks and adjusted for initial severity and center differences.

³ P-values from ANOVA F-tests. P-values for treatment and interactions with center and week are based on a linear model without the initial severity by treatment interaction.

⁴ Does not include nasal congestion.

** Statistically significantly different from placebo (p LE .05).

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2580

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TABLE D.3

SUMMARY OF REPEATED MEASURES ANALYSES SEPARATELY BY STUDY CENTER
PATIENTS' MEAN DAILY TOTAL SYMPTOM SEVERITY

PAR-1

Center	No. Pats.	ADJUSTED TREATMENT MEANS ¹			Treatment MSQ. ²	Error MSQ. ^{2,3}	P-Value ²
		Placebo	Cetr. 10 mg.	Cetr. 20 mg.			
0053	29	6.54	3.97	6.22	62.96	46.07	.278
0056	36	7.71	5.20**	4.89**	142.63	25.79	.007
0061	29	6.18	4.94	5.52	15.27	34.97	.651
0064	43	5.05	5.06	4.20	13.16	30.08	.649
0065	33	5.86	5.34	5.11	6.37	32.72	.824
0114	30	6.18	6.44	4.50	41.35	33.20	.304
Combined ⁴	205	6.33	5.11**	4.97**	152.90	33.54	.012

¹ Treatment averages over weeks, adjusted for differences in initial severity (as rated by the physician).

² From repeated measures analysis variance.

³ Among patient error.

⁴ From Table B.9.

** Statistically significantly different from placebo (p LE .05).

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TABLE D.4

SUMMARY OF REPEATED MEASURES ANALYSES SEPARATELY BY STUDY CENTER
PHYSICIANS' EVALUATION OF TOTAL SYMPTOM SEVERITY

PAR-1

Center	No. Pats.	ADJUSTED TREATMENT MEANS ¹			Treatment MSQ. ²	Error MSQ. ^{2,3}	P-Value ²
		Placebo	Cetr. 10 mg.	Cetr. 20 mg.			
0053	26	6.68	4.18	5.68	37.43	33.52	.347
0056	44	8.69	5.74**	5.89**	119.72	16.15	.002
0061	29	5.48	3.32	5.28	40.98	42.32	.394
0064	41	5.65	4.97	4.61	17.37	22.87	.475
0065	31	6.02	5.67	4.73	14.22	24.57	.567
0114	30	7.78	7.05	5.39	43.73	26.94	.216
Combined ⁴	199	6.80	5.06**	5.13**	195.40	26.88	.001

¹ Treatment averages over weeks, adjusted for differences in initial severity (as rated by the physician).

² From repeated measures analysis variance.

³ Among patient error.

⁴ From Table C.9.

** Statistically significantly different from placebo (p LE .05).

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TABLE A.14
SUMMARY OF ANALYSIS OF PATIENTS' MEAN DAILY PSEUDOEPHEDRINE CONSUMPTION¹

	Placebo		Cetirizine 10 mg		Cetirizine 20 mg	
	N	Mean ± S.D.	N	Mean ± S.D.	N	Mean ± S.D.
BY WEEK						
One	72	10.2 ± 18.50	72	5.8 ± 11.94	71	6.6 ± 13.92
Two	69	17.2 ± 31.54	71	6.1 ± 13.38	70	8.0 ± 20.80
Three	68	15.2 ± 29.78	70	6.9 ± 15.33	67	6.9 ± 17.88
Four	67	16.6 ± 29.31	68	6.6 ± 16.99	67	6.3 ± 15.57
OVER ENTIRE FOLLOW-UP	72	14.9 ± 23.48	72	6.2 ± 10.65	71	7.4 ± 13.74

	ADJUSTED MEAN CONSUMPTION ²			Treat. MSQ. ³	Error MSQ. ³	P-value
	Placebo	Cetr. 10 mg	Cetr. 20 mg			
BY WEEK						
One	10.1	5.3	6.6	437.91	228.69	.150
Two	16.5	5.3**	7.3**	2416.29	332.66	.012
Three	14.5	6.1**	6.1**	1585.79	467.77	.036
Four	15.9	5.9**	5.5**	2347.47	434.77	.005
OVER ENTIRE FOLLOW-UP	14.4	5.6**	6.8**	1630.31	279.23	.003

1. Amount of drug taken expressed as mg./day.
 2. Adjusted for differences in centers.
 3. From ANOVA with center and treatment as factors.
- ** Statistically significantly different from placebo (p LE .05).

10 841

TABLE A.9
SUMMARY OF ANALYSES OF PATIENTS' MEAN DAILY RATING OF SYMPTOM SEVERITY
DURING WEEK ONE OF TREATMENT

	ADJUSTED MEAN SEVERITY ^{1,2}			RELEVANT P-VALUES ³		
	Placebo	Cetir.	Diphen.	Treat.	Center	Initial
					Treat.	Treat.
NASAL CONGESTION	1.69	1.56	1.38**	.023	.051	.809
POST-NASAL DISCHARGE	1.38	1.13**	1.01**	.009	.734	.356
SNEEZING	1.10	0.66**	0.46***	.001	.387	.885
RUNNY NOSE	1.24	0.87**	0.67***	.001	.847	.389
ITCHING NOSE	0.91	0.68**	0.52**	.001	.248	.656
WATERING EYES	0.66	0.43**	0.31**	.001	.869	.013
ITCHING EYES	0.84	0.54**	0.43**	.001	.785	.314
TOTAL SEVERITY ⁴	6.12	4.34**	3.39***	.001	.378	.764

¹ Number of cases included in analysis: Placebo, 75; Cetir., 72; Diphen., 72. Number of cases varies slightly among symptoms due to scattered missing data.

² Treatment mean symptom severity adjusted for initial severity and center differences.

³ P-values from ANOVA F-tests. P-values for treatment and center by treatment are based on a linear model without the initial severity by treatment interaction.

⁴ Does not include nasal congestion.

** Statistically significantly different from placebo (P LE .05).

*** Statistically significantly different from cetirizine (P LE .05).

TABLE A.10
SUMMARY OF ANALYSES OF PATIENTS' MEAN DAILY RATING OF SYMPTOM SEVERITY
DURING WEEK TWO OF TREATMENT

	ADJUSTED MEAN SEVERITY ^{1,2}			RELEVANT P-VALUES ³		
	Placebo	Cetir.	Diphen.	Treat.	Center	Initial
					Treat.	Treat.
NASAL CONGESTION	1.54	1.46	1.24**	.036	.368	.737
POST-NASAL DISCHARGE	1.29	1.03**	0.90**	.006	.252	.722
SNEEZING	1.02	0.64**	0.46**	.001	.084	.828
RUNNY NOSE	1.08	0.80**	0.67**	.001	.102	.278
ITCHING NOSE	0.82	0.58**	0.46**	.002	.311	.157
WATERING EYES	0.54	0.29**	0.28**	.002	.650	.002
ITCHING EYES	0.77	0.47**	0.33**	.001	.360	.058
TOTAL SEVERITY ⁴	5.50	3.81**	3.03**	.001	.114	.421

¹ Number of cases included in analysis: Placebo, 72; Cetir., 69; Diphen., 67. Number of cases varies slightly among symptoms due to scattered missing data.

² Treatment mean symptom severity adjusted for initial severity and center differences.

³ P-values from ANOVA F-tests. P-values for treatment and center by treatment are based on a linear model without the initial severity by treatment interaction.

⁴ Does not include nasal congestion.

** Statistically significantly different from placebo (P LE .05).

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TABLE A.11
SUMMARY OF ANALYSES OF PATIENTS' MEAN DAILY RATING OF SYMPTOM SEVERITY
DURING WEEK THREE OF TREATMENT

	ADJUSTED MEAN SEVERITY ^{1,2}			RELEVANT P-VALUES ³		
	Placebo	Cetir.	Diphen.	Treat.	Center • Treat.	Initial • Treat.
NASAL CONGESTION	1.61	1.45	1.27**	.023	.297	.997
POST-NASAL DISCHARGE	1.27	1.05	0.90**	.019	.598	.627
SNEEZING	0.95	0.64**	0.51**	.001	.210	.331
RUNNY NOSE	1.00	0.79	0.65**	.010	.246	.421
ITCHING NOSE	0.74	0.62	0.45**	.026	.074	.187
WATERING EYES	0.50	0.31**	0.29**	.051	.356	.000
ITCHING EYES	0.68	0.46**	0.38**	.024	.185	.022
TOTAL SEVERITY ⁴	3.12	3.89**	3.17**	.001	.088	.560

- 1 Number of cases included in analysis: Placebo, 67; Cetir., 68; Diphen., 66. Number of cases varies slightly among symptoms due to scattered missing data.
 - 2 Treatment mean symptom severity adjusted for initial severity and center differences.
 - 3 P-values from ANOVA F-tests. P-values for treatment and center by treatment are based on a linear model without the initial severity by treatment interaction.
 - 4 Does not include nasal congestion.
- ** Statistically significantly different from placebo (P LE .05).

10 1142

TABLE A.12
SUMMARY OF ANALYSES OF PATIENTS' MEAN DAILY RATING OF SYMPTOM SEVERITY
DURING WEEK FOUR OF TREATMENT

	ADJUSTED MEAN SEVERITY ^{1,2}			RELEVANT P-VALUES ³		
	Placebo	Cetir.	Diphen.	Treat.	Center • Treat.	Initial • Treat.
NASAL CONGESTION	1.87	1.32	1.30	.395	.083	.893
POST-NASAL DISCHARGE	1.16	0.99	0.90	.154	.086	.614
SNEEZING	0.95	0.60**	0.48**	.001	.189	.103
RUNNY NOSE	0.96	0.78	0.66**	.050	.365	.065
ITCHING NOSE	0.68	0.52	0.42	.055	.201	.139
WATERING EYES	0.52	0.34	0.25**	.036	.298	.001
ITCHING EYES	0.67	0.39**	0.35**	.014	.390	.002
TOTAL SEVERITY ⁴	6.93	3.63**	3.06**	.002	.338	.245

- 1 Number of cases included in analysis: Placebo, 65; Cetir., 67; Diphen., 66. Number of cases varies slightly among symptoms due to scattered missing data.
 - 2 Treatment mean symptom severity adjusted for initial severity and center differences.
 - 3 P-values from ANOVA F-tests. P-values for treatment and center by treatment are based on a linear model without the initial severity by treatment interaction.
 - 4 Does not include nasal congestion.
- ** Statistically significantly different from placebo (P LE .05).

10 1144

Table 20. Summary of Patients' Ratings of Signs and Symptoms by Study Week 1,2

Symptom	WEEK 1			WEEK 2		
	Observed Mean ± SD (N)	Adjusted Mean ± SD (N)	Adjusted Mean ± SD (N)	Observed Mean ± SD (N)	Adjusted Mean ± SD (N)	Adjusted Mean ± SD (N)
Total Number of Lesions	1.61 ± 0.99 (1.60)	1.60 ± 1.01 ¹ (1.72)	1.63 ± 0.99 ² (1.70)	1.32 ± 1.07 (1.59)	0.97 ± 1.00 ² (1.51)	0.96 ± 0.99 ² (0.96)
Number of Episodes	1.61 ± 1.02 (1.50)	1.65 ± 0.99 ² (1.56)	1.66 ± 0.91 ² (1.50)	1.00 ± 1.05 (1.33)	0.99 ± 0.99 ² (0.99)	0.97 ± 0.99 (0.87)
Average Size of Lesions	1.60 ± 0.97 (1.56)	1.65 ± 0.91 ² (1.55)	1.60 ± 0.81 ² (1.50)	1.40 ± 0.97 (1.39)	0.98 ± 0.99 ² (0.98)	0.97 ± 0.81 ² (0.96)
Average Duration of Lesions	1.72 ± 1.05 (1.50)	1.10 ± 0.93 ² (1.73)	1.02 ± 0.91 ² (1.50)	1.62 ± 1.00 (1.33)	1.02 ± 0.90 ² (1.55)	1.00 ± 0.99 ² (1.50)
Degree of Pruritus and Discomfort	1.68 ± 0.86 (1.50)	0.85 ± 0.79 ² (0.96)	0.81 ± 0.70 ² (0.83)	1.20 ± 0.90 (1.50)	0.70 ± 0.82 ² (0.90)	0.81 ± 0.79 ² (0.96)
Symptom	WEEK 3			END OF THERAPY (WEEK 6)		
	Observed Mean ± SD (N)	Adjusted Mean ± SD (N)	Adjusted Mean ± SD (N)	Observed Mean ± SD (N)	Adjusted Mean ± SD (N)	Adjusted Mean ± SD (N)
Total Number of Lesions	1.55 ± 1.13 (1.57)	0.98 ± 1.07 ² (0.96)	0.97 ± 1.00 ² (0.96)	1.00 ± 1.10 (1.31)	0.93 ± 0.99 (0.96)	1.00 ± 0.96 (0.96)
Number of Episodes	1.51 ± 1.11 (1.52)	0.95 ± 0.99 ² (0.96)	0.96 ± 0.90 ² (0.83)	1.01 ± 1.00 (1.32)	0.99 ± 0.99 ² (0.83)	1.03 ± 0.97 (0.95)
Average Size of Lesions	1.50 ± 1.02 (1.33)	0.98 ± 0.90 ² (0.83)	0.87 ± 0.82 ² (0.80)	1.31 ± 1.03 (1.32)	0.90 ± 0.88 (0.80)	0.90 ± 0.90 (0.96)
Average Duration of Lesions	1.55 ± 1.00 (1.50)	1.01 ± 0.99 ² (1.50)	0.90 ± 0.90 ² (0.97)	1.00 ± 1.13 (1.30)	0.96 ± 1.01 (0.96)	1.00 ± 1.00 (1.50)
Degree of Pruritus and Discomfort	1.55 ± 0.91 (1.31)	0.72 ± 0.81 ² (0.96)	0.70 ± 0.79 ² (0.96)	1.30 ± 1.01 (1.33)	0.75 ± 0.83 ² (0.96)	0.90 ± 0.80 ² (0.83)

1 Observed Mean ± Standard Deviation. Rating scales are given in Table 6.
 2 Statistical analysis is based on adjusted means (shown in parentheses) which were adjusted for initial severity and center differences. Patient numbers vary slightly among the different symptoms because of clustered missing data. Actual N values and additional details of statistical analysis are provided in Appendix B, Tables B.1.1-B.1.3, B.2.0-2.3, B.3.1-1.3 and B.4.1-0.3.
 3 Treatments differ significantly superior to placebo (p less than 0.05).

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Appendix A
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Appendix E. Laboratory Test Abnormalities Possibly Related to Study Drug (Category 9)

<u>Drug/Daily Dose</u>	<u>Patient No.</u>	<u>Test</u>	<u>Normal Range</u>	<u>Baseline Value</u>	<u>Most Abnormal Value</u>	<u>Study Day</u>	<u>Last Recorded Value</u>	<u>Study Day</u>

10
295

* Indicates follow-up value

CSA/1171/11617

Appendix E. Laboratory Test Abnormalities Possibly Related to Study Drug (Category 9) (continued)

<u>Drug/Daily Dose</u>	<u>Patient No.</u>	<u>Test</u>	<u>Normal Range</u>	<u>Baseline Value</u>	<u>Most Abnormal Value</u>	<u>Study Day</u>	<u>Last Recorded Value</u>	<u>Study Day</u>

10

Blank

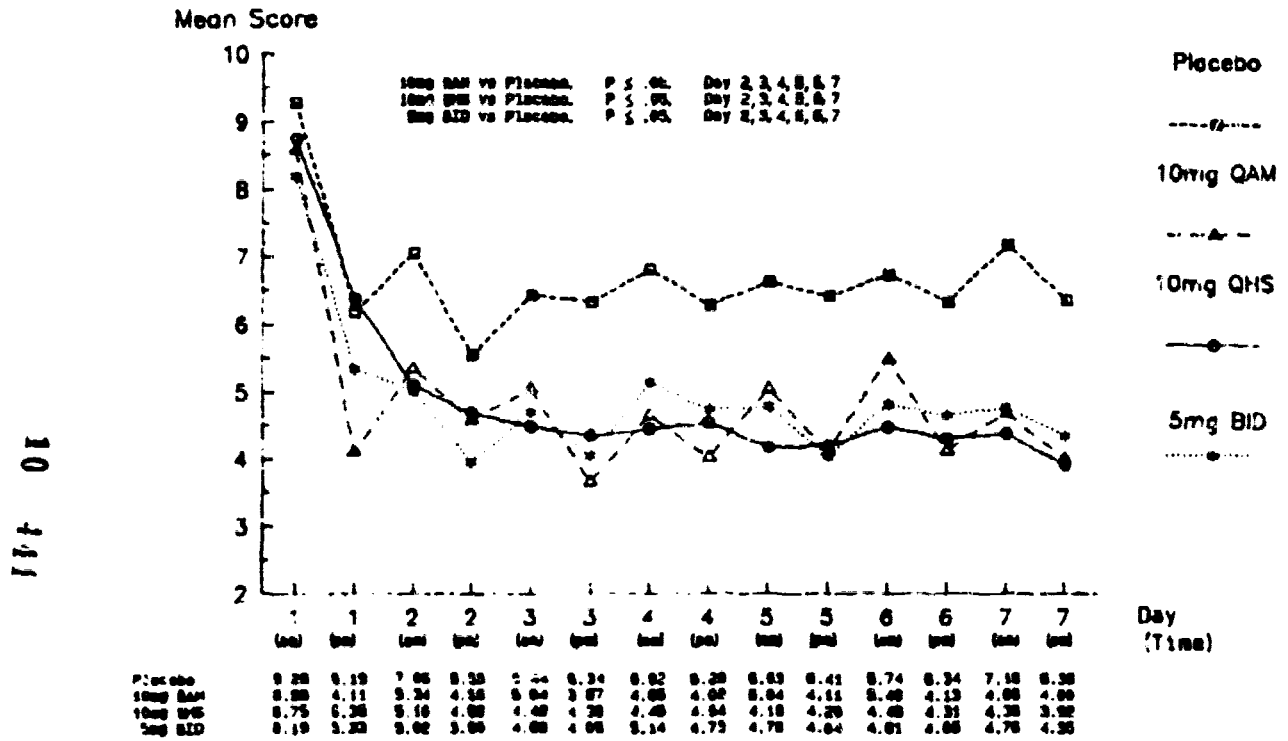
10

207

* Indicates follow-up value

FIGURE 3.a

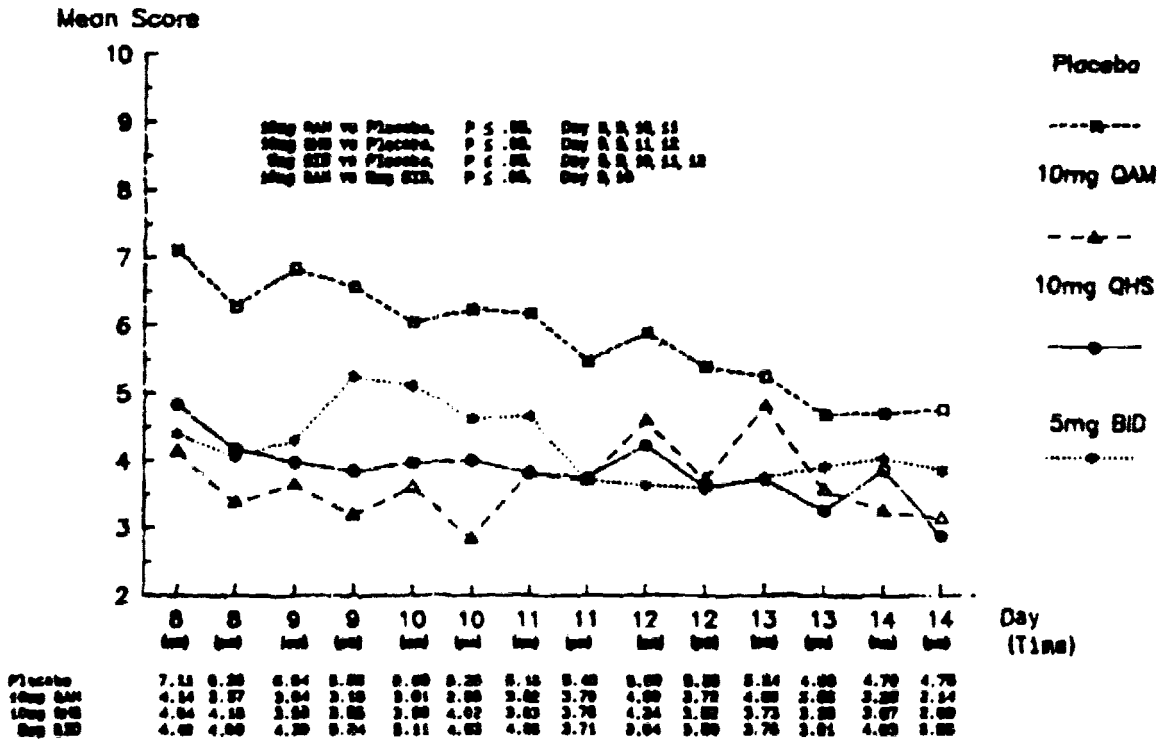
**Cetirizine Seasonal Rhinitis II
Patient's Total Daily Severity Ratings
(Days 1 to 7)**



10 111

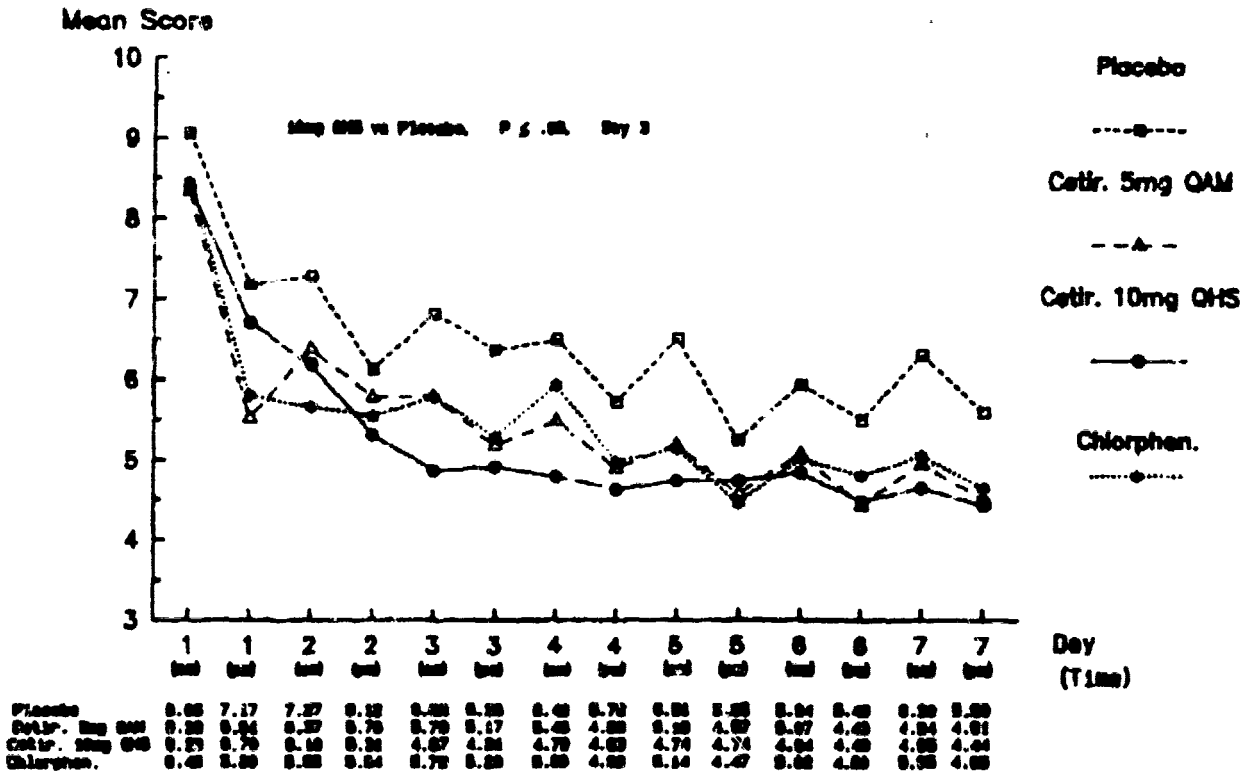
FIGURE 3.6

**Cetirizine Seasonal Rhinitis II
Patient's Total Daily Severity Ratings
(Days 8 to 14)**



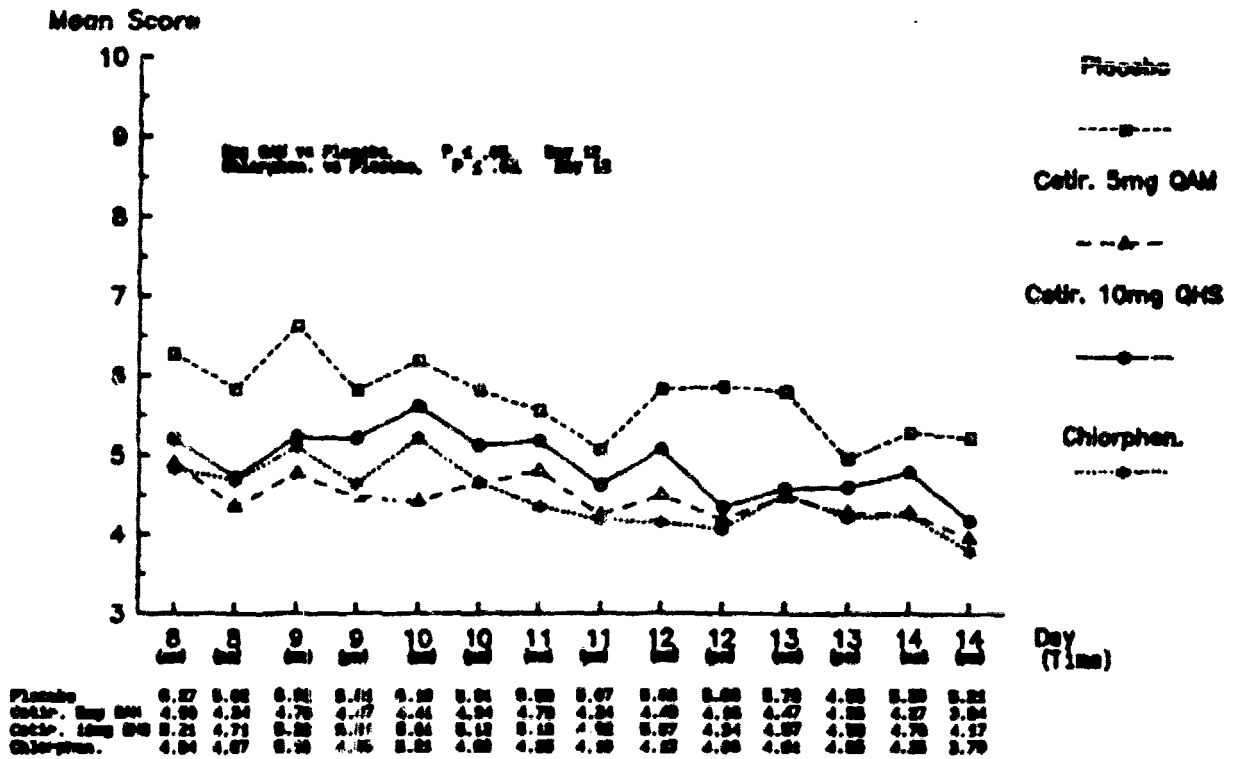
10 412

FIGURE 3.A
Cetirizine Seasonal Rhinitis III
Patient's Total Daily Severity Ratings
(Days 1 to 7)



10 343

FIGURE 3.3
Cetirizine Seasonal Rhinitis III
Patient's Total Daily Severity Ratings
(Days 8 to 14)



10 544

D. [unclear]

STATISTICAL REVIEW AND EVALUATION

NDA: 19-835

JAN 28 1992

Applicant: Pfizer Inc.

Name of Drug: Reactine (ceterizine) Tablets

Indication: Perennial Allergic Rhinitis

Documents Reviewed: Five volumes dated September 16, 1991

This review pertains to one placebo controlled study in patients with perennial allergic rhinitis.

Other studies in perennial allergic rhinitis, seasonal allergic rhinitis and chronic idiopathic urticaria were previously reviewed in a statistical review dated January 25, 1990. These studies were conducted using varying dosing regimens (Ceterizine 5mg, 10mg and 20mg). At a meeting with the sponsor on August 22, 1991 about their pending NDA, the sponsor mentioned that they had completed an additional perennial allergic rhinitis study. Dr. Burke (Division Director (HFD-150)) asked that they submit this study to help in the evaluation of the NDA.

I. Study Description and Method of Analysis:

This was a multicenter, parallel group, double-blind two month study comparing 5mg QAM and 10mg QAM doses of Ceterizine and placebo in patients with perennial allergic rhinitis. All patients had to have minimum two years history of perennial allergic rhinitis and a total severity score of 8 or more (out of a possible 21) based on seven signs and symptoms of rhinitis with at least one moderately severe symptom.

At entry to the study (Study Day 0) and after 2, 4, 6 and 8 weeks of treatment, the investigator recorded the severity of nasal congestion, post-nasal discharge, itching of the nose, sneezing, watery nasal discharge, itching of the eyes and watering of the eyes using a 4 point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). The report did not indicate when this assessment was made relative to when the patient took his/her dose.

Patients maintained a daily diary of the severity of each symptom over the 24 hours prior to each dose of study medication. The patient assessments were made just prior to taking study medication. The severity of each symptom was assessed using the same scale as above.

At the end of the eight week treatment period, or at the time of discontinuation, the investigator made an overall assessment of the effect of therapy using a scale (0 = no improvement or worse, 1 = slight improvement, 2 = definite improvement, 3 = highly effective, 4 = complete disappearance of signs and symptoms).

The primary efficacy parameter is the patient total symptom score, defined as 6 times the mean of the non-missing severity of six of the seven signs and symptoms. Severity of nasal congestion was not included (as in other Ceterizine studies) because antihistamines do not control congestion. There was very little missing daily symptom assessment scores (unless the whole day was missing). Therefore, this missing value assignment rule would have little effect on the total symptom score analysis. The sponsor analyzed patient weekly symptom scores (mean of daily diary scores) and biweekly investigator symptom scores using an analysis of covariance with factors treatment, center and treatment by center interaction with baseline investigator assessment as a covariate.

A repeated measures analysis of covariance of all weekly assessment data was also performed. Patients who did not complete the eight week treatment period were not included in this analysis.

The sponsor also analyzed investigator global assessment of treatments using a Cochran-Mantel-Haenszel test with centers as strata.

II. Results:

Eighty patients were randomized into each treatment. The sponsor considered 76 placebo patients, 78 5mg Ceterizine patients and 76 10mg Ceterizine patients evaluable for efficacy. The reason for non-evaluability was mainly the use of concomitant medication (steroids).

Fifty-three patients (19 placebo, 22 Ceterizine 5mg, 12 Ceterizine 10mg) discontinued prior to completion of the eight-week treatment period. The main reasons were intercurrent illness (22 patients) and adverse experiences (11 patients).

The treatment groups were comparable in demographic variables and baseline mean scores for the signs and symptoms of perennial allergic rhinitis with the exception of nasal congestion where the baseline means were 2.16, 2.37 and 2.16 for placebo, Ceterizine 5mg and Ceterizine 10mg respectively ($p = .061$). This baseline difference should have little effect on the study's conclusions since nasal congestion is not included in total symptom score and investigator's baseline assessment is used as a covariate in the analyses of nasal congestion. (Nasal congestion is not expected to be affected by antihistamines.)

Table 7A presents the adjusted treatment means and the P-value for overall treatment effect from the analysis of covariance. Significant differences between treatments were seen at only Week 1 for post nasal drip, itching of the eyes, watering of the eyes and watery nasal discharge; at Weeks 1 through 4 and Week 7 for sneezing and total symptom score. Further improvement was seen in all treatment groups after Week 1 until about Week 4. Treatment differences at later Weeks in the study were comparable to those at Week 1 (Treatment by Week - interactions were usually between .80 and .98). The failure to show significance after Week 1 for some of the symptoms appears to be attributable to the reduced sample size due to patient withdrawals.

Only sporadic significant treatment by center interactions were seen for patient assessments. The only analyses showing other than sporadic significant heterogeneity of slopes (covariate) was watering of the eyes. Since the baseline effect was always highly significant, the analysis of covariance model was appropriate for analyzing the sponsor's patient assessment data.

The pairwise comparisons done when the overall F test showed significant treatment differences always showed 10mg Ceterizine to be better than placebo. The only significant differences favoring 5mg Ceterizine over placebo were for watery nasal discharge at Weeks 1 and 2 and for sneezing and total symptom score at Week 2. Ceterizine 10mg was significantly better than Ceterizine 5mg for post-nasal discharge, sneezing, itching of the eyes and total symptom score at Week 1.

Table 8A shows the adjusted treatment means and P-values of overall treatment effects from the analysis of covariance for investigator assessments. The only significant differences between treatments were seen in watery nasal discharge and total symptom score at Week 2

and sneezing at Weeks 4 and 6 (the results at Week 2 for sneezing were approaching significance, $P = 0.06$). All the pairwise comparisons for Ceterizine 10mg compared to placebo were significant for these assessments. None of the comparisons of Ceterizine 5mg and placebo were significant. Ceterizine 10mg was significantly better than Ceterizine 5mg for sneezing at Weeks 2 and 4.

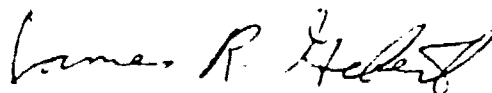
Table 11 presents the results of the investigator's global evaluation. Significant differences favoring Ceterizine 5mg over placebo were seen. Although the results of a pairwise test of Ceterizine 5mg and Ceterizine 10mg tended to favor the 5mg dose ($p = 0.077$), the interpretation of the results is problematic. The Ceterizine 5mg dose had more evaluations in the slight to definite improvement categories but less in the highly effective category (also less in the no improvement category).

Intent-to-treat analyses (not discussed here) gave similar results to the evaluable patient analyses discussed in this review (only 4.2% of the patients were considered non-evaluable).

III. Reviewer's Comments:

Significant differences favoring Ceterizine 10mg over placebo were seen in patient assessed total symptom score for 5 of the 8 weeks ($p < .01$ at Weeks 1 and 2, $p = .02$ at Weeks 3 and 4, $p = .04$ at Week 7, Table 7A). Sneezing was significant also at these weeks and was an important contributor to the total symptom score ($p < .01$ at Weeks 1, 2, 3 and 4; $p = .03$ at Week 7; Table 7A). Significant differences in patient assessments were also seen at Week 1 for four other assessments (post nasal drip, itching of the eyes, watering of the eyes and watery nasal discharge.) ($P \leq .01$ for all 4 symptoms, Table 7A). Generally, treatment differences after Week 1 were comparable to those seen at Week 1.

The results of this study are suggestive that Ceterizine 10mg QAM is the appropriate dosage for perennial allergic rhinitis. Significant differences favoring Ceterizine 10mg over Ceterizine 5mg and placebo were seen in both patient and physician assessments. The results of investigator global assessment however was more equivocal.



James R. Gebert, Ph.D.
Mathematical Statistician, HFD-713

This review consists of 5 pages of text and 5 pages of tables.

Concur: Dr. Chi

Chi
1/28/92

Dr. Dubey

Dubey
1-28-92

cc:

Original: NDA 19-835

HFD-150

HFD-150/Dr. Burke

✓ HFD-150/Ms. Dorsey

HFD-344/Dr. Lisook

HFD-713/Dr. Dubey [File: 1.3.2. NDA]

HFD-713/Dr. Chi

HFD-713/Dr. Gebert

Chron.

J.R.Gebert:x3-2814:SERB:skj:1/27/91:WP51:JG19-835.NDA

TABLE 6: MEAN(±SD) BASELINE AND DEMOGRAPHIC CHARACTERISTICS OF EVALUABLE PATIENTS (CONTINUED)

	TREATMENT GROUP			P-VALUE ¹
	PLACEBO (N= 76)	CETIR. 5 MG (N= 78)	CETIR. 10 MG (N= 76)	
SIGNS OF PERENNIAL ALLERGIC RHINITIS				
NASAL CONGESTION	2.16± 0.67	2.37± 0.61	2.16± 0.65	.061
ITCHING OF NOSE	1.42± 0.77	1.40± 0.90	1.43± 0.75	.954
SNEEZING	1.55± 0.66	1.55± 0.75	1.62± 0.70	.989
POST-NASAL DRIP	2.00± 0.75	2.03± 0.76	1.96± 0.74	.793
ITCHING OF EYES	1.29± 0.83	1.27± 0.86	1.47± 0.72	.197
WATERING OF EYES	1.03± 0.77	0.97± 0.79	1.17± 0.81	.387
WATERY NASAL DISCHARGE	1.75± 0.71	1.77± 0.77	1.76± 0.71	.906
TOTAL SYMPTOM SEVERITY	9.04± 2.33	8.99± 2.55	9.42± 2.30	.621

1. P-VALUE ASSOCIATED WITH THE F-TEST OF TREATMENT EFFECT FROM A TWO-WAY ANOVA.

 CETIRIZINE STUDY 89CE16-0448

TABLE 7A: SUMMARY OF PATIENT DIARY DATA - MEAN(±SD) SYMPTON SEVERITY BY STUDY WEEK FOR EVALUABLE PATIENTS

TABLE ENTRIES ARE ADJUSTED MEAN SEVERITY
TREATMENT GROUP

PARAMETER	WEEK	CETIRIZINE			P-VALUE ¹
		PLACEBO	5 MG QAM	10 MG QAM	
NASAL CONGESTION	1	1.9	1.9	1.8	.34
	2	1.9	1.7	1.7	.14
	3	1.9	1.7	1.6	.08
	4	1.9	1.7	1.6	.12
	5	1.7	1.7	1.5	.34
	6	1.7	1.5	1.5	.18
	7	1.8	1.5	1.5	.06
	8	1.7	1.6	1.5	.59
	MEAN	1.8	1.6	1.6	.17
ITCHING OF THE NOSE	1	1.2	1.1	0.9	.12
	2	1.1	0.8	0.8	.09
	3	0.9	0.8	0.7	.11
	4	0.9	0.7	0.7	.21
	5	0.9	0.7	0.7	.23
	6	0.9	0.7	0.6	.10
	7	0.9	0.6	0.7	.06
	8	0.9	0.6	0.7	.23
	MEAN	0.9	0.7	0.7	.13
SNEEZING	1	1.1	0.9 [#]	0.7 [#]	<.01
	2	1.1	0.8 [#]	0.6 [#]	<.01
	3	1.0	0.8	0.6 [#]	<.01
	4	1.0	0.8	0.5 [#]	<.01
	5	0.8	0.7	0.6	.17
	6	0.9	0.7	0.6	.06
	7	1.0	0.7	0.6 [#]	.03
	8	0.9	0.8	0.6	.16
	MEAN	1.0	0.8	0.6 [#]	<.01
POST NASAL DRIP	1	1.7	1.7	1.4 [#]	.01
	2	1.6	1.4	1.3	.06
	3	1.6	1.5	1.3	.13
	4	1.4	1.4	1.3	.43
	5	1.4	1.3	1.2	.40
	6	1.4	1.3	1.2	.45
	7	1.4	1.3	1.1	.12
	8	1.4	1.2	1.1	.25
	MEAN	1.4	1.3	1.2	.27

¹ : P-VALUE ASSOCIATED WITH F-TEST OF TREATMENT EFFECT FROM ANACOVA.

#; SIGNIFICANTLY DIFFERENT FROM PLACEBO MEAN CHANGE, P ≤ 0.05

CETIRIZINE STUDY 89CE16-0448

TABLE 7A: SUMMARY OF PATIENT DIARY DATA - MEAN(±SD) SYMPTOM SEVERITY BY STUDY WEEK FOR EVALUABLE PATIENTS (CONTINUED)

TABLE ENTRIES ARE ADJUSTED MEAN SEVERITY
TREATMENT GROUP

PARAMETER	WEEK	CETIRIZINE			P-VALUE ¹
		PLACEBO	5 MG QAM	10 MG QAM	
ITCHING OF THE EYES	1	1.0	1.0	0.7 ⁿ	<.01
	2	0.9	0.8	0.6	.09
	3	0.8	0.7	0.6	.06
	4	0.8	0.7	0.6	.22
	5	0.8	0.6	0.6	.15
	6	0.7	0.6	0.6	.47
	7	0.8	0.7	0.6	.14
	8	0.8	0.6	0.6	.31
	MEAN	0.8	0.7	0.6	.18
WATERING OF THE EYES	1	0.8	0.7	0.5 ⁿ	<.01
	2	0.6	0.6	0.4	.21
	3	0.6	0.6	0.4	.12
	4	0.6	0.5	0.4	.19
	5	0.6	0.5	0.5	.30
	6	0.6	0.5	0.5	.56
	7	0.7	0.5	0.4	.24
	8	0.6	0.4	0.4	.51
	MEAN	0.6	0.5	0.4	.33
WATERY NASAL DISCHARGE	1	1.5	1.2 ⁿ	1.0 ⁿ	<.01
	2	1.3	1.0 ⁿ	1.0 ⁿ	.05
	3	1.2	0.9	1.0	.12
	4	1.2	0.9	0.9	.07
	5	1.1	0.8	1.0	.14
	6	1.2	0.9	1.0	.22
	7	1.1	0.9	0.9	.33
	8	1.1	0.9	0.9	.40
	MEAN	1.1	1.0	1.0	.31
TOTAL SYMPTOM SCORE	1	7.3	6.5	5.2 ⁿ	<.01
	2	6.6	5.4 ⁿ	4.9 ⁿ	<.01
	3	6.1	5.3	4.5 ⁿ	.02
	4	5.9	5.1	4.3 ⁿ	.02
	5	5.7	4.6	4.5	.09
	6	5.7	4.7	4.5	.13
	7	5.9	4.6	4.2 ⁿ	.04
	8	5.6	4.5	4.3	.15
	MEAN	5.9	5.0	4.5 ⁿ	.05

¹ : P-VALUE ASSOCIATED WITH F-TEST OF TREATMENT EFFECT FROM ANACOVA.

ⁿ: SIGNIFICANTLY DIFFERENT FROM PLACEBO MEAN CHANGE, P ≤ 0.05

TABLE 8A: SUMMARY OF INVESTIGATOR ASSESSMENTS - MEAN(±SD) SYMPTOM SEVERITY BY STUDY WEEK FOR EVALUABLE PATIENTS (CONTINUED)

TABLE ENTRIES ARE ADJUSTED MEAN SEVERITY
TREATMENT GROUP

PARAMETER	WEEK	CETIRIZINE			P-VALUE ¹
		PLACEBO	5 MG QAM	10 MG QAM	
ITCHING OF THE EYES	2	0.8	0.8	0.6	.14
	4	0.7	0.6	0.6	.83
	6	0.8	0.7	0.6	.37
	8	0.7	0.7	0.6	.43
	MEAN	0.7	0.7	0.6	.54
WATERING OF THE EYES	2	0.6	0.5	0.4	.13
	4	0.5	0.4	0.4	.42
	6	0.6	0.4	0.4	.31
	8	0.5	0.5	0.4	.44
	MEAN	0.6	0.5	0.4	.28
WATERY NASAL DISCHARGE	2	1.3	1.0	0.8 [#]	.01
	4	1.0	1.0	0.9	.60
	6	1.1	0.8	1.0	.25
	8	0.9	0.9	0.8	.68
	MEAN	1.0	0.9	0.9	.57
TOTAL SYMPTOM SCORE	2	6.1	5.5	4.5 [#]	<.01
	4	5.4	5.0	4.2	.11
	6	5.9	4.9	4.3	.07
	8	4.8	4.7	3.9	.33
	MEAN	5.2	4.9	4.2	.15

¹ : P-VALUE ASSOCIATED WITH F-TEST OF TREATMENT EFFECT FROM ANCOVA.
: SIGNIFICANTLY DIFFERENT FROM PLACEBO MEAN CHANGE, P ≤ 0.05

CETIRIZINE STUDY 89CE16-8448

TABLE 11: SUMMARY OF INVESTIGATOR GLOBAL EVALUATIONS FOR EVALUABLE PATIENTS

EVALUATION	PLACEBO	CETIR. 5 MG	CETIR. 10 MG
NO IMPROVEMENT	31 (45%)	14 (19%)	21 (30%)
SLIGHT IMPROVEMENT	19 (28%)	29 (39%)	16 (23%)
DEFINITE IMPROVEMENT	9 (13%)	21 (28%)	15 (21%)
HIGHLY EFFECTIVE	6 (9%)	8 (11%)	16 (23%)
COMPLETE DISAPPEARANCE	4 (6%)	3 (4%)	3 (4%)
TOTAL	69	75	71

CMH TEST¹ P = 0.008

PAIRWISE COMPARISON OF TREATMENT:
 PLACEBO VS. 5 MG: P = 0.010
 PLACEBO VS. 10 MG: P = 0.133
 5 MG VS. 10 MG: P = 0.077

1. COCHRAN-MANTEL-HAENZEL TEST USING CENTER AS STRATA.

CETIRIZINE STUDY 89CE16-0448

TABLE 8A: SUMMARY OF INVESTIGATOR ASSESSMENTS - MEAN(1SD) SYMPTOM SEVERITY BY STUDY WEEK FOR EVALUABLE PATIENTS

TABLE ENTRIES ARE ADJUSTED MEAN SEVERITY
TREATMENT GROUP

PARAMETER	WEEK	CETIRIZINE			P-VALUE ¹
		PLACEBO	5 MG QAM	10 MG QAM	
NASAL CONGESTION	2	1.8	1.8	1.5	.89
	4	1.8	1.6	1.6	.15
	6	1.6	1.6	1.5	.77
	8	1.5	1.5	1.4	.59
	MEAN	1.6	1.5	1.5	.49
ITCHING OF THE NOSE	2	1.0	0.9	0.7	.17
	4	0.9	0.7	0.7	.34
	6	1.0	0.8	0.7	.13
	8	0.7	0.6	0.6	.69
	MEAN	0.8	0.7	0.7	.48
SNEEZING	2	1.0	0.8	0.7	.06
	4	0.9	0.9	0.5 ^M	<.01
	6	0.9	0.8	0.5 ^M	.02
	8	0.6	0.7	0.4	.22
	MEAN	0.8	0.8	0.5 ^M	.01
POST NASAL DRIP	2	1.5	1.5	1.3	.20
	4	1.4	1.4	1.2	.25
	6	1.4	1.3	1.2	.21
	8	1.3	1.3	1.2	.68
	MEAN	1.3	1.3	1.2	.52

¹ : P-VALUE ASSOCIATED WITH F-TEST OF TREATMENT EFFECT FROM ANACOVA.

^M: SIGNIFICANTLY DIFFERENT FROM PLACEBO MEAN CHANGE, P'50.05

CETIRIZINE STUDY 89CE16-9448

JAN 25 1990

Statistical Review and Evaluation

NDA #: 19-835/Drug Class:3C

Applicant: Pfizer, Inc.

Name of Drug: Cetirizine Hydrochloride

Indications: Seasonal Allergic Rhinitis, Perennial Allergic Rhinitis and Chronic Idiopathic Urticaria

Documents Reviewed: Volumes 2.1, 2.83-2.93 dated 7-01-88

The medical officer for this submission is R. Landesman M. D. (HFD-007), with whom this review was discussed.

This review pertains to five controlled studies in seasonal allergic rhinitis (SAR), three for perennial allergic rhinitis (PAR) and two for chronic idiopathic urticaria (URT).

I. Background

Cetirizine is the major human metabolite of hydroxyzine, which has been used over 30 years for the treatment of urticaria. Hydroxyzine is an approved ataractic which has antihistamine properties.

The proposed labelling states that the recommended initial daily dosage of cetirizine is 5 to 10 mg., depending on symptom severity, given as a single dose. It states that the time of administration may be varied to suit individual patient needs. It further states that if sufficient response is not obtained, the dose may be increased as necessary to the maximum recommended daily dose of 20 mg.

II. Chronic Idiopathic Urticaria

A. Study Design and Method of Analysis

These were double-blind, placebo-controlled, parallel group studies in patients with chronic idiopathic urticaria. One (URT-1) was a fixed-dose study of 10 and 20 mg cetirizine administered QHS (once a day at hour of sleep). The other

(URT-2) was a titration study of cetirizine 5 - 20mg QAM compared to hydroxyzine 25mg QHS - 25mg TID. Both studies employed a 4-week treatment period. In study URT-2, cetirizine dosing began at 5mg QAM with an intermediate step of 10mg QAM and a maximum of 20mg QAM. Hydroxyzine began at 25mg QHS with an intermediate step at 25mg BID and a maximum of 25mg TID. In this study the dosage could be increased at day 4 and at the end of the 1st week and then was maintained for the following 3 weeks.

Patients assessed daily, using 4-point scales, the total number of lesions (0 = none; 1 = 1-10; 2 = 11-20; 3 = greater than 20), the number of episodes - occurrences more than 1 hour apart (0 = none; 1 = 1; 2 = 2-3; 3 = greater than 3), the average size of lesions (0 = not present; 1 = up to 1/2 inch; 2 = 1/2 to 1 inch; 3 = greater than 1 inch), the average duration of each episode of lesions (0 = 0 hours; 1 = 0-4 hours; 2 = over 4 to 12 hours; 3 = greater than 12 to 24 hours), and the degree of itching and discomfort (0 = none; 1 = mild; 2 = moderate; 3 = severe). The investigator performed the same assessment at baseline and at scheduled visits (weekly for URT-1; Day 4, Week 1, Week 2 and Week 4 for URT-2). The investigator also made a global assessment of the effect of the therapeutic regimen on signs and symptoms of chronic urticaria. In URT-1 a 4-point scale was used for global assessment (failure, fair, good, excellent). In URT-2 a 5-point scale was used (no improvement or worse, slight but insufficient improvement, definite improvement in signs and symptoms, highly effective, complete disappearance of signs and symptoms).

The physician's global assessments were analyzed by a generalized Cochran-Mantel-Haenszel test using centers as strata.

The patient's mean daily rating for each of the other efficacy variables was computed separately for each week of observation as the mean of the non-missing daily ratings. The day 1 severity was not included in the week 1 (mid-week for URT-2) average because it was not an on-drug rating.

The patient's mean daily ratings and the investigator ratings were analyzed by a univariate repeated measures analysis of variance using weeks as the repeat factor. This analysis included centers, treatment, and investigator baseline rating as factors. Any cases where initial severity or any of the weekly scores were missing were excluded from the repeated measures analysis. [However, any patient who withdrew for lack of efficacy was included by carrying forward their last measurement to subsequent weeks.]

The sponsor tested for covariate by treatment interaction and treatment by center interaction in an expanded model but excluded these factors for the comparison of treatments.

The sponsor also did separate analyses at the times of clinic visits (weekly and mid-week for Week 1 in URT-2) of both patient's and investigator ratings using the model which included treatment, center and investigator baseline rating as factors.

B. Results

1. URT-1

One Hundred Fifty-Three patients from 6 centers entered the trial. Four patients were not included in any efficacy analyses (lost to follow up, inadequate treatment time, etc). The remaining 149 patients (49 placebo, 49 cetirizine 10mg, 51 cetirizine 20mg) were included in some or all of the efficacy analyses.

The treatment groups were comparable in baseline demographic variables (age, sex, race, smoking history), duration of urticaria, number of lesions and degree of itching and discomfort at baseline.

The repeated measures analysis of variance included 137 patients (43 placebo, 45 cetirizine 10mg, 49 cetirizine 20mg). The week by treatment interaction was not significant. However, the center by treatment interaction was significant for some of the efficacy

variables. The cause of this interaction is attributable to two centers. [If these centers were deleted the interaction was not significant ($P>0.18$) for all patient evaluated efficacy variables]. Center 044 had a large placebo response and a poor cetirizine 10mg response. This center had only 9 total patients, however. Center 049 which had 35 patients had a poor cetirizine 20mg response. This reviewer feels it is appropriate to use the repeated measures analysis results to compare treatments even though the center by treatment interaction was significant for some of the efficacy variables. This is because the results of small centers are not as reliable as large centers and any bias created favors placebo over the cetirizine treatments.

Table 1 contains the adjusted treatment means (over 4 weeks of treatment) from the repeated measures analysis having only factors treatments, centers and baseline severity. Significant differences favoring both dosages of cetirizine over placebo were seen for each of the efficacy variables. The differences between cetirizine dosages was not significant for any of the variables ($P>.5$ for all variables).

The results of the weekly analysis were fairly similar. Significant differences favoring cetirizine doses over placebo were detected at weeks 1 through 3 for all efficacy variables. The results at week 4 although directionally the same tended not to be significant. This is attributable to a slightly greater placebo response at this week.

The results of the physician's ratings were fairly similar.

Table A.17 provides the results of the generalized Cochran-Mantel-Haenszel test of the physician's global evaluation. Both cetirizine dosages had higher ratings (better therapeutic effect) than placebo ($P=.001$). The

difference between the cetirizine doses was not significant and the results slightly favor the lower dose.

2. URT-2

Two Hundred Nineteen patients from 14 centers entered the study. The data from eight patients (4 lost to follow up and 4 taking drug less than 4 days) were not included in any efficacy analyses.

The treatment groups were comparable in baseline demographic variables (age, sex, race, smoking history, duration of urticaria and baseline severity of symptoms of urticaria) with the exception of average duration of urticaria ($P=.016$) where the mean duration for hydroxyzine was 2.1 years versus 1.8 years for both placebo and cetirizine. Significantly fewer patients stayed at the lower dose [no titration] for placebo (14/17, 19.2%) compared to cetirizine (23/69, 33.3%) and hydroxyzine (27/69, 39.1%).

The sample sizes of the repeated measures analysis of the patient's ratings varied. They included 65-66 placebo patients, 61-63 cetirizine patients and 56-58 hydroxyzine patients.

The center by treatment interaction was not significant for any efficacy variable. However, the results for degree of itching and discomfort were approaching significance ($P=.077$). A significant week by treatment interaction was seen for number of lesions ($P=.025$) and average duration of lesions ($P=.037$). [The cause of these interactions will be discussed later.]

Table 2 contains the least squares adjusted treatment means (over 4 weeks of treatment) from the repeated measures analysis of patient ratings having only factors treatments, centers and baseline severity. Significant differences favoring cetirizine and hydroxyzine over placebo were seen in all patient assessed efficacy

analyses except average duration of lesions. No significant differences between cetirizine and hydroxyzine were observed ($P > .338$). [It should be noted that the repeated measures analysis here slightly overweights early treatment since it includes both the mid-week and week 1 data whereas the other weeks have only a single weight.]

The results for the weekly and mid-week analyses by the patients gave similar results as did the analysis of physician assessments. The cause of the week by treatment interaction seen in this study appears to be attributable to two sources. The first is a very slight favoring of hydroxyzine over cetirizine in the early week measurements. The later week measurements are more similar for the two treatments. It should be emphasized that the difference between hydroxyzine and cetirizine was never significantly different. The second cause of treatment by week interaction was due to placebo response. Although all treatments showed improvement over time, the difference between placebo and the other treatments was smaller at weeks 3 and 4 than at the earlier weeks. These differences were, however, always significant except for average duration of lesions.

Table A.18 provides the results of the generalized Cochran-Mantel-Haenszel test of the physician's global evaluation. Both treatments were significantly more effective than placebo with results slightly favoring hydroxyzine over cetirizine.

Reviewer's Comments

This reviewer tried alternative analyses on the data that went into the repeated measures analyses. These alternative analyses were not necessarily thought to be more appropriate but were done to see if the sponsor's conclusions were analysis dependent.

The sponsor used SAS type II sums of squares in his analyses

(this analysis gives each patient equal weight in the analysis and is appropriate if treatment by center interaction does not exist). Treatment by center interaction was found, however, in study URT1.

This reviewer used the type III analysis which weighs centers equally. This analysis is more appropriate if treatment by center interaction is not negligible. This reviewer got essentially the same results using the type III analyses.

This reviewer also got significant results using Wilcoxon's Rank Sum tests (except for duration of lesions). Tests were done both ignoring centers and blocking for centers.

The repeated measures analysis deletes patients who do not have values for all observation times. Its results could be biased if patients had differential treatment-related reasons for being excluded. [Bias is not caused by dropouts due to lack of efficacy because these patients have their last value carried forward.] This reviewer does not think the bias is appreciable. The inclusion rates appeared to be similar for the different treatments. Moreover, the results of the repeated measures analysis tended to be confirmed by the weekly analysis which are not affected by patient deletion in other weekly evaluations.

Therefore, these studies demonstrate efficacy of cetirizine for chronic idiopathic urticaria.

III. Seasonal Allergic Rhinitis

A. Study Description and Method of Analyses

These were randomized, double-blind, multi-center, placebo-controlled, parallel group studies in patients with documented pollen allergy. Some of the studies contained active controls. The treatment periods were from one to four weeks duration.

These studies assessed various symptoms of seasonal allergic rhinitis. All studies assessed nasal congestion, sneezing, runny nose, itching of the nose, itching of the

eyes and watering of the eyes. Two studies (SAR-1 and SAR-2) assessed itching of the roof of the mouth. In addition, SAR-1 assessed redness of the eyes. All symptoms were assessed by both the patient and the physician using a 4-point scale (0=none, 1=mild, 2=moderate, 3=severe). The physician's assessment was made prior to treatment and at weekly visits (biweekly for studies SAR-4 and SAR-5). The patients rated symptom severity on a daily basis in the evening (and in the morning also in studies SAR-2 and SAR-3).

At the end of treatment the physician made a global assessment of treatment. The 4-point scale (failure, fair, good, excellent) was used in studies SAR-2, SAR-4 and SAR-5. A 3-point scale (ineffective, effective with significant adverse experiences, effective and well tolerated) was used in study SAR-1. In study SAR-3 the global assessment was made by the patient using the 4-point scale (no relief, some relief, considerable relief, complete relief).

The symptom severity score of each of the symptoms as rated by the investigator and the patient's weekly average, as well as, the investigator's and patient's Total Symptom Severity Score (always excluding nasal congestion) were compared among treatment groups using analyses of covariance that adjusted for centers and baseline severity (as measured by the investigator's rating). [The sponsor tested for treatment by center and baseline by treatment interactions and except for sporadic instances found these non-significant.] If the treatment period was multi-week, a repeated measures analysis was done using an analysis which included weeks as a repeat factor.

Global assessments were compared among treatment groups using a generalized Cochran-Mantel-Haenszel test stratifying by study center.

B. Results

Table 3 shows the treatment regimens and duration of treatment in these 5 parallel group studies. Table 4 shows the number of patients evaluable for efficacy. [Except for study SAR-5 where the data from one center were excluded, very few patients were excluded from efficacy analyses.]

Except for a few sporadic results, treatment groups were comparable at baseline in demographic variables and baseline symptomatology of disease.

Table 6 presents the results from the repeated measures analysis of patient ratings for individual symptoms and total symptom severity. It is felt that these analyses adequately summarize the treatment efficacy results because center by treatment interactions and week by treatment interactions were only sporadically significant except for study SAR-4 which will be discussed later.

Significant differences between cetirizine treatments and placebo were seen in the patient ratings for total symptom score in 3 of the 5 studies (SAR-1, SAR-2, SAR-4). The differences from placebo in the other studies were not significant for this response variable although the data favored cetirizine. In the symptoms themselves, significant differences favoring all cetirizine treatments over placebo was seen for sneezing in all 5 studies, for rhinorrhea in 3 of 5 studies, for nasal pruritus in 4 of 5 studies (except for the 10mg QHS treatment in study SAR-3), for ocular pruritus in 3 of 5 studies (except for cetirizine 5mg BID in study SAR-2), and for tearing in 2 of 5 studies. A few other symptoms were significant in only 1 study (SAR-1).

The results of the repeated measures analyses of patient symptoms were supported by the analyses of physician rated symptoms and the analyses by weeks of both

patient and physician ratings.

The results of the global efficacy ratings are given in table 5. Significant results favoring cetirizine over placebo were seen in SAR-1 and SAR-4. [In study SAR-2 only the cetirizine 10mg QHS group was different from placebo.] It should be noted that SAR-3 used a relief scale which in this summary is equated to an efficacy scale.

Reviewer's Comments

The medical officer noticed that the total symptom score was imputed at times when some symptoms were missing. The sponsor used a rule that gave the patient a value equal to the total number of symptoms assessed in the study times the average symptom score of symptoms marked by the patient. The medical officer wanted to know if this was appropriate and whether it would have much effect on the study results.

This reviewer found that this imputation rule did not have much effect. The number of patients receiving imputed values was small (one or two patients per treatment group per study). Furthermore, the rule is logical and does not favor any particular treatment. It should be noted that the analyses of individual symptoms are not affected by this imputation rule.

This reviewer was able to duplicate the sponsor's analyses with the computer NDA data and programs provided. A non-parametric analysis of the patient mean symptom scores was also done as a confirmatory analysis and similar results were obtained.

In the results section it was mentioned that significant week by treatment interaction was seen in study SAR-4 [itching eyes ($P=.023$), watering eyes ($P=.002$), total severity ($P=.016$)]. (Table 7 presents the least squares treatment means by weeks of treatment for these variables from the week analyses.) Although the results at weeks 3 and 4 were not as strong as the results from week 1 and 2, this reviewer felt that it is appropriate to stress the overall repeated measures result for

In study SAR-5, the sponsor dropped Dr. Fallier's center from the overall analysis because of significant treatment by center interaction. In this center the terfenadine patients had almost complete symptom improvement whereas cetirizine showed a level of symptom improvement consistent with other studies. This level of symptom improvement for terfenadine was not seen in the other three centers in study SAR-5 nor in all centers in study SAR-4. Although there is something unexplained going on here, the sponsor is justified in excluding Dr. Fallier's center.

This reviewer noted that in study SAR-1 one center had 120 patients which was over 1/4 of the patients entered into the study (this is twice as many patients as any other center). It was determined that significant results were obtained when this center was deleted or when giving centers equal weight (SAS type III analyses of variance). Therefore, this imbalance is not important to the study results.

The sponsor's labelling is partially supported by the study results. Cetirizine 5mg, 10mg and 20mg QAM were shown to be effective. There was only one study for the 20mg QAM dosage. Study SAR-2 shows relative equivalence of the 10mg dosages studied (QAM, QHS and 5mg BID). Whether the results of this one study supports the labelling that "the time of administration may be varied to suit individual patient needs" must be left for clinical judgement.

IV. Perennial Allergic Rhinitis

A. Study Design and Method of Analysis

These were double-blind, placebo-controlled, multi-center parallel group studies in patients with perennial allergic rhinitis. There were two fixed dose studies and one titration study (PAR-3). In PAR-1, cetirizine 10mg QAM and cetirizine 20mg QAM were compared to placebo over 4 weeks of treatment. In PAR-2, cetirizine 15mg (5mg QAM and 10mg QHS) was compared to chlorpheniramine S. R. 8mg BID and placebo over 6 weeks

of treatment. In PAR-3, cetirizine 5-10mg QAM was compared to diphenhydramine 25-50mg TID and placebo over 4 weeks of treatment during its double-blind phase. In this later study, drugs were titrated to the higher dose during the first week of the study if necessary. There was an open label continuation of study PAR-3 for active drugs which will not be discussed here.

The efficacy variables and methods of analysis were similar to the SAR studies with the exception that, additionally, the symptom post-nasal discharge was also assessed with the same 4-point severity scale. This symptom was also included in the total symptom severity score. [Oral pruritus was only assessed in study PAR-1.] The physician's assessments were made at weeks 1, 2, 4 for PAR-1; weeks 1, 3, 6 for PAR-2; and weeks 1, 4, for the double-blind phase of study PAR-3.

Global evaluation of therapeutic effect was assessed on a 4-point scale (failure, fair, good, excellent) in studies PAR-1 and PAR-2 and on a 5-point scale (no improvement/worse, insufficient improvement, definite improvement, highly effective, complete disappearance of symptoms). For summarization purposes the sponsor called the last two categories excellent and treated this study as the 4-point scale (failure, fair, good, excellent). [The sponsor did the generalized Cochran-Mantel-Haenszel test on the original 5-point scale, however.]

B. Results

1. PAR-1

There were 220 patients at 6 centers entered into the study. There were 205 patients (69 placebo, 68 for both cetirizine 10mg and 20mg) used in the repeated measures analysis of patient ratings. Two hundred fifteen (215) patients supplied data to the weekly analyses.

The treatment groups were comparable in demographic variables (age, duration of allergic rhinitis, pre-

treatment severity of nasal congestion, total severity, sex, race and smoking history).

In the repeated measures analysis of patient rated symptoms, the week by treatment and initial severity by treatment interactions were only significant for the itching mouth symptom. The center by treatment interaction was never significant. Therefore, the repeated measures analysis is an appropriate summarization of treatment results. Table 8 contains the adjusted mean severities of symptoms (adjusted for centers and initial severity) over the four weeks of treatment for this study. Significant differences favoring both cetirizine treatments over placebo were seen in post-nasal discharge, sneezing and total symptom severity. The 20mg cetirizine group also showed significantly more improvement than placebo in rhinorrhea. No significant differences between cetirizine treatments were seen in this study.

The repeated measures analysis of physician ratings of symptoms showed similar results but with a few more significant comparisons of the cetirizine treatments with placebo.

Table 9 provides a summarization of the global evaluation of effectiveness. Both cetirizine treatments showed significantly more improvement than placebo using Cochran-Mantel-Haenszel tests.

2. PAR-2

There were 182 patients at 5 centers who entered the trial. Only 132 patients (46 placebo, 42 cetirizine, 44 chlorpheniramine) were included in the repeated measures analysis of patient ratings. [The sponsor stressed the weekly analyses because these analyses included about 40 more patients. This reviewer will stress the repeated measures analysis because it gives an assessment over the whole treatment period.]

The center by treatment and week by treatment interactions were only sporadically significant in the repeated measures analysis of patient rated symptoms. The repeated measures analysis is, therefore, appropriate for judging the effectiveness of treatments over the full 6 weeks of treatment. Table 8 shows that both cetirizine and chlorpheniramine were significantly better than placebo for sneezing, rhinorrhea and total symptom severity (only nearly significant for cetirizine). Chlorpheniramine was also significantly better than placebo for nasal pruritus. No significant differences were seen between cetirizine and chlorpheniramine.

The ratings of global effectiveness of treatment are provided in table 9. No significant differences between treatments were seen in this study.

3. PAR-3

There were 227 patients at 6 centers who entered into the study. There were 192 patients (63 placebo, 67 cetirizine, 62 diphenhydramine) used in the repeated measures analysis of patient ratings of symptoms. Two hundred nineteen (219) were included in the weekly analyses of patient ratings. The treatment groups were comparable in demographic variables. The percentage of patients staying at the minimum dose for cetirizine (37%) and diphenhydramine (51%) were significantly higher than the percentage for placebo (18%). The center by treatment and week by treatment interactions were never significant in the repeated measures analysis of patient ratings. The initial severity by treatment interaction was significant only for the symptoms of watering eyes and itching eyes. The model using separate slopes for each treatment for these variables gave nearly identical least squares means and did not essentially change the P-values of the differences between treatment least squares means. It is, therefore appropriate to use the repeated measures analyses of patient ratings to summarize study results.

Table 8 contains the adjusted mean severities of symptoms (adjusted for centers and initial severity) over the four weeks of treatment. Significant differences favoring cetirizine and diphenhydramine over placebo were seen in total symptom severity and all symptoms except nasal congestion for both treatments and post-nasal discharge for the cetirizine group. No significant differences between active drugs were seen for any symptom although the results always favored diphenhydramine.

Table 9 presents the summarization of ratings of global efficacy. Both cetirizine and diphenhydramine showed significantly more improvement than placebo using the Cochran-Mantel-Haenszel test.

C. Reviewer's Comments

This reviewer was able to duplicate the sponsor's results with the data and programs provided.

It should be noted that center 056 strongly influenced the significant results seen in study PAR-1. The differences between both cetirizine treatments and placebo were significant within this center for the patient rated symptom runny nose and for total symptom severity. However, since the other centers were also showing cetirizine treatments better than placebo, the analysis including all centers is appropriate. [The treatment by center interaction p-value in the repeated measures analyses of patient rated symptoms was greater than 0.426 for all symptoms except itching of the mouth which had a p-value 0.176.]

These studies demonstrate efficacy of cetirizine. These studies used QAM dosing except for PAR-2 which used 15mg cetirizine (5mg QAM and 10mg QHS). Whether a labelling that states "that the time of administration may be varied to suit individual patient needs" can be

made rather than being limited to QAM dosing must be left for clinical judgment.

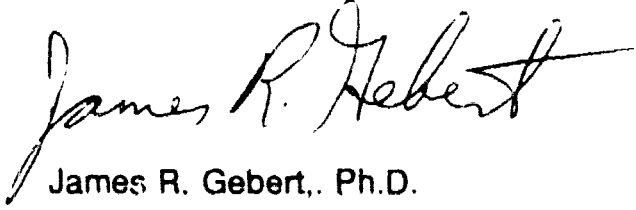
V. Conclusions (May be conveyed to the sponsor)

These studies demonstrate the effectiveness of cetirizine for the indications chronic idiopathic urticaria, seasonal allergic rhinitis and perennial allergic rhinitis. These studies support a recommended dosage of 5-10mg QAM with the need for a 20mg dosage for some patients. These studies do not adequately support the labelling claim that the time of administration can be varied to suit individual patient needs. Only one study showed relative equivalence of 10mg QAM with 10mg QHS. It must be left to clinical judgment whether the time of administration claim is appropriate.

In the two urticaria studies, cetirizine was superior to placebo in the repeated measures analysis of all efficacy variables except average duration of lesions in URT-2.

In the seasonal allergic rhinitis studies, cetirizine was superior to placebo in the repeated measures analysis of patient rated total symptom severity in 3 of 5 studies. The repeated measures analyses of the individual patient rated symptoms showed superiority of cetirizine over placebo for sneezing (5 out of 5 studies), for nasal pruritus (4 out of 5 studies), for rhinorrhea and ocular pruritus (3 out of 5 studies) and for tearing (2 out of 5 studies). A few other symptoms were significant in only 1 study.

In the perennial allergic rhinitis studies, cetirizine was superior to placebo in the repeated measures analysis of patient rated total symptom severity in 2 out of 3 studies with the third study being nearly significant ($P=.059$). The repeated measures analysis of individual patient rated symptoms showed superiority of cetirizine over placebo in sneezing and nasal pruritus (3 out of 3 studies) and in rhinorrhea (2 out of 3 studies). A few other symptoms were significant in only 1 study.

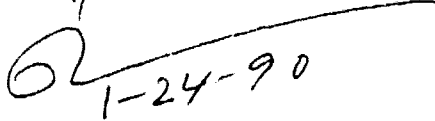


James R. Gebert, Ph.D.
Mathematical Statistician
HFD-713

Concur: Dr. Sanathanan

J.R.G.
1/23/90

Dr. Dubey


1-24-90

cc

Orig. NDA 19-835

HFD-150

HFD-007 ✓

HFD-007/Dr. Landesman

HFD-344/Dr. Lisook

HFD-713/Dr. Dubey [File 1.3.2 NDA]

HFD-713/Dr. Gebert

HFD-713/Dr. Sanathanan

Chron.

ajd/SERB/writenow/NDA-19-835/12-08-89

1-10-90/1/12/90

This review contains 17 pages and 11 tables.

TABLE 1

PATIENT RATINGS
ADJUSTED TREATMENT MEANS
REPEATED MEASURES ANALYSIS
(OVER 4 WEEKS OF TREATMENT)

STUDY URT-1

	<u>PLACEBO</u> <u>(n=43)</u>	<u>CETIRIZINE</u> <u>10mg (n=45)</u>	<u>CETIRIZINE</u> <u>20mg (n=49)</u>
NUMBER OF LESIONS	1.45	1.04**	0.96**
NUMBER OF EPISODES	1.45	0.95**	0.89**
AVG. SIZE OF LESIONS	1.38	0.93**	0.92**
AVG. DUR. OF LESIONS	1.5	1.04**	1.04**
ITCHING/DISCOMFORT	1.49	0.79**	0.78**

** SIGNIFICANT AT 0.05 LEVEL

TABLE A.17 (URT1)

INVESTIGATOR'S GLOBAL EVALUATION OF THERAPEUTIC EFFECT

<u>Rating</u>	<u>Number of Cases</u>			<u>Mantel-Haenszel Statistic (p-value)¹</u>
	<u>Placebo</u>	<u>Cetir. 10 mg</u>	<u>Cetir. 20 mg</u>	
0 = Failure	22	8	6	
1 = Fair	8	7	13	
2 = Good	10	13	13	
3 = Excellent	5	20	17	
Mean Rating	.96	1.94	1.84	18.58 (.001)

<u>Pairwise Comparison</u>	<u>M-H Statistic (1 d.f.)</u>	<u>P-value</u>
Cetir. 10 mg vs placebo	15.73	.001
Cetir. 20 mg vs placebo	11.85	.001
Cetir. 10 mg vs cetir. 20 mg	.33	.563

¹ Generalized Mantel-Haenszel statistic with 2 d.f., stratified by study center

**TABLE 2
 PATIENT RATINGS
 ADJUSTED TREATMENT MEANS
 REPEATED MEASURES ANALYSIS
 (OVER 4 WEEKS OF TREATMENT)**

STUDY URT-2

	PLACEBO (N=66)	CETIRIZINE (N=63)	HYDROXYZINE (N=58)
NUMBER OF LESIONS ^a	1.43	0.96**	0.90**
NUMBER OF EPISODES	1.51	0.99**	0.87**
AVG. SIZE LESIONS	1.4	1.06**	0.92**
AVG. DUR LESIONS ^a	1.15	1.02	0.88
ITCHING/DISCOMFORT	1.48	0.85**	0.76**

**** SIGNIFICANT AT 0.05 LEVEL**

^a THE TREATMENT BY WEEK INTERACTION WAS SIGNIFICANT FOR NUMBER OF LESIONS AND AVERAGE DURATION OF LESIONS

CETIRIZINE URTICARIA II

TABLE A.18 (URT2)

INVESTIGATOR'S GLOBAL EVALUATION OF THERAPEUTIC EFFECT

<u>Rating of Improvement</u>	<u>Number of Cases</u>		
	<u>Placebo</u> (n=66)	<u>Cetirizine</u> (n=67)	<u>Hydroxyzine</u> (n=65)
0 = None or Worse	30	9	7
1 = Slight	8	10	9
2 = Definite	11	21	24
3 = Highly Effective	9	20	14
4 = Complete	8	7	11
Mean Rating	1.35	2.09	2.20

Mantel-Haenszel Statistic¹ = 16.81, p = .001

<u>Pairwise Comparison</u>	<u>M-H Statistic (1 d.f.)²</u>	<u>P-value</u>
Hydroxyzine vs Placebo	13.20	.001
Cetirizine vs Placebo	9.87	.002
Hydroxyzine vs Cetirizine	.62	.433

¹ Generalized Mantel-Haenszel statistic with 2 d.f., stratified by study center

² Generalized Mantel-Haenszel statistic with 1 d.f., stratified by study center

Table 3. Adequate and Well-Controlled Studies for the Indication: Seasonal Allergic Rhinitis*

NDA Report No.	Duration of Treatment (Weeks)	Cetirizine Regimen(s)	Positive Control Regimen
SAR-1	1	5 mg QAM 10 mg QAM 20 mg QAM	None
SAR-2	2	10 mg QAM 10 mg QHS 5 mg BID	None
SAR-3	2	5 mg QAM 10 mg QHS	Chlorpheniramine 8 mg S.R. BID
SAR-4	4	5 mg QAM	Terfenadine 60 mg BID
SAR-5	4	10 mg QAM	Terfenadine 60 mg BID

* All Studies Utilized a Randomized, Double-Blind, Placebo-Controlled, Parallel Design.

NDA 19835

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Table 4. Summary of Patient Enrollment and Efficacy Evaluability in Seasonal Allergic Rhinitis Studies

NDA Report No.	No. of Study Sites	Total Number of Patients Entered				Number of Efficacy Evaluable Patients			
		Cetirizine	Active Control	Placebo	Total	Cetirizine	Active Control	Placebo	Total
SAR-1	9	313	0	104	419	310	0	102	412
SAR-2	3	152	0	32	204	147	0	51	198
SAR-3	5	158	78	73	314	152	75	76	303
SAR-6	5	79	78	78	235	79	78	74	231
SAR-5	4	70	70	70	210	69	67	69	205*
Total	26	774	226	382	1382	757	220	372	1349

* Includes 54 patients in Study No. 35-N-0051. This site was excluded from the multicenter analysis because of an extreme center x treatment effect.

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Table 3. Summary of Global Efficacy Ratings (a) in Seasonal Allergic Rhinitis Studies

NDA Report No.	Treatment Regimen	Total No. of Patients Rated	Global Assessment: Number (%)			
			Failure	Fair	Good	Excellent
SAK-1 (b)	Cet 5 mg QAM *	99	27 (27%)		72 (73%)	
	Cet 10 mg QAM *	106	22 (21)		84 (79)	
	Cet 20 mg QAM *	103	25 (24)		78 (76)	
	Placebo	102	8 (67)		94 (93)	
SAK-2	Cet 10 mg QAM	47	11 (23)	10 (21)	18 (38)	8 (17)
	Cet 10 mg QHS *	47	6 (13)	10 (21)	19 (40)	12 (26)
	Cet 5 mg BID	48	11 (23)	10 (21)	17 (31)	10 (21)
	Placebo	51	19 (37)	10 (20)	16 (27)	8 (16)
SAK-3	Cet 5 mg QAM	73	22 (30)	26 (36)	20 (27)	5 (7)
	Cet 10 mg QHS	78	17 (22)	35 (49)	22 (28)	1 (1)
	Chlorphen. 8 mg SR BID	73	13 (18)	33 (43)	23 (32)	4 (6)
	Placebo	74	21 (31)	30 (41)	21 (28)	0 (0)
SAK-4	Cet 5 mg QAM *	79	16 (20)	21 (27)	27 (34)	15 (19)
	Terfenadine 60 mg BID *	75	15 (19)	25 (32)	26 (33)	12 (15)
	Placebo	71	21 (30)	29 (35)	20 (28)	5 (7)
SAK-5	Cet 10 mg QAM	48	10 (21)	24 (30)	12 (23)	2 (4)
	Terfenadine 60 mg BID	49	12 (25)	13 (27)	20 (41)	4 (8)
	Placebo	51	20 (35)	12 (24)	11 (22)	8 (16)

* p < 0.05 vs Placebo

(a) In SAK-1, 2, 4 and 5 global efficacy was rated by the investigator; in SAK-3 it was rated by the patient in the presence of the investigator.

(b) In SAK-1 global efficacy was rated as either effective or not effective.

TABLE 6
PATIENT RATINGS
ADJUSTED MEAN SEVERITY RATING¹
OVER ENTIRE TREATMENT PERIOD
SAR-1 (1 WEEK OF TREATMENT)

	TREATMENT REGIMEN			
	PLACEBO (N=101)	CETIRIZINE 5mg QAM ² (N=101)	CETIRIZINE 10mg QAM (N=105)	CETIRIZINE 20mg QAM (N=102)
SNEEZING	1.37	0.97**	0.91**	0.83**
RHINORRHEA	1.41	1.03**	0.96**	0.89**
NASAL PRURITUS	1.13	0.86**	0.77**	0.65**
OCULAR PRURITUS	1.17	0.81**	0.75**	0.79**
TEARING	0.99	0.67**	0.66**	0.50**
REDNESS OF EYES	0.99	0.64**	0.66**	0.53**
PALATAL PRURITUS	0.5	0.43	0.45	0.31**
NASAL CONGESTION	1.51	1.44	1.25**	1.32**
TOTAL SYMPTOM SEVERITY ²	7.48	5.41**	5.20**	4.44**

**SIGNIFICANTLY DIFFERENT FROM PLACEBO (P LESS THAN OR EQUAL TO 0.05)

¹ TREATMENT MEAN SYMPTOM SEVERITY ADJUSTED FOR INITIAL SEVERITY AND CENTER DIFFERENCES

² DOES NOT INCLUDE NASAL CONGESTION

TABLE 6 cont.
 ADJUSTED MEAN SEVERITY RATING¹
 OVER ENTIRE TREATMENT PERIOD
 (REPEATED MEASURES ANALYSIS)
 SAH-2 (2 WEEKS OF TREATMENT)

	TREATMENT REGIMEN			
	PLACEBO (N=45)	CETIRIZINE 10mg QAM (N=46)	CETIRIZINE 10mg QHS (N=45)	CETIRIZINE 5mg BID (N=46)
SNEEZING	1.18	0.72**	0.54**	0.67**
RHINORRHEA	1.27	0.93**	0.90**	0.82**
NASAL PRURITIS	1.23	0.89**	0.78**	0.84*
OCULAR PRURITIS	1.17	0.74**	0.77**	0.92
TEARING	0.87	0.54**	0.56**	0.67
REDNESS OF EYES	#	#	#	#
PALATAL PRURITIS	0.52	0.27	0.38	0.43
NASAL CONGESTION	1.53	1.39	1.36	1.32
TOTAL SYMPTOM SEVERITY ²	6.18	4.20**	3.94**	4.38**

** SIGNIFICANTLY DIFFERENT FROM PLACEBO (P LESS THAN OR EQUAL TO 0.05)

NOT ASSESSED

¹ TREATMENT MEAN SYMPTOM SEVERITY ADJUSTED FOR INITIAL SEVERITY AND CENTER DIFFERENCES

² DOES NOT INCLUDE NASAL CONGESTION

TABLE 5 cont.
 ADJUSTED MEAN SEVERITY RATING¹
 OVER ENTIRE TREATMENT PERIOD
 (REPEATED MEASURES ANALYSIS)
 SAR -3 (2 WEEKS OF TREATMENT)

	TREATMENT REGIMEN			
	PLACEBO (N=71)	CETIRIZINE 5mg QAM (N=72)	CETIRIZINE 10mg QHS (N=76)	CHLORPHEN (N=71)
SNEEZING	1.15	0.80**	0.84**	0.90**
RHINORRHEA	1.34	1.12	1.14	1.11
NASAL PRURITUS	1.23	0.92**	1.02	0.97**
OCULAR PRURITUS	1.11	0.92	0.96	0.89
TEARING	0.91	0.81	0.74	0.79
REDNESS OF EYES	#	#	#	#
PALATAL PRURITUS	#	#	#	#
NASAL CONGESTION	1.72	1.63	1.6	1.6
TOTAL SYMPTOM SEVERITY ²	5.7	4.57	4.74	4.61

** SIGNIFICANTLY DIFFERENT FROM PLACEBO (P LESS THAN OR EQUAL TO 0.05)

NOT ASSESSED

1 TREATMENT MEAN SYMPTOM SEVERITY ADJUSTED FOR INITIAL SEVERITY AND CENTER DIFFERENCES

2 DOES NOT INCLUDE NASAL CONGESTION

TABLE 6 cont

ADJUSTED MEAN SEVERITY RATING¹
 OVER ENTIRE TREATMENT PERIOD
 (REPEATED MEASURES ANALYSIS)
 SAR- 4 (4 WEEKS OF TREATMENT)

	TREATMENT REGIMEN		
	PLACEBO (N=68)	CETIRIZINE 5mg QAM (N=72)	TERFENADINE 60mg BID (N=74)
SNEEZING	1.13	0.85**	0.81**
RHINORRHEA	1.14	0.81**	0.88**
NASAL PRURITUS	1.19	0.82**	0.86**
OCULAR PRURITUS	1	0.76**	0.65**
TEARING	0.62	0.52	0.45
REDNESS OF EYES	#	#	#
PALATAL PRURITUS	#	#	#
NASAL CONGESTION	1.53	1.34	1.32
TOTAL SYMPTOM SEVERITY ²	5.08	3.77**	3.6**

** SIGNIFICANTLY DIFFERENT FROM PLACEBO (P LESS THAN OR EQUAL TO 0.05)

NOT ASSESSED

¹ TREATMENT MEAN SYMPTOM SEVERITY ADJUSTED FOR INITIAL SEVERITY AND CENTER DIFFERENCES

² DOES NOT INCLUDE NASAL CONGESTION

TABLE 6 cont
 ADJUSTED MEAN SEVERITY RATING¹
 OVER ENTIRE PTREATMENT PERIOD
 (REPEATED MEASURES ANALYSIS)
 SAR- 5 (4 WEEKS OF TREATMENT)

	TREATMENT REGIMEN		
	PLACEBO (N=46)	CETIRIZINE 10mg QAM (N=44)	TERFENADINE 60mg (N=46)
SNEEZING	1.22	0.88**	0.83**
RHINORRHEA	1.20	1.00	0.97
NASAL PRURITUS	1.05	0.88	0.86
OCULAR PRURITUS	0.98	0.83	0.76
TEARING	0.60	0.64	0.58
REDNESS OF EYES	#	#	#
PALATAL PRURITUS	#	#	#
NASAL CONGESTION	1.59	1.48	1.54
TOTAL SYMPTOM SEVERITY ²	5.02	4.27	4.00

** SIGNIFICANTLY DIFFERENT FROM PLACEBO (P LESS THAN OR EQUAL TO 0.05)

NOT ASSESSED

¹ TREATMENT MEAN SYMPTOM SEVERITY ADJUSTED FOR INITIAL SEVERITY AND CENTER DIFFERENCES

² DOES NOT INCLUDE NASAL CONGESTION

TABLE 7
ADJUSTED TREATMENT MEANS¹
FOR SYMPTOMS WITH SIGNIFICANT TREATMENT BY WEEK
INTERACTION IN SAR-4

	ITCHING OF EYES			WATERING EYES			TOTAL SEVERITY		
	P	C	T	P	C	T	P	C	T
WEEK 1	1.34	0.89**	0.64**	0.95	0.63**	0.57**	6.41	4.40**	4.58**
WEEK 2	0.96	0.73**	0.56**	0.6	0.49**	0.40**	5.03	3.62**	3.28**
WEEK 3	0.97	0.70**	0.59**	0.55	0.45	0.44	4.86	3.37**	3.41**
WEEK 4	0.81	0.69	0.6	0.46	0.48	0.36	4.34	3.57	3.36**

** SIGNIFICANTLY DIFFERENT FROM PLACEBO (P LESS THAN OR EQUAL TO 0.05)
 FOR THAT WEEKLY ANALYSIS

P = PLACEBO, C = CETIRIZINE 5mg, T = TERFENADINE

¹ TREATMENT MEAN SYMPTOM SEVERITY ADJUSTED FOR INITIAL SEVERITY
 AND CENTER DIFFERENCES

Table 8 Summary of Patient Symptom Severity Ratings in Perennial Allergic Rhinitis Studies

NDA Report No.	Treatment Regimen	Mean Severity Rating Over the Entire Treatment Period ^b								Total ^d Symptom Severity
		Nasal Congestion	Post-Nasal Discharge	Sneezing	Rhinorrhea	Nasal Pruritus	Tearing	Ocular Pruritus	Oral Pruritus	
PAR-1 ^c	Cetirizine 10 mg QAM	1.61	1.12*	0.79*	0.96	0.72	0.56	0.70	0.26	5.11*
	Cetirizine 20 mg QAM	1.43	1.11*	0.72*	0.86*	0.70	0.66	0.70	0.29	4.97*
	Placebo	1.59	1.37	0.97	1.12	0.89	0.72	0.84	0.38	6.33
PAR-2 ^c	Cetirizine 15mg (3mg QAM & 10mg QHS)	1.03	1.10	0.48*	0.81*	0.56	0.33	0.56	-	3.87*
	Chlorpheniramine S.R. 8mg B.I.D.	1.21	0.96	0.48*	0.77*	0.50*	0.37	0.55	-	3.61*
	Placebo	1.38	1.05	0.82	1.08	0.80	0.48	0.73	-	4.95
PAR-3 ^{c,d}	Cetirizine 5-10mg QAM	1.44	1.05	0.63*	0.81*	0.58*	0.34*	0.45*	-	3.89*
	Diphenhydramine 25-50mg T.I.D.	1.34	0.95*	0.50*	0.66*	0.48*	0.30*	0.39*	-	3.27*
	Placebo	1.59	1.25	1.03	1.10	0.77	0.60	0.76	-	5.51

* Treatment effect significantly superior to placebo (p less than or equal to 0.05).

* p = 0.059 compared to placebo.

^a Rating scale: 0=none; 1=mild; 2=moderate; 3=severe. Means were adjusted for initial severity and center differences.

^b Computed as the sum of the ratings of individual symptoms excluding nasal congestion.

^c Repeated measures analyses were done only on patients with complete data.

^d Rating over the first four weeks (double-blind phase).

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Table 9. Summary of Investigator Global Efficacy Ratings in Perennial Allergic Rhinitis Studies

NDA Report No.	Treatment	Total No. of Patients	Number of Patients (%)			
			Failure	Fair	Good	Excellent
PAR-1	Cetirizine 10mg QAM*	72	17 (23.6)	20 (27.8)	22 (30.5)	13 (18.1)
	Cetirizine 20mg QAM*	68	14 (20.6)	17 (25.0)	24 (35.3)	13 (19.1)
	Placebo	70	25 (35.7)	28 (40.0)	10 (14.3)	7 (10.0)
PAR-2	Cetirizine 15mg (5mg QAM & 10mg QHS)	55	16 (29.1)	18 (32.7)	16 (29.1)	5 (9.1)
	Chlorpheniramine S.R. 8mg B.I.D.	57	14 (24.6)	19 (33.3)	18 (31.6)	6 (10.5)
	Placebo	54	20 (37.0)	21 (38.9)	9 (16.7)	4 (7.4)
PAR-3 ^a	Cetirizine* 5-10mg QAM	71	11 (15.5)	18 (25.4)	23 (32.4)	19 (26.8)
	Diphenhydramine* 25-50mg TID	73	7 (9.6)	25 (34.2)	19 (26.0)	22 (30.1)
	Placebo	75	33 (44.0)	26 (34.7)	12 (16.0)	4 (5.3)

Rating scale: failure=no improvement/worse; fair=slight/insufficient improvement; good=definite improvement; excellent=highly effective/complete disappearance of signs and symptoms.

^a Double-blind phase.

* Treatment effect significantly superior to placebo (p less than or equal to 0.05).

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NOV 15 1995

Clinical Pharmacology and Biopharmaceutics Review

Cetirizine HCl Tablets
(ZYRTEC®)
NDA 19-835

Submission Dates:
January 9, 1995
April 25, 1995
May 12, 1995

Pfizer, Inc.
235 East 42nd Street
New York, NY 10017

Reviewer:
Brad Gillespie, PharmD
Purpose:
Consistency for Labeling

Background Cetirizine hydrochloride is a selective H₁-receptor antagonist of the cyclizine class. It is proposed to be used to treat the symptoms of urticaria and allergic rhinitis. It is the principal human metabolite of hydroxyzine, having a carboxyl group in place of the hydroxyl group of hydroxyzine. The sponsor of this submission is licensing the drug product from UCB, Belgium. At various times since the original submission of this NDA, the sponsor has submitted studies performed by UCB. The purpose of this review is to examine these studies and ensure that their results are consistent with those already submitted in the NDA.

Summary An interaction study dosed azithromycin or placebo (500 mg QD for one day, then 250 mg for the next four days) concomitantly with cetirizine (20 mg QD for ten days). No significant changes in the pharmacokinetics of cetirizine or QTc interval were observed. Another interaction study examined the effect of acute and chronically administered cetirizine on glipizide's hypoglycemic potential. Subjects received either cetirizine 10mg once daily or placebo for 7 days. A single 5 mg dose of glipizide was administered before the first (baseline), after the first (acute) and after the 7th dose (chronic). No major differences in glipizide-induced hypoglycemia were evident when glipizide was administered alone versus with cetirizine, either acutely or chronically. However, unsatisfactory assay validation data submitted for this study prevents its inclusion to the product's Labeling. A bioequivalence study which enrolled both males (n=8) and females (n=8) allowed a comparison to evaluate the effect of gender on drug disposition. While a significant weight-normalized difference in apparent clearance was detected between the genders in the tablet arm of the study (females: +52%, p=0.046 versus males), this difference was minimized in the solution arm (+33%, p=0.074), suggesting that differences between gender in drug disposition is somehow linked to absorption. However, due to a lack of satisfactory assay validation data, this gender difference cannot be documented. The last study reviewed reported that maternal milk is a minor route of excretion for cetirizine, thus nursing mothers should avoid using this drug.

Comments

1. The sponsor has submitted revised labeling (see Attachment) reflecting:
 - a) the non-interaction of cetirizine with azithromycin
 - b) the maternal milk route of elimination for cetirizine
 - c) that inadequate data exist to evaluate the effect of gender on cetirizine disposition.
2. The sponsor's proposed labeling does not reference the unsatisfactory glipizide-cetirizine interaction.
3. If the sponsor wishes to further explore the results of either of the unacceptable studies, they are encouraged to submit protocols to FDA before beginning any studies.

Recommendation

Four new cetirizine pharmacokinetic studies have been reviewed by the Division of Pharmaceutical Evaluation II. The results of these studies have been adequately reflected in the product's proposed labeling.

Bradley K. Gillespie 11/15/95
Bradley K. Gillespie, PharmD
Division of Pharmaceutical Evaluation II

DPC 11/15/95

FT Dale P. Conner, PharmD, Team Leader

cc:

- HFD-155 (NDA-19-835)
- HFD-570 (Division File)
- HFD-570 (Saavedra-Delgado)
- HFD-570 (Lee)
- HFD-870 (Conner)
- HFD-880 (Fleischer)
- HFD-870 (Chen, Mei-Ling)
- HFD-860 (Malinowski)
- HFD-850 (Chron)
- HFD-870 (Gillespie, Brad)
- HFD-850 (Reviewer File)
- HFD-850 (Drug File)
- HFD-340 (Viswanthan)
- HFD 019 (FOI)

A Multiple Dose Study to Evaluate the Pharmacokinetic and/or ECG Effects on Concomitant Administration of a Course of Azithromycin Therapy with Cetirizine

Study No.: 93CK16-0624

Investigator and Location: Russell Dixon; Besselaar Clinical Research Unit, Madison, WI.

Objective: To assess the effect of azithromycin on steady state cetirizine pharmacokinetics and QTc interval.

Formulations: All tablets were manufactured by Pfizer, Inc.

Dosage Form	Lot Number
Cetirizine 10mg Tabs	C0385
Placebo for Cetirizine 10mg Tabs	C0378
Azithromycin 250mg Caps	C2150
Placebo for Azithromycin 250mg Caps	C1225

Study Design: This randomized, multiple dose, open label (ECG reader blinded), parallel study enrolled 42 healthy young males into three treatment groups. The dosing regimens are detailed below. All subjects received placebo on day 1 so that baseline ECGs could be established. Subjects in Treatment Groups A and B then completed a 5 day run in period with cetirizine only. After cetirizine pharmacokinetics and ECGs without azithromycin were recorded, subjects received either azithromycin or placebo. Details of the dosing scheme are presented below.

Day	Group A	Group B	Group C
1	Placebo for cetirizine, QD	Placebo for cetirizine, QD	Placebo for cetirizine, QD
2 - 6	20 mg cetirizine, QD	20 mg cetirizine, QD	Placebo for cetirizine, QD
7	500 mg azithromycin, QD & 20 mg cetirizine, QD	Placebo for azithromycin, QD & 20 mg cetirizine, QD	Placebo for azithromycin, QD & Placebo for cetirizine, QD
8 - 11	250 mg azithromycin, QD & 20 mg cetirizine, QD	Placebo for azithromycin, QD & 20 mg cetirizine, QD	Placebo for azithromycin, QD & Placebo for cetirizine, QD

Serial blood samples for the determination of plasma cetirizine and azithromycin were obtained on Days 6 (before addition of azithromycin or placebo) and 11. Serial 12-lead ECGs were performed at baseline (Day 1) and 15 minutes before blood sampling (Days 6 and 11).



DATA ANALYSIS

Statistical Analysis of QT Interval The measured QT interval was corrected for heart rate using Hodges' and Bazett's Formulae. Hourly changes from baseline for Study Days 6 and 11 were then calculated to measure the relative effects of the treatments on changes in QT interval.

Pharmacokinetic Data Analysis AUC_{0-24} , C_{max} , T_{max} and $t_{1/2}$ were determined for cetirizine on Study Days 6 and 11. These parameters, with the exception of $t_{1/2}$, were also calculated for azithromycin on Day 11. Statistical analysis was performed on only the cetirizine data. Mean azithromycin parameters were compared to published data.

COMMENT

1. The pharmacokinetic parameter T_{max} is non-parametric, it could be better described by its median than by its mean (as the sponsor has done).

RESULTS

All 42 study participants completed all phases of the study and are included in the final report. No significant changes in vital signs were noted over the course of the study, and no subjects discontinued study participation due to an adverse experience. Mean cetirizine

and azithromycin plasma concentration versus time plots are presented in Figures 1 and 2, respectively, while pharmacokinetic parameters are listed in Table 1. No significant pharmacokinetic or QTc interval changes were detected between Day 6 and 11. When individual maximum QTc changes (via Bazett's formula) were plotted against maximum changes in C_{max} (see Figure 3), a nonsignificant ($p=0.26$) negative correlation was observed. It should be noted that any trend observed is probably due to only one or two data points (circled).

CONCLUSION: While individual increases in QTc interval and plasma cetirizine concentrations were observed, the lack of significant mean changes and a linking correlation suggests that these changes are random, and benign. Thus, according to the results of this study, azithromycin can be safely administered with cetirizine.

Figure 1.

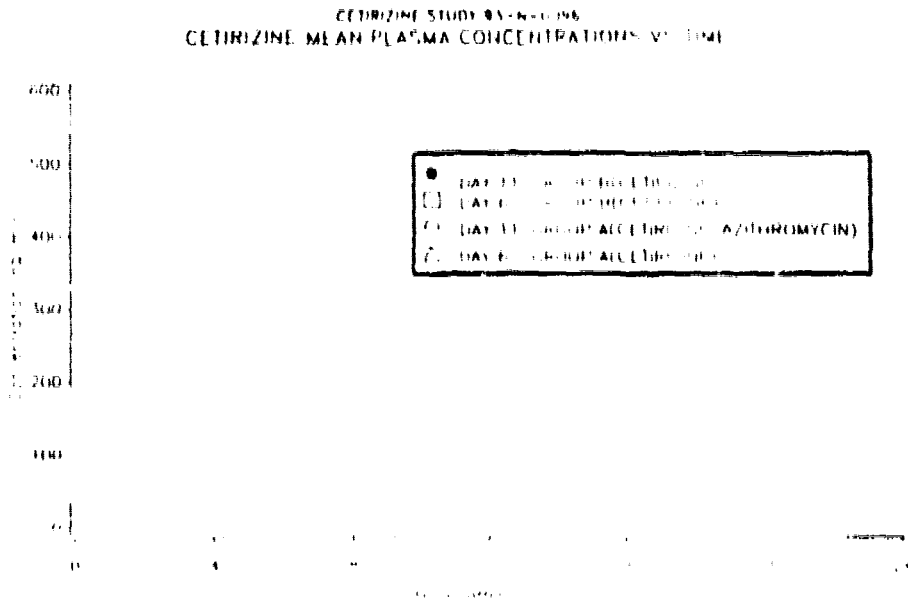


Figure 2.

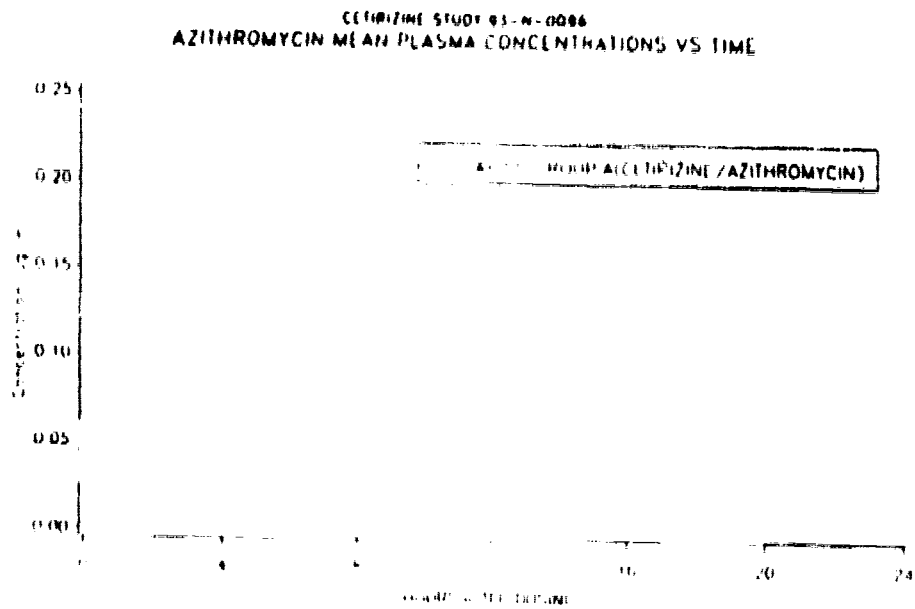
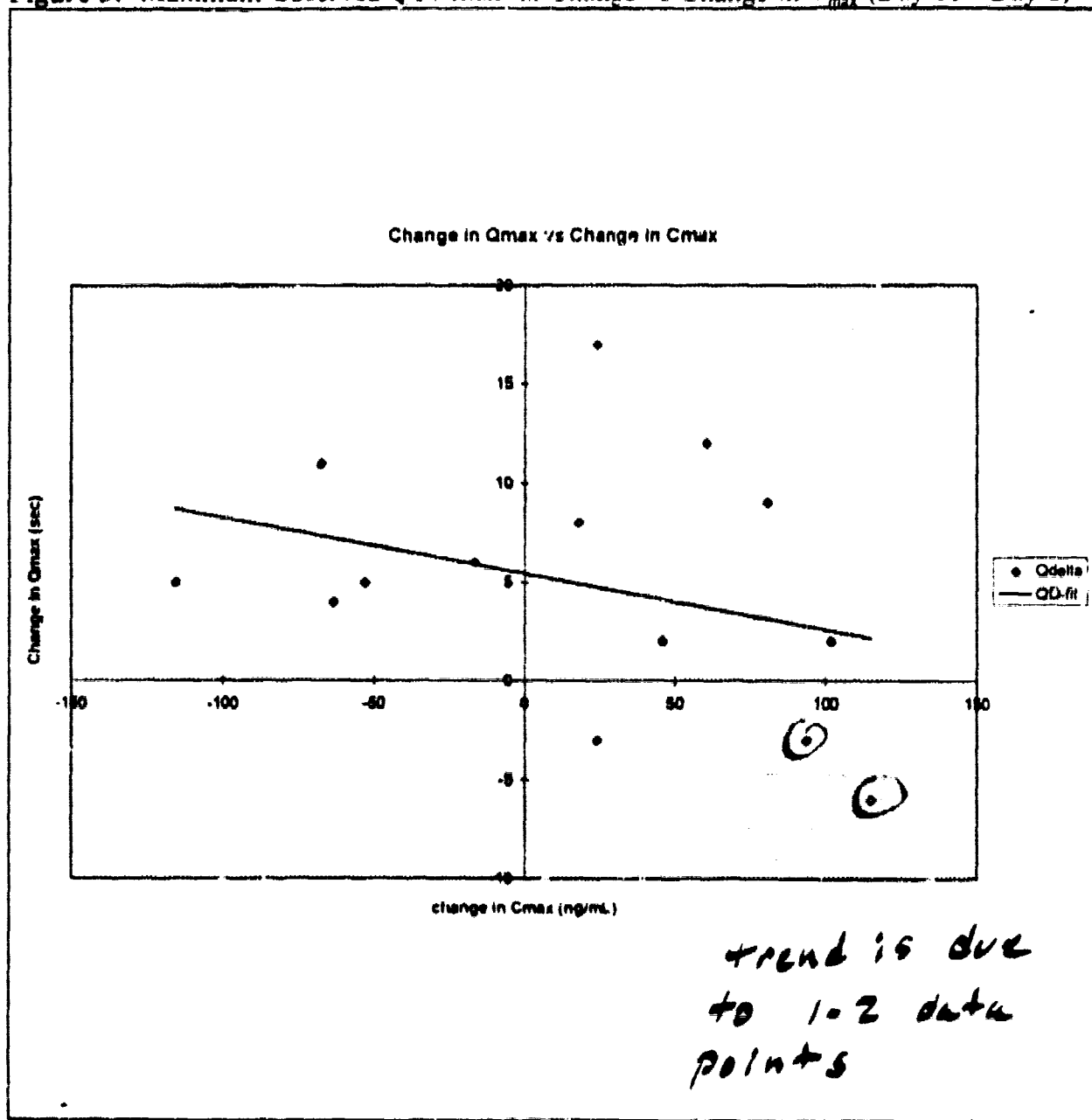


Table 1. Cetirizine and Azithromycin Mean Pharmacokinetic Parameters (%CV) on Day 6 (Cetirizine Alone) and on Day 11 (Cetirizine and Azithromycin)

	AUC_{0-24}	C_{max}	T_{max}	Cl/F	Vd/F	$T_{1/2}$
Units	ng·hr/mL	ng/mL	hours	mL/min	L	hours
Cetirizine (Day 6)	4756 (15)	554 (15)	1.14 (32)	71.5 (15)	48.9 (11)	7.97 (10)
Cetirizine (Day 11)	4847 (16)	572 (16)	1.14 (32)	70.4 (16)	49.0 (12)	8.13 (11)
Change	+1.91%	+3.24%	-----	-----	-----	-----

Azithromycin
(Day 11) 1.41 (31) 0.22 (36) 2.79 (15)

Figure 3. Maximum Observed QTc Interval Change vs Change in C_{max} (Day 11 - Day 6)



A Double-Blind, Randomized, Complete Crossover Study to Determine the Existence of an Interaction Between Cetirizine and Glipizide in Healthy Volunteers

Study No.: UCB 116

Investigator and Location:

Objectives: To determine the effect of cetirizine after a single dose and following chronic administration on glipizide-induced hypoglycemia.

Formulations: All 10mg cetirizine capsules were supplied by the sponsor. Detailed lot information was not provided.

Study Design: This double-blind, randomized two-way crossover study enrolled 12 healthy volunteers. Subjects assigned to Group A received cetirizine 10 mg on Days 1 - 7, and placebo on Days 8 - 14. Subjects were administered single 5mg glipizide tablets on Days 1, 8 and 15. Blood samples were obtained for glucose determinations prior to (0 hour) and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8 and 10 hours after glipizide administration. Blood samples for plasma cetirizine determinations were obtained after the first dose to determine the drug's C_{max} and T_{max} . Also, a sample was obtained on Study Day 5 to monitor compliance. Subjects in Group B received an identical treatment in the opposite order, with a blood sample for plasma cetirizine determination obtained on Study Day 12.

Data Analysis The primary endpoint examined was mean blood glucose levels of the subjects at the individual time points. The three treatment groups compared were as follows: glipizide alone (with placebo for cetirizine), after a single concomitant dose of cetirizine (acute) and following a seven day course of cetirizine (chronic). Mean blood glucose nadir values for each treatment regimen (and the time of their occurrence) were also compared. Lastly, area under the blood glucose concentration versus time curve from 0 to 10 hours were compared for the three treatments. All comparisons were carried out using a two-way analysis of variance with the level of significance set at $p < 0.05$.

Results Eight male and 4 female volunteers completed the study with only minimal side

effects reported. None of the adverse events were serious enough to interrupt the study. Mean blood sugar concentrations over the 10 hour observation period are presented in Table 2. Areas under the plasma glucose concentration-time curve are depicted in Table 3, while glucose nadirs and cetirizine C_{max} and T_{max} appear in Table 4.

Discussion No major differences in glipizide-induced hypoglycemia were evident when glipizide was administered alone versus with cetirizine, either acutely or chronically.

Comments

- 1) No detailed lot or formulation information was provided.
- 2) No assay validation data was submitted for either the plasma glucose or cetirizine method.

Conclusion While no major pharmacodynamic effect was detected by this study, any interpretation of the results is compromised by the lack of assay methodology description and validation. If the firm wishes to utilize the results of this study (in the labeling, or otherwise), they will have to provide satisfactory assay validation information.

Table 2.

MEAN BLOOD SUGAR CONCENTRATIONS (mg/100ml) FOLLOWING GLIPISTOL ADMINISTRATION

TIME	PLACEBO		CETIRIZINE (ACUTE)		CETIRIZINE (CHRONIC)		COMBINED PLACEBO & CHRONIC	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
- 10'	88	± 1.6	87	± 1.9	84	± 1.6	87	± 1.6
+ 15'	70	± 1.0	88	± 1.9	87	± 1.5	88	± 1.8
BREAKFAST								
+ 30'	102	± 7.0	103	± 7.3	105	± 9.0	104	± 6.5
+ 45'	116	± 7.1	121	± 9.0	142	± 5.0	139	± 6.0
+ 1.00 H	122	± 8.4	111	± 9.9	131	± 9.5	126	± 9.0
+ 1.30 H	88	± 2.7	82	± 7.2	88	± 7.9	88	± 6.8
+ 2.00 H	81	± 4.3	79	± 5.0	82	± 4.6	81	± 4.4
+ 2.30 H	78	± 3.8	67	± 5.5	78	± 3.8	78	± 3.8
+ 3.00 H	64	± 3.1	68	± 3.1	70	± 3.2	67	± 3.1
+ 3.30 H	57	± 3.2	61	± 3.3	57	± 2.4	57	± 2.8
+ 4.00 H	62	± 2.6	66	± 2.9	62	± 2.4	62	± 2.5
LUNCH								
+ 5.00 H	93	± 7.0	91	± 3.1	97	± 5.2	95	± 6.1
+ 6.00 H	98	± 2.7	90	± 5.0	95	± 3.1	92	± 3.7
+ 8.00 H	94	± 1.0	92	± 2.7	94	± 1.7	96	± 1.4
SNACK								
+ 10.00 H	94	± 2.0	100	± 4.0	101	± 4.8	99	± 3.4

The data from subject No 4 have been omitted from the means (see results section).

Table 3.

AREAS UNDER THE GLUCOSE PLASMA CONCENTRATIONS
TIME CURVE (0-100) FOLLOWING CONCOMITANT
GLIPISTOL AND CETIRIZINE ADMINISTRATION

SUBJECT NO.	PLACEBO	ACUTE	CHRONIC
	(mg hr ml ⁻¹)	CETIRIZINE (mg hr ml ⁻¹)	CETIRIZINE (mg hr ml ⁻¹)
MEANS ± S.E.	918 ± 20	889 ± 24	923 ± 27

* Subject No 4 omitted-see Results section 3.2 Blood Sugar

Table 4.

CETIRIZINE AND GLUCOSE PHARMACOKINETIC PARAMETERS

Subject ID	Cetirizine (1)		Glucose						
	C max (ng/ml)	T max (h)	pk Cet. T max (h)	Mean			Time of Peak		
				A	C	"	A	C	P

Mean *	431	0.7	106	53	56	50	1.8	1.4	1.31
* SEM	15	0.1	6	3	2	2	0.2	0.1	0.1

* The means represent the average of eleven subjects excluding subject # 1.
 Abbreviations: A = Acute Cetirizine, C = Chronic Cetirizine, P = Plasma
 (1) Acute administration Day 1 (Group A), Day 8 (Group B)

In the original Biopharmaceutics review, only one study allowed a gender comparison. However, the ratio of subjects enrolled (86 males, 3 females) was not optimal. A UCB bio-study enrolled 8 males and 8 females.

BIOEQUIVALENCE STUDY OF A SOLUTION FORM COMPARED WITH TABLETS OF CETIRIZINE IN HEALTHY ADULT SUBJECTS

Study No.: UCB 112

Objective: To compare the bioavailability of a cetirizine solution with a 10mg tablet. The inclusion of both males and females would also allow for the assessment of a gender effect on drug disposition.

Formulations: 1mg/mL solution of cetirizine (Batch 88), 10mg cetirizine tablets (Batch 63R).

Study Design: A total of 16 healthy adults (8 female, 8 male) were enrolled in this single dose, open-label, two-way crossover study. The two study periods (10mg tablet and 10mg solution) were separated by a washout period of one week. Subjects were administered the study drugs between 0800 and 0900 hours on an empty stomach. Venous blood samples were taken immediately prior to, and 0.5, 1, 1.5, 2, 3, 5, 8, 12, 24, 36 and 48 hours after medication administration.

Data Analysis: The sponsor determined C_{max} , T_{max} , AUC, CL_{ap} , Vd_{ap} , and $t_{1/2}$.

Results: Mean pharmacokinetic parameters, divided by gender, are presented in Tables 5 and 6 for solution and tablet, respectively. Weight normalized volumes of distribution appear similar (-0.4.-0.48L/kg) between genders, and maximum plasma concentrations seem inversely proportional to subject weights. However, observed AUCs do not seem to follow this pattern. A possible cause of this discrepancy is the faster weight-normalized clearance rate observed in females versus males. While this difference is significant ($p=0.046$) when the drug was administered as a tablet, when given as a solution the difference was not significant ($p=0.075$).

Discussion Since cetirizine is mainly excreted as the unchanged drug in the urine, a clearance gender effect might not be expected. The presence of a significant difference

could be attributable to variations in absorption. This hypothesis is supported by the finding of a significant difference in the tablet but not in the solution groups.

Comments

1. Since satisfactory assay validation data has not been submitted in support of this study, any conclusions reached are tentative, at best.
2. If the sponsor wishes to further explore the effect of gender, any protocols should be submitted to FDA before beginning the study.

Conclusion From the data available, it is impossible to identify the source of the clearance gender effect observed. However, since a statistically significant difference is evident, clinical efficacy and safety data should be scrutinized to determine the effect's clinical importance. If it is determined that this effect should be further investigated, it will be necessary to first request further validation data.

Table 5 Mean (%CV) Pharmacokinetic Parameters (Solution)

Parameter	unit	males	females	change ¹	p-value
Weight	kg	73.5 (9)	56.8 (12)	- 29%	
C _{max}	ng/mL	799 (20)	1080 (22)	+35%	
T _{max}	hr	0.81	1.00	+23%	
AUC	ng hr/mL	8436 (29)	8466 (30)	- 0.4%	
V _d	L	32.1 (20)	24.8 (36)	- 23%	
t _{1/2}	hr	9.1 (22)	6.9 (29)	- 24%	
Cl _(app)	mL/min	42.3 (26)	42.4 (28)	+0.2%	
	mL/min kg	0.57 (22)	0.76 (32)	+33%	0.074

Table 6 Mean (%CV) Pharmacokinetic Parameters (Tablets)

Parameter	unit	males	females	change ¹	p-value
Weight	kg	73.5 (9)	56.8 (12)	- 29%	
C _{max}	ng/mL	771 (17)	1011 (22)	+31%	
T _{max}	hr	1.19	.94	- 21%	
AUC	ng hr/mL	8299 (20)	7604 (29)	- 8.4%	
V _d	L	31.2 (16)	27.5 (26)	- 12%	
t _{1/2}	hr	8.8 (17)	7.0 (27)	- 20%	
Cl _(app)	mL/min	41.6 (20)	47.8 (36)	+15%	
	mL/min kg	0.56 (17)	0.85 (39)	+52%	0.046

¹females vs males

STUDY ON THE PASSAGE OF CETIRIZINE IN THE MATERNAL MILK

Study No.: UCB 114

Objective: To verify the passage of cetirizine in maternal milk following administration of a single 20 mg dose of cetirizine 2HCl.

Formulations: Two 20mg cetirizine 2HCl tablets

Study Design: Six institutionalized, healthy, women in their post-partum period who did not wish to nurse their children were enrolled in this study. All subjects had uncomplicated deliveries and took no other drugs except oxytocin and bromocriptine. Further, women with mammary hepatic or renal pathology were not included in the study. Subjects fasted for 16 hours prior to drug administration. Fasting continued until the 1 hour time point, when breakfast was served. Blood and milk were collected at 2, 8 and 24 hours after drug administration for cetirizine determinations.

Results: Whole blood and milk cetirizine concentration-time data are presented in Table 7. Mean data are plotted in Figure 7. Results indicate a rapid absorption of cetirizine and nearly complete elimination within 24 hours.

Conclusion: Cetirizine milk concentrations obtained suggest that maternal milk is a minor route of excretion for cetirizine. Thus, nursing mothers should avoid using cetirizine.

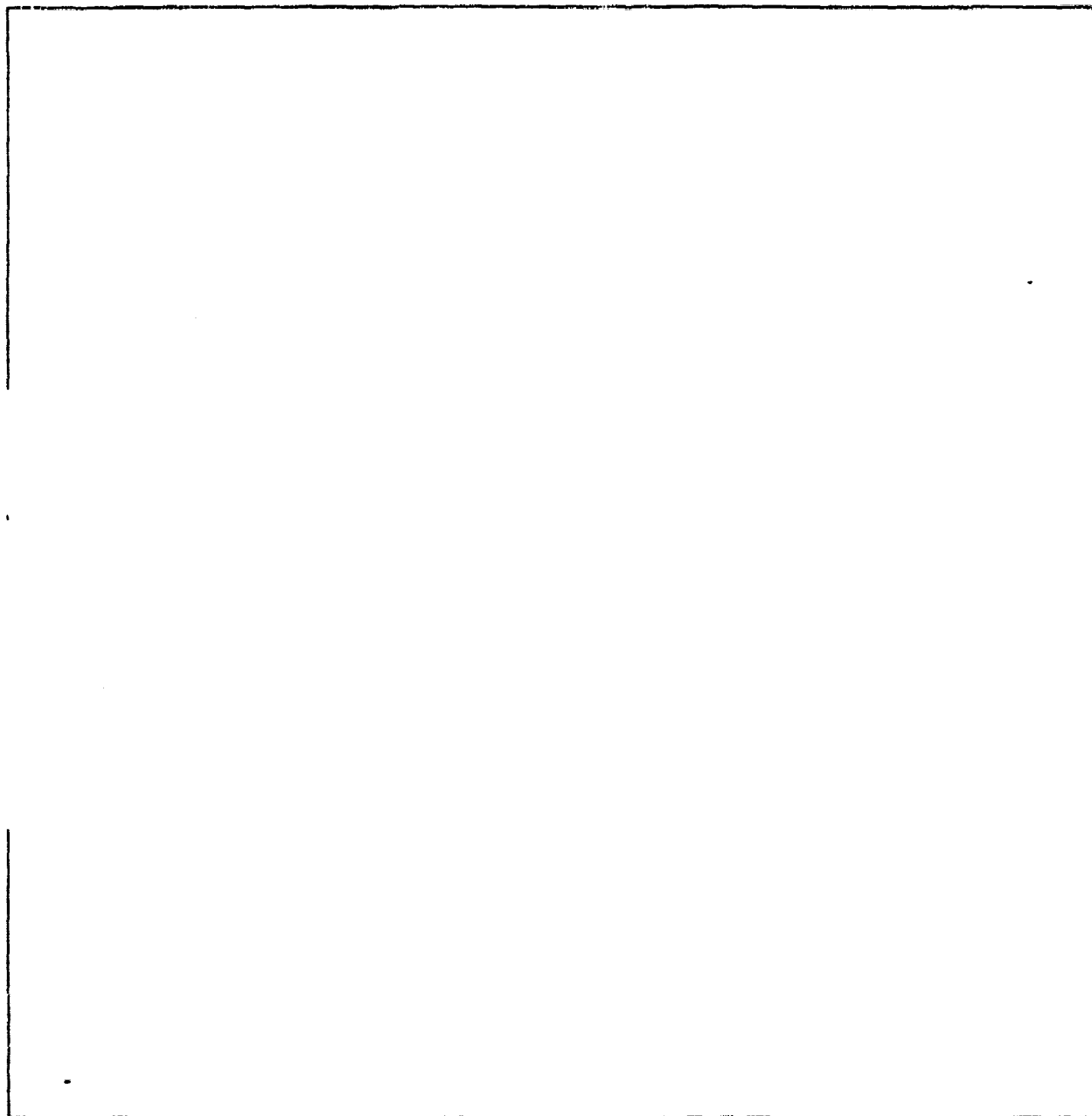
Table 7. Cetirizine Maternal Milk and Blood Concentration-Time (ng/mL) Data

Subject	2hr-blood	8hr-blood	2 4 h r - blood	2hr-milk	8hr-milk	24hr-milk
mean	333.2	136.7	11.5	57.2	80.2	9
sd	46.3	23.9	18.4	47.4	106.9	12.4
%CV	14	18	160	83	133	137

²Values of zero represent concentrations below the lower level of quantitation

³Missing value

Figure 4. Cetirizine Concentrations in Blood and Maternal Milk



ANNOTATED PACKAGE INSERT

ZYRTEC

cetirizine hydrochloride

Tablets

For Oral Use

DESCRIPTION

Cetirizine hydrochloride, the active component of ZYRTEC tablets, is an orally active and selective H₁-receptor antagonist. The chemical name is (±)-(2-[4-(p-chloro-α-phenylbenzyl)-1-piperazinyl]ethoxy) acetic acid, dihydrochloride. Cetirizine hydrochloride is a racemic compound with an empirical formula of C₂₁H₂₅ClN₂O₃·2HCl. The molecular weight is 461.82 and the chemical structure is shown below:

SEE GALLEY

Cetirizine hydrochloride is a white, crystalline powder and is water soluble. ZYRTEC is formulated as a white (dye-free), film-coated, rounded-off rectangular shaped tablet for oral administration and is available in 5 and 10 mg strengths. Inert ingredients are: lactose; magnesium stearate; povidone; titanium dioxide; hydroxypropyl methylcellulose; polyethylene glycol; and corn starch.

CLINICAL PHARMACOLOGY

Mechanism of Actions: Cetirizine, a human metabolite of hydroxyzine is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H₁ receptors. The antihistaminic activity of cetirizine has been clearly documented in a variety of animal and human models. *In vivo* and *ex vivo* animal models have shown negligible anticholinergic and antiserotonergic activity. In clinical studies, however, dry mouth was more common with cetirizine than with placebo. *In vitro* receptor binding studies have shown no measurable affinity for other than H₁ receptors. Autoradiographic studies with radiolabeled cetirizine in the rat have shown negligible penetration of the brain. *Ex vivo* experiments in the mouse have shown that systemically administered cetirizine does not significantly occupy cerebral H₁ receptors.

Pharmacokinetics: Cetirizine is rapidly absorbed after oral administration of a tablet, which had bioavailability similar to an oral solution. Food had no effect on the extent of cetirizine absorption, but T_{max} was delayed by 1.7 hours and C_{max} was decreased by 23% in the presence of food. A mass balance study in 6 healthy male volunteers indicated that 70% of the administered radioactive dose was recovered in the urine and 10% in the feces, for a combined total recovery of about 80%. Approximately 50% of the administered radioactive dose was

excreted in urine as unchanged drug. Most of the rapid increase in peak plasma radioactivity is associated with parent drug indicating low first pass metabolism. Cetirizine is metabolized to a very limited extent by oxidative o-dealkylation to a metabolite with negligible antihistaminic activity.

Cetirizine exhibits linear kinetics over the dosage range of 5 to 60 mg. In pharmacokinetic studies in 146 healthy volunteers, the mean $\pm$ SD terminal half-life was 8.3 ± 1.8 hours, oral clearance was 54 ± 13 mL/min, and the apparent volume of distribution was 0.50 ± 0.08 L/kg. No accumulation was observed for cetirizine following daily doses of 10 mg for 10 days. The steady-state maximum plasma concentration was 311 ± 40 ng/mL and was achieved within 1.0 ± 0.5 hour. Individual histograms of cetirizine C_{max} and AUC showed unimodal distributions with a two- to four-fold variability in healthy subjects. Plasma protein binding of cetirizine is 93 ± 0.3 % and was independent of concentration in the range of 0.025 to 1.0 mcg/mL; this concentration range covers the therapeutic plasma levels.

SPECIAL POPULATIONS

Effect of Age: Following a single 10 mg oral dose, half-life increased by about 50% and clearance decreased by 40% in 16 elderly subjects as compared to the 14 normal subjects. The decrease in cetirizine clearance in these elderly volunteers appeared to be related to their decreased renal function.

Effect of Gender: The effect of gender on cetirizine pharmacokinetics has not been adequately studied.

Effect of Race: No race-related differences were observed in the kinetics of cetirizine between 86 white adult males and 11 black adult males.

Renally Impaired Patients: The kinetics of cetirizine were studied following multiple oral daily doses of 10 mg for 7 days in 7 normal volunteers (creatinine clearance 89-128 mL/min), 8 patients with mild renal function impairment (creatinine clearance 42-77 mL/min) and 7 patients with moderate renal function impairment (creatinine clearance 11-31 mL/min). The pharmacokinetics of the drug were similar in patients with mild impairment and normal volunteers. Moderately renally impaired patients had a 3-fold increase in half-life and 70% decrease in clearance compared to normal volunteers.

Patients (N=5) on hemodialysis (creatinine clearance less than 7 mL/min) given a single oral 10 mg dose of cetirizine had a 3 fold increase in half-life and a 70% decrease in clearance compared to normals. Cetirizine was not completely cleared by hemodialysis as less than 10% of the administered dose was removed during the dialysis session.

Dosing adjustment is necessary in patients with moderate or severe renal impairment and patients on dialysis. (See also DOSAGE AND ADMINISTRATION).

Hepatically Impaired Patients: Sixteen patients with chronic liver diseases (hepatocellular, cholestatic, and biliary cirrhosis) given 10 or 20 mg of cetirizine as a single oral dose had a 50% increase in half-life along with a 40% decrease in clearance compared to 16 healthy subjects.

Dosing adjustment may be necessary in hepatically impaired patients. (See also DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Formal pharmacokinetic interaction studies were conducted with cetirizine and pseudoephedrine, antipyrine, ketoconazole, erythromycin, and azithromycin. No pharmacokinetic interactions were observed. In a multiple dose study of theophylline (400 mg once daily) and cetirizine, there was a small (16%) decrease in clearance of cetirizine.

Pharmacodynamics: Studies in normal volunteers show that ZYRTEC at doses of 5 and 10 mg strongly inhibits the skin wheal and flare caused by the intradermal injection of histamine. The onset of this activity after a single 10 mg dose occurs within 20 minutes in 50% of subjects and in 95% of subjects within one hour, and this activity persists for at least 24 hours. In a 35 day study in children ages 5 to 12, no tolerance to the antihistaminic (suppression of wheal and flare response) effects of ZYRTEC was found. The effects of intradermal injection of various other mediators or histamine releasers are also inhibited by cetirizine, as is response to a cold challenge in patients with cold-induced urticaria. In mildly asthmatic subjects, ZYRTEC at 5 to 20 mg blocked bronchoconstriction due to nebulized histamine, with virtually total blockade after a 20 mg dose. In studies conducted for up to 12 hours following cutaneous antigen challenge, the late phase recruitment of eosinophils, neutrophils and basophils, components of the allergic inflammatory response, is inhibited by ZYRTEC at a dose of 20 mg.

In four clinical studies in healthy adult males, no clinically significant mean increases in QTc were observed in ZYRTEC treated subjects. In the first study, a placebo-controlled crossover trial, ZYRTEC was given at doses up to 60 mg per day, 6 times the maximum clinical dose for 1 week, and no significant mean QTc prolongation occurred. In the second study, a crossover trial, ZYRTEC 20mg and erythromycin (500 mg every 8 hours) were given alone and in combination. There was no significant

effect on QTc with the combination or with ZYRTEC alone. In the third trial, also a crossover study, ZYRTEC 20 mg and ketoconazole (400 mg per day) were given alone and/or in combination. ZYRTEC caused a mean increase in QTc from baseline of 9.1 msec after 10 days of therapy. Ketoconazole also increased QTc by 8.3 msec. The combination caused an increase of 17.4 msec ~~about~~ equal to the sum of the individual effects. Thus, there was no significant drug effect on QTc with the combination of ZYRTEC and ketoconazole. In the fourth study, a placebo-controlled parallel trial, ZYRTEC 20 mg was given alone or in combination with azithromycin (500 mg as a single dose on the first day followed by 250 mg once daily). There was no significant increase in QTc with ZYRTEC 20 mg alone or in combination with azithromycin.

In a six-week, placebo-controlled study of 186 patients with allergic rhinitis and mild to moderate asthma, ZYRTEC 10 mg QD improved rhinitis symptoms and did not alter pulmonary function. This study supports the safety of administering ZYRTEC to allergic rhinitis patients with mild to moderate asthma.

Clinical Studies: Nine multicenter, randomized, double-blind, clinical trials comparing cetirizine 5 to 20 mg to placebo in patients with seasonal or perennial allergic rhinitis were conducted in the United States. Five of these showed significant reductions in symptoms of allergic rhinitis, 3 in seasonal allergic rhinitis (one to 4 weeks in duration) and 2 in perennial allergic rhinitis for up to 8 weeks in duration. Two 4-week multicenter, randomized, double-blind, clinical trials comparing cetirizine 5 to 20 mg to placebo in patients with chronic idiopathic urticaria were also conducted and showed significant improvement in symptoms of chronic idiopathic urticaria. In general, the 10 mg dose was more effective than the 5 mg dose and the 20 mg dose gave no added effect.

INDICATIONS AND USAGE

Seasonal Allergic Rhinitis: ZYRTEC is indicated for the relief of symptoms associated with seasonal allergic rhinitis due to allergens such as ragweed, grass and tree pollens. Symptoms treated effectively include sneezing, rhinorrhea, nasal pruritus, ocular pruritus, tearing and redness of the eyes.

Perennial Allergic Rhinitis: ZYRTEC is indicated for the relief of symptoms associated with perennial allergic rhinitis due to allergens such as dust mites, animal dander and molds. Symptoms treated effectively include sneezing, rhinorrhea, post-nasal discharge, nasal pruritus, ocular pruritus and tearing.

Chronic Urticaria: ZYRTEC is indicated for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria. It significantly reduces the occurrence, severity and duration of hives and significantly reduces pruritus.

CONTRAINDICATIONS

ZYRTEC is contraindicated in those patients with a known hypersensitivity to it or any of its ingredients or hydroxyzine.

PRECAUTIONS

Activities Requiring Mental Alertness: In clinical trials, the occurrence of somnolence has been reported in some patients taking ZYRTEC; due caution should therefore be exercised when driving a car or operating potentially dangerous machinery. Concurrent use of ZYRTEC with alcohol or other CNS depressants should be avoided because additional reductions in alertness and additional impairment of CNS performance may occur.

Drug-drug interactions: No clinically significant drug interactions have been found with theophylline at a low dose, azithromycin, pseudoephedrine, ketoconazole, or erythromycin. There was a small decrease in the clearance of cetirizine caused by a 400 mg dose of theophylline; it is possible that larger doses could have a larger effect.

Carcinogenesis, mutagenesis and impairment of fertility: No evidence of carcinogenicity was observed in a 2-year carcinogenicity study in rats at dietary doses up to 20 mg/kg/day (15 times the recommended human dose on a mg/m²/day basis). An increased incidence of benign liver tumors was found in a 2-year carcinogenicity study in male mice at a dietary dose of 16 mg/kg/day (6 times the recommended human dose on a mg/m²/day basis). The clinical significance of these findings during long-term use of ZYRTEC is not known. Cetirizine was not mutagenic in Ames test, and not clastogenic in human lymphocyte assay, mouse lymphoma assay, and in vivo micronucleus test in rats. No impairment of fertility was found in a fertility and general reproductive performance study in mice at a dose of 64 mg/kg/day (26 times the recommended human dose on a mg/m²/day basis).

Pregnancy Category B: Cetirizine was not teratogenic in mice, rats and rabbits at doses up to 96, 225, and 135 mg/kg/day (or 40, 180, and 216 times the recommended human dose on a mg/m²/day basis), respectively. There are no adequate and well-controlled studies in pregnant

women. Because animal studies are not always predictive of human response, ZYRTEC should be used in pregnancy only if clearly needed.

Nursing Mothers: Retarded pup weight gain was found in mice during lactation when dams were given cetirizine at 96 mg/kg/day (40 times the recommended human dose on a mg/m²/day basis). Studies in beagle dogs indicate that approximately 3% of the dose is excreted in milk. Cetirizine has been reported to be excreted in human breast milk; use of ZYRTEC in nursing mothers is not recommended.

Geriatric Use: The safety and efficacy of ZYRTEC has been demonstrated in patients 65 years and older. (See CLINICAL PHARMACOLOGY section)

Pediatric Use: Safety and effectiveness in the pediatric population has not been established.

ADVERSE REACTIONS

Controlled and uncontrolled clinical trials *conducted in the United States and Canada* included more than 6000 patients, with more than 3900 receiving ZYRTEC at doses of 5 to 20 mg per day; the duration of treatment ranged from 1 week to 6 months, with a mean of exposure of 30 days.

Most adverse reactions reported during therapy with ZYRTEC were mild or moderate. In placebo-controlled trials, the incidence of discontinuations due to adverse reactions in patients receiving ZYRTEC 5 mg or 10 mg was not significantly different from placebo (2.9% vs 2.4%, respectively).

The most common adverse reactions that occurred more frequently on cetirizine than placebo was somnolence. The incidence of somnolence associated with ZYRTEC was dose related, 6% in placebo, 11% at 5 mg and 14% at 10 mg. Discontinuations due to somnolence for ZYRTEC were uncommon (1.0% on Zyrtec vs 0.6%, on placebo). Fatigue and dry mouth also appeared to be treatment-related adverse reactions. There was no difference by age, race, gender or by body weight with regard to the incidence of adverse reactions.

Table 1 lists adverse experiences which were reported for ZYRTEC 5 and 10 mg in controlled clinical trials in the United States and that were more common on ZYRTEC than placebo.

Table 1. ~~Adverse Experiences-Reactions~~ Reported in Placebo-Controlled United States ZYRTEC Trials (Maximum Dose of 10mg) at Rates of 2% or Greater

(Percent Incidence)

Adverse Experience	ZYRTEC (N=2034)	Placebo (N=1612)
Somnolence	13.7	6.3
Fatigue	5.9	2.6
Dry Mouth	5.0	2.3
Pharyngitis	2.0	1.9
Dizziness	2.0	1.2

In addition, headache and nausea occurred in more than 2% of the patients, but were more common on placebo.

The following events were observed infrequently (less than 2%), in 3982 patients who received ZYRTEC in U.S. trials, including an open study of six months duration; a causal relationship with ZYRTEC administration has not been established.

Autonomic Nervous System: anorexia, urinary retention, flushing, increased salivation

Cardiovascular: palpitation, tachycardia, hypertension, cardiac failure

Central and Peripheral Nervous Systems: ~~insomnia~~, paresthesia, confusion, hyperkinesia, hypertonia, migraine, tremor, vertigo, cramps legs, ataxia, dyspnoea, abnormal coordination, hyperesthesia, hypoesthesia, myelitis, paralysis, ptosis, twitching, visual field defect

Gastrointestinal: increased appetite, dyspepsia, abdominal pain, diarrhea, flatulence, constipation, vomiting, ulcerative stomatitis, aggravated tooth caries, stomatitis, tongue discoloration, tongue edema, gastritis, recurrent hemorrhage, hemorrhoids, melena, abnormal hepatic function

Genitourinary: polyuria, urinary tract infection, cystitis, dysuria, hematuria

Hearing and vestibular: earache, tinnitus, deafness, ototoxicity

Metabolic/Nutritional: thirst, dehydration, diabetes mellitus

Musculoskeletal: myalgia, arthralgia, arthrosis, arthritis, muscle weakness

Psychiatric: insomnia, nervousness, depression, emotional lability, impaired concentration, anxiety, depersonalization, paranoia, abnormal thinking, agitation, amnesia, decreased libido, euphoria

Respiratory System: epistaxis, rhinitis, coughing, bronchospasm, dyspnea, upper respiratory tract infection, hyperventilation, sinusitis, increased sputum, bronchitis, pneumonia

Reproductive: dysmenorrhea, female breast pain, intermenstrual bleeding, leukorrhea, menorrhagia, vaginitis

Reticuloendothelial: lymphadenopathy

Skin: pruritus, rash, dry skin, urticaria, acne, dermatitis, rash erythematous, increased sweating, alopecia, angioedema, furunculosis, bullous eruption, eczema, hyperkeratosis, hypertrichosis, photosensitivity reaction, photosensitivity toxic reaction, maculo-papular rash, seborrhea, purpura

Special Senses: taste perversion, taste loss, parosmia

Vision: blindness, loss of accommodation, eye pain, conjunctivitis, xerophthalmia, glaucoma, ocular hemorrhage

Body as a Whole: increase weight, back pain, malaise, fever, asthenia, generalized edema, periorbital edema, peripheral edema, rigors, legs edema, face edema, hot flushes, enlarged abdomen, nasal polyp

Occasional instances of transient, reversible hepatic transaminase elevations have occurred during cetirizine therapy. There was a single report of possible drug-induced hepatitis with significant transaminase elevation (500 to 1000 IU/L) and elevated bilirubin.

In foreign marketing experience the following additional rare, but potential severe adverse events have been reported: hemolytic anemia, thrombocytopenia, orofacial dyskinesia, severe hypotension, anaphylaxis, hepatitis, glomerulonephritis, stillbirth, and cholestasis.

DRUG ABUSE AND DEPENDENCE

There is no information to indicate that abuse or dependency occurs with ZYRTEC.

OVERDOSAGE

Overdosage has been reported with ZYRTEC. In one patient who took 150 mg of ZYRTEC, the patient was somnolent but did not display any other signs or abnormal blood chemistry or hematology results. Should overdose occur, treatment should be symptomatic or supportive, taking into account any concomitantly ingested medications. There is no known specific antidote to ZYRTEC. ZYRTEC is not effectively removed by dialysis, and dialysis will be ineffective unless a dialyzable agent has been concomitantly ingested. The minimal lethal oral dose in rodents is approximately 100 times the maximum recommended clinical dose on a mg/m² basis and the liver was the target organ of toxicity.

DOSAGE AND ADMINISTRATION

The recommended initial dose of ZYRTEC is 5 or 10 mg, depending on symptom severity. Most patients in clinical trials started at 10 mg. ZYRTEC is given as a single daily dose, with or without food. The time of administration may be varied to suit individual patient needs.

In patients with decreased renal function (creatinine clearance 11-31 mL/min), patients on hemodialysis (creatinine clearance less than 7 mL/min), and in hepatically impaired patients, a dose of 5 mg QD is recommended.

HOW SUPPLIED:

ZYRTEC tablets are white (dye free), film coated, rounded-off rectangular shaped containing 5 mg or 10 mg cetirizine hydrochloride.

5 mg tablets are engraved with "PFIZER" on one side and with "550" on the other.

Bottles of 100: (NDC 0069-5500-66)

10 mg tablets are engraved with "PFIZER" on one side and with "551" on the other.

Bottles of 100: (NDC 0069-5510-66)

Cetirizine is licensed from UCB, Pharma Inc.

STORAGE: Store at room temperature 59° to 86°F (15° - 30°C).

FEB 25 1994

Ledet

NDA: 19-835

Submission Dates:

June 30, 1988, December 20, 1991
July 7, 1993, July 8, 1993
July 9, 1993, July 22, 1993
July 22, 1993, August 11, 1993
August 19, 1993, September 16, 1993
September 28, 1993, September 30, 1993
October 8, 1993, October 29, 1993
February 17, 1994, February 18, 1994

Generic Name, Dose and Formulation:

**Cetirizine Dihydrochloride 5, 10 and 20 mg
Film-Coated Oval Tablets for Oral
Administration**

Brand Name: REACTINE

**Sponsor: Pfizer Inc
New York, N.Y. 10017**

Reviewer: Safaa Ibrahim

Type of Submission: Review of NDA

SYNOPSIS

Cetirizine is rapidly absorbed and is equally available from a tablet as from an oral solution ($F_r = 104\%$). About 70% of an administered radioactive dose of 10 mg is recovered in the urine and about 10% is seen in the feces, for a combined recovery of 80%. Approximately 45% to 58% of the administered radioactive dose was excreted in urine as unchanged drug. Cetirizine is metabolized to a very limited extent by oxidative O-dealkylation to one inactive metabolite. Food decreased C_{max} by 23% and increased T_{max} by 1.7 hours when compared to the fasted state; the extent of absorption remained unchanged. Plasma protein binding of cetirizine was about 93% and was independent of concentration in the range of 0.025 to 1.0 $\mu\text{g/mL}$; these concentrations cover the therapeutic range. Cetirizine exhibits linear kinetics over the dose range of 5 to 60 mg. No accumulation of the drug is observed following a daily dosing regimen of 10 mg for 10 days.

Elderly subjects showed a 50% increase in half-life and a 40% decrease in oral clearance when compared to normals. No gender related differences were noted between normal white adult males ($n=86$) and white adult females ($n=3$). No race related differences were observed between white adult males ($n=86$) and black adult males ($n=11$) and other adult males ($n=4$).

Moderately renally impaired patients ($CL_{cr}=11-31 \text{ mL/min}$, $n=7$) and patients on hemodialysis ($CL_{cr} < 7 \text{ mL/min}$, $n=5$) had a 3-fold increase in $T_{1/2}$ and a 70% reduction in

clearance compared to normals ($CL_{cr}=89-128$ mL/min, $n=7$). Cetirizine was not completely cleared by hemodialysis as less than 10% of the administered dose was removed during the dialysis session.

Hepatically impaired patients with chronic liver diseases (e.g., hepatocellular, cholestatic, and biliary cirrhosis) had a 50 % increase in half life and a 40 % reduction in clearance compared to healthy subjects.

No pharmacokinetic drug--drug interaction was observed between cetirizine and pseudoephedrine, antipyrine, ketoconazole, and erythromycin. A low dose of theophylline (400 mg QD) produced a 50% increase in $T_{1/2}$ and 27% decrease in oral clearance of cetirizine; volume of distribution remained unchanged. In the same study, cetirizine showed 11% increase in AUC of theophylline; this is of no clinical significance.

Cetirizine tablets (5, 10 , and 20 mg) are compositionally proportional to each other. The 10 mg to be marketed tablet was shown to be equivalent to the clinically studied 10 mg capsule. A scale-up batch (4.5 million units of the 10 mg tablet) showed comparable availability to a 10 mg solution.

Dissolution data in water were submitted for all cetirizine tablet strengths (5, 10 , and 20 mg) and the scale-up batch of 10 mg tablet. The 10 mg tablet was also studied in pH 1.2, pH 3.5 and pH 7.5 media. (See also Comment 5).

Note: This Biopharmaceutics review package is presented in two parts: Part I has the review for the NDA when it was submitted in June 1988; tables and figures relevant to that review are provided. Part II is the review of the more recent material; detailed Appendices pertaining to these reviews are in the Division of Biopharmaceutics and are available on request.

COMMENTS

(To the Medical Officer):

1. The drug interaction study between cetirizine (20 mg QD for 3 days) and theophylline (400 mg QD for 3 days) indicated that there was no effect of cetirizine on theophylline. However, theophylline decreased the clearance of cetirizine by about 27%. It should be noted that the dose of theophylline in this multiple dose study was lower than the usually recommended therapeutic daily dose which is 800 mg QD. In addition, theophylline is known to exhibit non-linear kinetics. Therefore, it is possible that if the usual recommended daily doses of theophylline are administered, the influence of theophylline on the kinetics of cetirizine may be more pronounced

possibly leading to greater sedation.

2. Pharmacokinetic Labeling is being provided as APPENDIX A in this review.

3. In this NDA program gender effect has not been adequately established due to the few female adult subjects (n=3) studied compared to the number of male adult subjects (n=86). In the sponsor's pursuit of the clinical program toward performing a dose escalating study for evaluating the cardiac safety of the drug, it is requested that they recruit comparable number of male and female patients. Further, the study should obtain pharmacokinetic information along with pharmacodynamic measurements. The sponsor is encouraged to submit a protocol in this regard.

(To be sent to the firm)

4. The sponsor is encouraged to ascertain the type of plasma protein involved in the binding of cetirizine.

5. The dissolution data submitted are acceptable, provided that the firm adopts the following specification for cetirizine dihydrochloride 5, 10, and 20 mg tablets:

RECOMMENDATION:

The NDA #19-835, for cetirizine dihydrochloride 5, 10, and 20 mg tablets is acceptable from the Division of Biopharmaceutics' standpoint, provided that the sponsor adopts the proposed dissolution specification as outlined in Comment 5 and incorporates Labeling as provided in APPENDIX A.

Please forward this Recommendation and Comments 4 and 5 to the firm.

Safaa Ibrahim, 2/25/94
Safaa Ibrahim, Ph.D.
Pharmacokinetics Evaluation Branch

RD/FT Initialed by R. Baweja, Ph.D. R. Baweja 2/25/94

cc: NDA 19-835 (Orig.), HFD-155, HFD-426 (Ibrahim, Baweja, Fleischer), Drug, Chron,
Division, FOI (HFD 19), HFD-340 (Vish) and Reviewer Files.

APPENDIX A

(LABELING FOR CETRIZINE TABLETS)

Pharmacokinetics: Cetirizine is rapidly absorbed after oral administration of a tablet. The drug is equally available from a tablet as from an oral solution (relative availability = 104 %). Food did not have any effect on the extent of cetirizine absorption. However, T_{max} was delayed by 1.7 hours and C_{max} was decreased by 23% in the presence of food. A mass balance study in 6 healthy male volunteers indicated that about 70% of the administered radioactive dose was recovered in the urine and 10% in the feces, for a combined total recovery of about 80%. Approximately 45 to 58% of the administered radioactive dose was excreted in urine as unchanged drug. Cetirizine is metabolized to a very limited extent by oxidative O-dealkylation to one inactive metabolite.

Cetirizine exhibits linear kinetics over the dosage range of 5 to 60 mg. The mean $\pm$ SD terminal half-life is 8.5 ± 1.2 hours and oral clearance is 54 ± 13 mL/min. No accumulation was observed for cetirizine following daily doses of 10 mg, for 10 days. The steady-state maximum plasma concentration was 311 ± 40 ng/mL and was achieved within 1.0 ± 0.5 hour.

Plasma protein binding of cetirizine is $93 \pm 0.3\%$ and was independent of concentration in the range of 0.025 to 1.0 μ g/mL; this concentration range covers the therapeutic plasma levels.

Special Populations:

Effect of Age: Following a single 10 mg oral dose, half-life increased by about 50% and clearance decreased by about 40% in elderly subjects (N=16) as compared to normal subjects (N=14).

Effect of Gender: No gender-related differences were observed in the kinetics of cetirizine between white adult males (N=86) and white adult females (N=3).

Effect of Race: No race-related differences were observed in the kinetics of cetirizine between White adult males (n=86), Black adult males (n=11), and Other adult males (n=4, Hispanics and Unknown race).

Renally Impaired Patients: The kinetics of cetirizine were studied following multiple oral daily doses of 10 mg for 7 days in normals (CLcr=89-128 mL/min, n=7), mild (CLcr=42-77 mL/min, n=8) and moderately (CLcr=11-31 mL/min, n=7) renally impaired patients. The pharmacokinetics of the drug were similar between the mild group and normals. Moderately renally impaired patients had a 3-fold increase in half-life and 70% decrease in clearance compared to normals. Accumulation of cetirizine was also more pronounced in this group.

Following a single oral 10 mg dose of cetirizine, patients on hemodialysis (CLcr < 7 mL/min, n=5) had a 3-fold increase in half-life accompanied by a 70% decrease in clearance. Cetirizine was not completely cleared by hemodialysis as less than 10% of the administered dose was removed during the dialysis session.

Dosing adjustment may be necessary in moderately renally impaired patients (CL_{cr}=11-31 mL/min) and patients under dialysis (CL_{cr} < 7 mL/min). (See also DOSAGE AND ADMINISTRATION).

Hepatically Impaired Patients: Following single oral doses of 10 mg (n=6) and 20 mg (n=10) cetirizine, patients with chronic liver diseases (hepatocellular, cholestatic, and biliary cirrhosis) had a 50% increase in half-life along with a 40% decrease in clearance compared to healthy subjects (n=16).

Dosing adjustment may be necessary in hepatically impaired patients. (See also DOSAGE AND ADMINISTRATION).

Drug Interactions:

Theophylline: Cetirizine (20 mg QD for 3 days) has no effect on theophylline (400 mg QD for 3 days) kinetics. However, theophylline increased the half-life of cetirizine by about 50% and decreased its clearance by about 27%. (See also PRECAUTIONS)

Pseudoephedrine: A multiple dose study showed that no significant differences were observed in any of the pharmacokinetic parameters of either cetirizine or pseudoephedrine when they were concomitantly administered to 24 healthy male subjects for 6 days.

Antipyrine: When cetirizine was co-administered with antipyrine to 10 healthy male volunteers for 9 days, no changes were observed in plasma clearance or elimination half-life of antipyrine. Therefore, cetirizine does not alter the oxidative metabolizing enzyme activity in the liver.

Ketoconazole: Following a multiple dose study involving 16 healthy male volunteers, cetirizine (20 mg QD) and ketoconazole (400 mg QD) did not alter the pharmacokinetics of each other when given in combination as compared to single entities.

Erythromycin: Following a multiple dose study involving 16 healthy male volunteers, cetirizine (20 mg QD) and erythromycin (500 mg Q8h) did not alter the pharmacokinetics of each other when given in combination as compared to single entities.

PRECAUTIONS

Theophylline is known to exhibit non-linear kinetics. It is possible that if the usual daily doses of theophylline are administered with cetirizine, the influence of theophylline on the kinetics of cetirizine may be more pronounced possibly leading to greater sedation.

DOSAGE AND ADMINISTRATION

The recommended initial dose of REACTINE is 5 or 10 mg, depending on symptom severity, given as a single daily dose, with or without food. Most patients in clinical trials

started at 10 mg (59). The dose may be adjusted as necessary. The maximum recommended daily dose is 20 mg. The time of administration may be varied to suit individual patient needs.

In elderly patients, patients with moderate renal function ($CL_{cr} = 11-31$ mL/min), patients on hemodialysis ($CL_{cr} < 7$ mL/min), and in hepatically impaired patients, a starting dose of 5 mg QD is recommended.

Part I

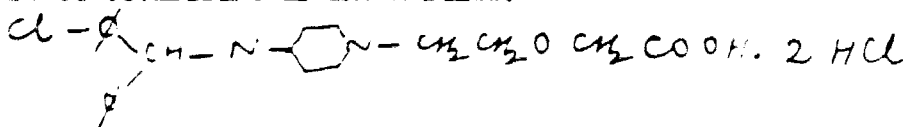
Cetirizine HCl 5, 10
NDA 19,835

Tablets

Pfizer Pharmaceuticals, Inc.
New York, N.Y. 10017
Submission Dated: June 30, 1988

Review of a Submission

Cetirizine hydrochloride is a selective H-1 receptor antagonist of the cyclizine class, active in patients with urticaria and allergic rhinitis. It is the principal human metabolite of hydroxyzine having a terminal carboxyl group in place of the hydroxyl group of hydroxyzine. The chemical structure of cetirizine is shown below:



It has a molecular weight of 461.8 and it is a white, crystalline powder which is soluble in water.

The firm plans to market cetirizine as a conventional film coated tablet formulation in different strengths — 5-, 10-, mg tablets; the intended dose is a 5 mg tablet or a 10 mg tablet given once daily. The formula of the 'to be marketed' tablet formulations is shown in Appendix I and the firm mentions that the three strengths are compressed from a common blend formulation at proportionally adjusted fill weights (1:2:4) to achieve the intended strength. The tablets contain cetirizine

Metabolism studies for cetirizine indicated that it was rapidly absorbed and was mainly excreted in the urine. Therefore, all biopharmaceutical and pharmacokinetic studies presented in this NDA can justifiably be approached by looking at the amount of unchanged cetirizine present in the biological fluids.

The firm has presented various studies to support the biopharmaceutical and pharmacokinetic aspects for this dosage form(s). At one time it was believed by the firm that they would be marketing cetirizine as a capsule dosage form, and therefore, a considerable amount of research pertaining to the clinical studies was performed with the capsule form. Subsequently it was decided to market cetirizine as a tablet dosage form, and the firm has conducted studies linking the clinically studied capsule formulation to the 'to be marketed' tablet formulation.

The studies for cetirizine are divided into three major categories: bioequivalence/bioavailability, pharmacokinetics, and metabolism.

Two studies are included under the bioequivalence/bioavailability section:

Study CPK-1: Determination of the relative bioavailability of the 10 mg capsule and the 10 mg tablet dosage forms of cetirizine hydrochloride used in clinical studies with a reference oral solution.

Study CPK-2: Comparison of the 10 mg capsule dosage form of cetirizine hydrochloride used in the clinical trials with the final 'to be marketed' tablet dosage form.

The pharmacokinetic studies which were conducted in healthy volunteers and in special populations are:

Study CPK-3: A dose proportionality study to determine the bioavailability and pharmacokinetics of a single dose of the three strengths of the tablet formulation.

Study CPK-4: A multiple dose study over 10 days using the 10 mg capsule formulation.

Study CPK-5: "Food study" utilizing the 10 mg tablet formulation.

Study CPK-7: In vitro study to ascertain protein binding characteristics.

Study CPK-8: A pharmacokinetic study involving an adult group and a geriatric group.

Study CPK-10: A pharmacokinetic study in renally impaired patients and in healthy volunteers.

Study CPK-11: Pharmacokinetics of cetirizine in young children with allergic rhinitis.

Study CPK-12: Metabolism of ^{14}C -cetirizine in healthy adult volunteers (after a single oral dose of 10 mg of cetirizine solution).

Study CPK-13: Influence of cetirizine on the clearance of antipyrine in healthy volunteers.

These studies are reviewed and are followed by Comment(s) as necessary. The Comments provided are numbered sequentially throughout the study.

A. IN VIVO STUDIES:

I. Study Number: 05-N-0140; (CPK-1)

1. Title: Comparative Bioavailability of Three Dosage Forms of Cetirizine (Tablet, Capsule and Oral Solution).

2. Objective: To determine the comparative bioavailability of a single dose of the tablet and capsule formulations of cetirizine used in clinical trials with an oral solution as a reference dosage form.

3. Investigator:

4. Formulation/Treatment:

Cetirizine 10 mg capsule — Lot No: C5357
(clinically studied capsule)

Cetirizine 10 mg tablet — Lot No: C6108
(called the clinically studied tablet in this study but which is identical to the 'to be marketed' tablet)

Cetirizine oral solution -- Lot No: C6230
(concentration 1mg/ml; dose 10 mg)

5. Study Design and Dosing: Seventeen healthy male volunteers between the ages of 20 and 34 years participated in the study. The inclusion/exclusion criteria are adequately explained. This single dose study was an open, randomized, three-way crossover study. There was a one-week washout period between the study phases. The subjects reported to the study site on the evening preceding the study day and remained in a fasting state till three hours after the dose was administered in the morning. The dose was given at 7 a.m., and the capsule or tablet was administered with 180 ml of water. The oral solution which was administered as a 10 mg dose (via 10 ml of solution) was prepared by carefully pipetting 10 ml of the solution and diluting it to 180 ml with water. A low fat breakfast (contents not provided) was served three hours after the dose had been administered. Other meals were served at 1 p.m. and at 6 p.m.

6. Sampling schedule: Seven milliliters of blood samples were withdrawn at 0-hour (prior to dosing), and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 36, 48, and 60 hours after dosing. These samples were immediately centrifuged at 5°C for 15 minutes to obtain plasma which was then frozen at -20°C until assayed.

8. Adverse Drug Reactions: No clinically significant adverse drug reactions were found in the subjects during the course of the study.

9. Results:

It is to be noted that the tablet formulation is clinically studied and it is identical to the tablet formulation that the firm eventually intends to market. The firm had at one stage planned to market cetirizine as a capsule dosage form but later it switched toward marketing it as the tablet dosage form. Of importance in this study is the establishing of the relative bioavailability of the clinically studied capsule formulation to the oral solution, and also of the tablet to the oral solution. It will also become clear in this section that the results of this study demonstrate bioequivalency between the capsule and the solution, between the tablet and the solution, and between the tablet and the capsule formulations.

The values of the pharmacokinetic parameters of AUC, C_{max}, T_{max}, for each subject are shown in Table 1a. Figure 1 shows the mean cetirizine plasma concentration versus time profile over 60 hours for the three treatments - capsules, tablets and the oral solution.

The mean (s.d.) values of the pharmacokinetic parameters for the three treatments are shown below:

<u>Parameter</u>	<u>Capsule</u>	<u>Tablet</u>	<u>Oral Solution</u>
AUC (0-60) ng*hr/ml	2917 (713)	2903 (705)	2784 (650)
AUC (0-inf) ng*hr/ml	2924 (717)	2911 (720)	2784 (650)
C _{max} , ng/ml	351 (95)	315 (84)	326 (73)
T _{max} , hr	0.8 (0.3)	1.0 (0.6)	0.7 (0.3)
t _{1/2} , hr	8.6 (1.5)	8.5 (1.2)	8.2 (1.1)

The mean $\pm$ s.d. AUC (0-60) for the capsule and the oral solution were 2917 $\pm$ 713 ng*hr/ml and 2784 $\pm$ 650 ng*hr/ml, respectively. There was no increase when the AUC (0-inf) values were calculated indicating that AUC (0-60) adequately represented the concentration - time profile for cetirizine. Based on the AUC results it is seen that the relative bioavailability (F) of the clinically studied capsule dosage form to the oral solution is about 104 %, (i.e., 2924/2784 X 100).

The mean C_{max} of the capsule and the solution were 351 $\pm$ 95 ng/ml and 326 $\pm$ 73 ng/ml, respectively; the T_{max} values were quite proximal - 0.8 hours (capsule) and 0.7 hours (oral solution). Half life values were comparable (8.6 hours versus 8.2 hours) and with this as a basis, it is reasonable to conclude that the characterization of AUC over 60 hours is adequate as it covers '7' t_{1/2} values.

The mean (s.d.) AUC (0-60) for the tablet and the oral solution were 2903 (705) ng*hr/ml and 2784 (650) ng*hr/ml, respectively. Again there was no increase when the AUC (0-inf) values were calculated indicating that AUC (0-60) adequately represented the complete concentration - time profile for the drug from the formulations. Based on these results it is seen that the relative bioavailability (F) of the clinically studied tablet dosage form to the oral solution is about 104 %, (i.e., 2903/2784 X 100).

The mean C_{max} of the tablet and the solution were 315 (84) ng/ml and 326 (73) ng/ml, respectively; the T_{max} values were similar - 1.0 hours (tablet) and 0.7 hours (oral solution); the half life values were comparable (8.5 hours tablet versus 8.2 hours solution).

The reviewer obtained the results of the 90 % confidence interval testing

performed on AUC and Cmax values using two one sided t tests, and using the oral solution as the reference treatment. Similarly these values were also obtained for a comparison between the tablet and the capsule treatment using the latter as the reference. The results are as follows:

<u>Comparison</u>	<u>Parameter</u>	<u>90 % C.I.</u>	<u>p-values</u>	<u>Inference</u>
Capsule vs Soln	AUC (0-∞)	100.9-109.1	0.20	Pass
Capsule vs Soln	C max	102.3-113.0	0.01	Pass
Tablet vs Soln	AUC (0-∞)	105.5-108.7	0.20	Pass
Tablet vs Soln	C max	91.3-102.0	0.01	Pass
Tablet vs Cap	AUC (0-∞)	95.6-103.5		Pass
Tablet vs Cap	C max	84.8- 94.7		Pass

The 90 % confidence interval testing results using the oral solution as the reference showed that the capsule and the solution formulations were bioequivalent to each other, and also that the tablet was bioequivalent to the solution. Finally, it was seen that the tablet was bioequivalent to the capsule.

10. Conclusion: This study was conducted with a view toward obtaining the relative bioavailability of the capsule form to the oral solution, and of the tablet form to the oral solution. The study results showed an 'F' value of about 104 % for both the capsule and the tablet relative to the solution at the 10 mg dose. Furthermore, by obtaining the 90 % confidence interval results it was seen that both the capsule and the tablet dosage forms are individually bioequivalent to the (reference) oral solution. The tablet and the capsule were bioequivalent to each other.

II. Study Number: 87-N-0063; (CPK-2)

1. Title: Comparative Bioavailability of Osetirizine Capsule and Tablet Dosage Forms.
2. Objective: To determine the bioequivalence of the tablet dosage form intended for commercial production to the capsule dosage form used in a majority of the clinical trials.

3. Investigator

ca

4. Formulation/Treatment:

Cetirizine 10 mg capsule — Lot No: C6021
(clinically studied capsule)

Cetirizine 10 mg tablet — Lot No: C6180
(‘to be marketed’ tablet)

5. Study Design and Dosing: This was an open, two way crossover, single dose study with a seven day washout period between the treatments. The study involved eighteen healthy adult male volunteers between the ages of 19 and 39 years; mean $\pm$ s.d. weight was 160.7 $\pm$ 18.2 pounds (range 125 to 188 pounds). The inclusion/exclusion criteria are adequately explained. Subjects reported to the study site the evening preceding the commencement of the study day and they remained fasting till three hours after the administration of the dose. Dose was given at 7 a.m. Each dose, one capsule or one tablet, was administered with 180 ml of water. A low fat breakfast (contents not provided) was served three hours later. The firm mentions that other meals were served at 1 p.m. and 6 p.m. on day 1, and at 8 a.m., 1 p.m., and 5 p.m. on day 2, and that the timings and the menu for each study day were the same.

6. Sampling Schedule: Seven milliliters of blood samples were withdrawn at 0-hour (prior to dosing), and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 36, and 48 hours after dosing. These samples were immediately centrifuged at 5°C for 15 minutes to obtain plasma which was then frozen at -20°C until assayed.

7. Analytical methodology:

8. Adverse Drug Reactions: Six subjects reported mild headache and one subject reported mild drowsiness during the course of this study. The study proceeded to completion as planned by the firm.

9. Results: The values of the pharmacokinetic parameters of AUC, C_{max}, T_{max}, for each subject are shown in Table 1b, and the mean values for the pharmacokinetic parameters are shown in Table 1c in the Appendix part of the review. Shown below are the mean $\pm$ s.d. results of the pharmacokinetic parameters and following this are the 90 % c.i. values obtained using two one sided t tests.

<u>Parameter</u>	<u>Tablet</u>	<u>Capsule</u>
AUC (0-48), ng.hr/ml	2918 (628)	2815 (553)
AUC (0-inf), ng.hr/ml	2951 (672)	2846 (586)
C max, ng/ml	347 (79)	334 (73)
T max, hr	0.9 (0.5)	0.9 (0.3)
t 1/2, hr	7.8 (1.1)	7.9 (1.0)

It is noticed that there was very little difference (of less than 1.0 %) between AUC (0-48) values and the AUC (0-inf) values for both treatments. This difference of less than 1 % was comparable to what was observed between AUC (0-60) and AUC (0-inf) values in the previous study, - study CPK-1.

The results of the 90 % confidence interval testing performed on AUC and Cmax values using two one sided t tests and with the capsule treatment as the reference, showed the following features:

<u>Parameter</u>	<u>p-values</u>	<u>Power</u>	<u>90 % C.I.</u>	<u>Inference</u>
AUC (0-48)	0.13	99.9%	99.6-107.7	Pass
AUC (0-inf)	0.15	99.9%	99.4-108.0	Pass
C max	0.34	99.4%	96.9-110.9%	Pass

The 90 % confidence results for AUC and for Cmax were within the acceptable range of 80 - 120 %. The power as well as the p-values also lend strong support to the declaration that in this single dose study the clinically studied capsule and the 'to be marketed' tablet formulation are bioequivalent.

10. Conclusion: The clinically studied capsule formulation and the 'to be marketed' tablet formulation are bioequivalent based on AUC, Cmax, and comparable Tmax.

III. Study Number: 86-N-0096; (CPK-3):

- Title: Dose Proportionality Study of Cetirizine: Three-way Crossover Comparison of Single Doses of 5, 10, and 20 ng.

2. Objective: To evaluate the comparative bioavailability and pharmacokinetics after a single dose of 5, 10 and 20 mg cetirizine in healthy volunteers.

3. Investigator:

4. Formulation/Treatment:

Cetirizine 5 mg tablet — Lot No: C6106

Cetirizine 10 mg tablet — Lot No: C6108

Cetirizine 20 mg tablet — Lot No: C6110

All three tablets strengths are 'to be marketed' tablet formulations and all three formulations are compositionally proportional (see Appendix I).

5. Study Design and Dosing: The study was an open, randomized, three way crossover, single dose study with a one week washout period between the treatments. The inclusion/exclusion criteria are adequately explained. The age of the subjects was between 19 and 34 years, and the weight ranged from 136 to 192 pounds. Subjects reported to the study site on the evening preceding the study day and remained fasting till three hours after the dose had been administered. The treatment dose (one tablet of 5 mg or 10 mg or 20 mg) was administered at 7 a.m. on each study day and each tablet treatment was administered with 180 ml of water. A low fat breakfast (contents not mentioned) was served three hours after dosing.

6. Sampling schedule: Seven milliliters of blood samples were withdrawn at 0- hour (prior to dosing), and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours after dosing. These samples were immediately centrifuged at 5°C for 15 minutes to obtain plasma which was then frozen at -20°C until assayed.

7. Analytical methodology: --

8. Adverse Drug Reactions: The study was completed as planned by the firm as no adverse drug reactions were seen during the study.

9. Results: The individual plasma concentration - time values for the three treatments, and the values of the pharmacokinetic parameters of AUC, C_{max}, T_{max}, for each subject are shown in Table 2. Analysis of variance was used to compare AUC and C_{max}, both normalized to the 10 mg dose (which the firm believes will be the expected clinical dose). In addition to the analysis of variance of the normalized AUC (NAUC) and normalized C_{max} (NC_{max}), dose proportionality of the 5-, 10-, and 20 mg tablets was also assessed by regression analysis of AUC versus dose and C_{max} versus dose.

The mean cetirizine plasma concentration-time curves from 0 - 72 hours for the three treatments are shown in Figure 2. Table 3 shows the mean AUCs and mean Cmax's normalized to the 10 mg dose and it shows that there is no statistical difference between the three treatments for NAUC (p-value for NAUC = 0.11) and NCmax (p value for NCmax = 0.73).

Dose proportionality of the 5, 10, and 20 mg tablets was also examined by regression analysis of AUC versus dose (Figure 3) and Cmax versus dose (Figure 4). Regression analysis for AUC - dose resulted in an 'r' value of 0.92, whereas the same value for Cmax - dose was 0.95. The results of regression analysis demonstrate excellent goodness of fit for the line. It is shown that the regressed line passes through the origin indicating dose proportionality.

The reviewer proceeded and obtained 90 % confidence intervals using two one sided t tests for comparisons between NAUC of the 5 mg tablet and the 10 mg tablet, and between the NAUC values of the 20 mg tablet and the 10 mg tablet. Corresponding comparisons were also obtained for the NCmax parameter. Recall that the 10 mg tablet is the reference treatment. The 90 % c.i. values were:

89.6 - 99.2 % for NAUC comparison between 5 mg and 10 mg tablets, and
94.1 - 103.7 % for NAUC comparison between 20 mg and 10 mg tablets.

92.4 - 106.9 % for NCmax comparison between 5 mg and 10 mg tablets, and
96.0 - 110.4 % for NAUC comparison between 20 mg and 10 mg tablets.

All of the results above, i.e., analysis of variance, regression analysis, and the 90 % confidence interval support dose proportionality of cetirizine tablets. This is not surprising when it is realized that the firm has mentioned that the three strengths of the tablet are all compressed from a common blend formulation at proportionally adjusted fill weights of 1:2:4 to achieve the intended strengths.

10. Conclusion: Based on AUC and Cmax the bioavailability of cetirizine tablet is shown to be proportional to dose after a single dose administration of 5-, 10-, and 20 mg tablets.

IV. Study Number: 86-N-0100: (CPK-4)

1. Title: Multiple-dose Pharmacokinetics of Cetirizine After Once Daily Administration of the 10 mg Capsule in Healthy Volunteers.
2. Objective: To determine the multiple dose pharmacokinetics of cetirizine following once a day dosing of 10 mg cetirizine for ten days in healthy volunteers.
3. Investigator:

4. Formulation/Treatment:

Cetirizine 10 mg capsule — Lot No: CS357

5. Study Design and Dosing: Eighteen healthy male volunteers between the ages of 22 and 35 years participated in the study. The weight ranged from 141 - 201 pounds while the height ranged from 66 - 76 inches. The inclusion/exclusion criteria are adequately explained. The study was an open, single-phase, multiple dose study in which the subjects were administered one 10 mg cetirizine capsule daily for ten days. Subjects reported to the study site on the evening preceding the first study day and fasted for a minimum of 10 hours prior to each dose administration. A 10 mg dose was administered at 8 a.m. on each study day with 180 ml of water. A low fat breakfast was served two hours after the dose had been administered. Meals were served, and consistently so, throughout the study at 1 p.m. and at 6 p.m.

6. Sampling schedule: Ten milliliters of blood samples were drawn into heparinized vacutainers at 0-hour (pre-dose), and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, and 24 hours on day one, and at 1, 8, and 24 hours after dosing on days 2-9, and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 36, 48, 60, 72, and 96 hours post dosing on day 10. All Blood samples were immediately centrifuged at 5° C for 15 minutes, and the plasma frozen until assayed.

The total urine voided for each study was collected for 96 hours and the volume noted, and a 20 ml aliquot of each day's sample was frozen at -20° C until assayed.

8. Adverse Drug Reactions: The adverse drug reactions were rather mild in nature and involved one subject reporting slight lightheadedness and five subjects reporting sore throats.

9. Results: The plasma cetirizine concentration for each blood sample for each individual as well as the values of the pharmacokinetic parameters of AUC, C_{max}, T_{max}, for each subject are shown in Table 4. Individual urinary recovery values for each day are shown in Table 5. The mean ± s.d. pharmacokinetic parameters on day 1 and day 10 following oral administration of one cetirizine 10 mg capsule daily for 10 days is shown in Table 6. Figure 5 characterizes the mean cetirizine plasma concentration - time profile from day 1 of the study to day 13. Figure 6 shows the mean plasma concentration - time profiles for days 1 and 10.

The mean cetirizine plasma concentration - time profile obtained on day 1 of dosing did not differ considerably from the profile obtained on day 10 (Figure 6). The firm has not provided formal ANOVA statistics, and therefore, a confidence interval comparison is not possible between the first dose and the tenth (last) dose. However, it is possible to provide

a comparative set of values for day 1 and 10: the C_{max} (297- and 311 ng/ml, respectively), C_{min} (27.5- and 29.9 ng/ml, respectively), T_{max} (0.9- and 1.0 hours, respectively), and T_{1/2} (8.1- and 8.3 hours, respectively) values for day 1 and for day 10 were not statistically significant; the p-values were > 0.05 for each of these pharmacokinetic parameters.

The mean AUC (0-24) value for day 10 was greater than that for day 1 (day 1: 2206-, and day 10: 2502 ng*hr/ml). This showed that there was a 13 % change between the first and the last doses. Similarly the AUC (0-inf) values showed a corresponding 13 % change between days 1 and 10, (day 1: 2514-, and day 10: 2856 ng hr/ml). This difference was therefore reflected in the accumulation index which was found to be 1.14. This accumulation is in agreement with pharmacokinetics principles, where; in this instance, the drug has a half life of about 8 hours and is being dosed every 24 hours, and therefore, the accumulation index is seen to be around 1. The relative bioavailability or the accumulation index to compare dose 10 to dose 1 yielded a mean value of 1.14 (± 0.16) with a range of 0.93 — 1.39.

To characterize the multiple dose behaviour after the last dose, the mean ± s.d. fluctuation index was 2.77 ± 0.53 with a range of 2.14 — 3.69.

Urine results showed that the mean daily urinary excretion of unchanged drug during the 10 day period was about 60 % of the daily dose administered; (range 52 - 70 %). No other information was presented for urine data.

10. Conclusion: The pharmacokinetic parameters of AUC, C_{max} and C_{min} for the first and the last dose are comparable resulting in an accumulation factor of 1.14. Urinary excretion of the unchanged drug appeared to be about 60 % of the daily dose over a 24 hour period.

V. Study Number: 86-N-0105; (CPK-5)

1. Title: Bioavailability of a 10 mg Cetirizine Tablet Given Under Fasting Conditions or Following a Meal.
2. Objective: To determine the bioavailability and pharmacokinetics of a 10 mg cetirizine tablet given as a single dose under fed and fasting conditions.
3. Investigator:

4. Formulation/Treatment:

Cetirizine 10 mg tablet -- Lot No: C6108
('to be marketed' formulation)

5. Study Design and Dosing: This study was conducted with twenty three healthy male volunteers between the ages of 19 and 35 years, and having an average weight of 170 pounds, (range: 142 - 214 pounds). The inclusion/exclusion criteria are adequately explained. The study was an open, randomized, two period, two-way crossover study with a one week washout period between the two periods. Subjects reported to the study site on the evening previous to the commencement of the study. The subjects in the 'fasted' phase of the study remained fasting till three hours after the administration of the dose which occurred at 7 a.m. on the study day. The subjects in the 'fed' phase of the study received a high fat breakfast consisting of two strips of bacon, one egg, 2 slices of buttered toast and eight ounces of whole milk about 30 minutes before dosing. The 10 mg dose was administered on the study days at 7 a.m. Three hours after dosing the subjects in the fasted phase of the study received a low fat breakfast. All subjects then received a meal at 1 p.m. and at 6 p.m.

6. Sampling schedule: Seven milliliters of blood samples were withdrawn from all subjects at 0-hour (prior to dosing), and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 36, 48, and 60 hours after dosing. These samples were immediately centrifuged at 5°C for 15 minutes to obtain plasma which was then frozen at -20° C until assayed.

7. Analytical methodology:

is
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8. Adverse Drug Reactions: A mild rash developed for one subject and this disappeared in twenty four hours. Other than this incident there were no other ADRs.

9. Results: The individual concentration - time values as well as the pharmacokinetic parameters (AUC, C_{max} and T_{max}) for each subject are shown in Table 7. The mean pharmacokinetic parameters are presented in Table 8. Graphically the mean data for the fed and the fasting states is presented in Figure 7. Shown below are the mean ± s.d. results of the pharmacokinetic parameters.

<u>Parameter</u>	<u>Fed</u>	<u>Fasting</u>
AUC (0-60), ng.hr/ml	2468 (418)	2550 (450)
AUC (0-inf), ng.hr/ml	2471 (423)	2553 (454)
C max, ng/ml	221 (34)	289 (46)
T max, hr	2.7 (1.2)	1.0 (0.5)
t 1/2, hr	7.7 (1.2)	7.4 (1.1)

The results of the 90 % confidence interval testing performed on AUC, Cmax, and Tmax values using two one sided t tests, showed the following features:

<u>Parameter</u>	<u>p-values</u>	<u>Power</u>	<u>90 % C.I.</u>	<u>Inference</u>
AUC (0-60)	0.22	99.9%	92.9-100.7	Pass
AUC (0-inf)	0.23	99.9%	92.9-100.7	Pass
C max	0.01	99.4%	71.7-81.3	Fail
T max	0.01	10.8	226.0-314.0	Fail

It is noticed that there was no difference between AUC (0-60) values and the AUC (0-inf) values for both treatments. The 90 % confidence results for the AUC in the 'fed' group was within the acceptable range of 80 - 120 % of the 'fasted' group indicating that there was no difference in the extent of absorption between the fed and fasted groups. However, both C max and T max showed significant differences (p-value = 0.01). Furthermore, the 90 % confidence intervals were 71.7-81.3 % for the Cmax and were 226.0-314.0 % for the Tmax and these values indicate that Cmax and Tmax (means) are not comparable between the two treatments (see Figure 7 also). It is seen that the Cmax value for the 'fed' treatment decreased considerably whereas the Tmax increased, compared to the fasting treatment. Applying ratio analysis to AUC and to Cmax, 22 out of the 23 subjects (i.e., 95.7 %) in the fed group had AUCs that were within 0.75 - 1.25 of fasted group while only 15 out of the 23 subjects (i.e., 65.2 %) in the fed group had Cmax values within 0.75 - 1.25 of the fasted group.

All this implies that food appears to have an effect on the bioavailability profile of cetirizine in that the rate of absorption was slower with food, but the overall extent of absorption remained the same.

10. Conclusion: It may be stated that the effect of food on cetirizine bioavailability was to reduce the rate of absorption, (lower Cmax and longer Tmax), while keeping the extent of absorption, (AUC), unchanged.

VI. Study Number: CPK-7

1. Title: Pharmacokinetic Aspects in Healthy Volunteers Following Repeated Administration.
2. Objective: To determine the plasma protein binding of cetirizine.
3. Investigator:
4. Formulation/Treatment:

Cetirizine 10 mg capsule — Lot No: nr 86
(clinically studied capsule)

5. Study Design and Dosing: The study was conducted with six healthy adult male volunteers having an average weight of 70 ± 6 Kg. They received one 10 mg capsule of cetirizine at 8 a.m. and another 10 mg capsule at 8 p.m. The capsule was taken with 150 ml of water and it is mentioned that the dosage administration was at least an hour after breakfast or dinner. This dosing schedule continued for 10 days and it involved the administration of 21 total doses.

Determination of protein binding was the main feature of this study where it was thought that it would be possible to ascertain the plasma protein binding of cetirizine since a wide array of samples, differing in concentration, were readily available. Therefore three sample time points were studied for all six subjects for protein binding characterization, viz., from the first dose, the 1 hour sample; from the last dose, the 1 hour sample and the 1.5 hour sample. The choosing of the 1 hour or the 1.5 hour was appropriate as it was known that C_{max} would occur at about 1 to 1.5 hours after dosing. The doses chosen were the first dose and the last dose - (the 21st dose), and this was done with a view toward ascertaining whether the binding was constant over this span.

6. Sampling schedule: Seven milliliters of blood samples were collected into heparinized tubes at 10-, 20-, 40-, 60-, and 90 minutes, and at 2, 3, 4, 6, 9, and 12 hours after the administration of the first dose; then at 12 hours after the second, fourth, eighth, sixteenth and twentieth doses; and finally at 10-, 20-, 40-, 60-, 90 minutes and at 2, 3, 4, 6, 9, 12, 24, 36, and 48 hours after the 21st (last) dose. The blood samples were centrifuged and the plasma samples were frozen until ready for analysis.

8. Results: The average binding amount of cetirizine on the plasma proteins is 93 % based on the results of the spiked plasma samples and it is seen that binding is independent of concentration in the range of concentrations tested, i.e., 25 to 1,000 ng/ml; (Table 9). This concentration range covers the concentrations measured after the administration of an oral single dose of 10 mg of cetirizine..

In the samples of plasma collected 1 hour after the administration of the first dose to the subjects, the mean (n=6) binding was 93 ± 0.4 % (Table 10). The 1 hour sample from the last dose (i.e., the 21st dose) showed a mean value of 92.3 ± 1.2 %, and for the 1.5 hour sample of the last dose, the mean binding value was 92.4 %. The firm did not provide the observed concentration at 1 hour the first dose and 1- and 1.5 hours after the last dose. It was observed that the protein binding of cetirizine at the expected maximum concentration level was comparable to that obtained from spiked samples of 25 - 1,000 ng/ml concentration.

Pharmacokinetic results accompanying this study are very brief and essentially mention that after the single dose the mean AUC (0-inf) value was 3.2 ± 0.9 ug*hr/ml and the mean C_{max} value was 0.29 ± 0.13 ug/ml. The mean AUC value after the last dose was 3.70 ± 0.64 ug*hr/ml and the mean C_{max} value was 0.54 ± 0.18 ug/ml.

9. Conclusion: The mean in vitro binding of cetirizine to plasma proteins is approximately 93 % in the concentration range of 25 — 1,000 ng/ml. Plasma protein binding studies performed with the 1 hour samples for the first dose and 1 hour and 1.5 hour samples for the last (21st) dose also showed the mean binding to be about 93 %.

VII. Study Number: 85-N-0073; (CPK-8)

1. Title: Comparative Serum and Urine Levels After Administration of 10 mg Cetirizine Capsules to Volunteers of Different Ages.
2. Objective: To determine the pharmacokinetics of cetirizine in subjects of different ages, especially the geriatric population.
3. Investigator:

4. Formulation/Treatment:

Cetirizine 10 mg capsule -- Lot No. C4002
(clinically studied capsule)

5. Study Design and Dosing: This was an open, single dose study of parallel design to determine the pharmacokinetics of cetirizine in young adults and in the geriatric population. A total of thirty volunteers between the ages of 37 and 86 years of age were assigned to two groups, viz., those below 65 years of age (called the adult group), and those above 65 years (called the geriatric group). Fourteen subjects, 6 males and 8 females, were in the adult group (mean $\pm$ s.d. age: 53 ± 9 years); and sixteen subjects, 7 males and 9 females, were in the geriatric group (mean $\pm$ s.d. 77 ± 5 years). The subjects were all healthy and the inclusion/exclusion criteria are adequately explained. Subjects reported to the study site on the evening preceding the study day. On the morning of the study day, each subject received a single 10 mg dose of cetirizine capsule with 120 ml of water.

6. Sampling schedule: Seven milliliters of blood samples were drawn at 0-hour (just before dosing), and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours after dosing. The serum samples were immediately separated off from the clotted blood samples, and the former were frozen till analysis was performed.

Urine samples were collected at 0-24, 24-48, and 48-72 hours. Aliquots of the urine samples were frozen at -20° C until analyzed.

8. Adverse Drug Reaction: One subject experienced mild drowsiness; other than this minor incident there were no other adverse drug reactions.

9. Results: The individual plasma concentration - time values for the subjects as well as the values of the pharmacokinetic parameters of AUC, C_{max}, T_{max}, for each subject are shown in Table 11; similarly the amounts of urine recovered in the urine of each subject over the various time periods is shown in Table 11 also. The mean values for the pharmacokinetic parameters are shown in Table 12. The plasma profile of cetirizine in the two groups is shown in Figure 8. All these tables and figure appear in the Appendix part of the review. Shown below are the mean $\pm$ s.d. results of the pharmacokinetic parameters: the ANOVA p-values shown below were provided by the firm.

<u>Parameter</u>	<u>Adult Subjects</u>	<u>Geriatric Subjects</u>	<u>p-value</u>
AUC (0-72), ng.hr/ml	3317 (903)	5593 (1773)	0.01
AUC (0-inf), ng.hr/ml	3318 (903)	5653 (1824)	0.01
C max, ng/ml	384 (105)	460 (59)	0.02
T max, hr	1.0 (0.5)	0.9 (0.3)	0.55
t 1/2, hr	7.4 (1.6)	11.0 (3.0)	0.01

It is noticed that there was very little difference (less than 1.0 %) between AUC (0-72) values and the AUC (0-inf) values for both treatments. There were significant differences in AUC, Cmax, and t 1/2 between the two groups. The extent of absorption, (AUC), for the geriatric group was about 70 % more compared to the extent of absorption (AUC) noticed for the adult group. An increase of about 20 % was seen in the Cmax value for the geriatric group compared to the adult group. Only Tmax showed no significant differences (p-value: 0.55). Thus it may be stated that both the Cmax and the extent of absorption of cetirizine were significantly different between the two groups. (No confidence interval information was provided by the firm).

The mean cumulative urinary recovery of cetirizine (unchanged) for the periods of 0-24 hour, and 0-72 hour after dose were 47 % and 52 % of the dose for those in the adult group, respectively, and were 38 % and 45 %, respectively, for those in the geriatric group. The recovery values for the 0-24 hour were significantly different (p=0.03) between the two groups of subjects, but the values for the 0-72 hour were not significantly different (p=0.21).

A comparison of the pharmacokinetic parameters (AUC, Cmax and Tmax) was also made between the two sexes regardless of the age of the subject. The mean AUC results indicated that females had a mean AUC value about 17 % higher than the male subjects — 4944.7 ± 1770.0 ng*hr/ml for females versus 4065.2 ± 1944.4 for males. Similarly the mean Cmax value was higher for females than for males by about 26 % - [females: 466.7 ± 78.6 ng*hr/ml; males: 369.6 ± 73.3 ng*hr/ml. Tmax values were comparable for the two sexes - 0.9 ± 0.4 hours.

10. Conclusion: The study shows that the pharmacokinetic profile of cetirizine for the geriatric group of volunteers (i.e., those above 65 years of age) was considerably different than the profile obtained for the adult group in that the normal geriatric subjects cleared the drug slower than the normal adult subjects and that the elderly subjects had higher Cmax than the normal volunteers. It was also shown that female subjects appeared to have higher AUC and Cmax than the male subjects in this study.

VIII. Study Number: 85-N-0034; (CPK-10)

1. Title: Pharmacokinetics of Orally Administered Cetirizine 10 mg in Subjects with Normal and Abnormal Renal Function and with End Stage Renal Disease on Hemodialysis.
2. Objective: The objective of this study was to compare the single dose pharmacokinetics of cetirizine following oral administration in patients with renal disease with that of normal subjects.
3. Investigator:
4. Formulation/Treatment: Cetirizine 10 mg capsule -- Lot No: C4002
5. Study Design and Dosing: This was an open, single dose study in normal subjects and in patients with varying degrees of renal impairment as measured by creatinine clearance. Twenty volunteers: 5 normal subjects, 5 patients with mild renal impairment (creatinine clearances between 31-60 ml/min), 5 patients with moderate renal impairment (creatinine clearances between 7-30 ml/min), and 5 patients on hemodialysis (creatinine clearance < 7ml/min), were each administered a single oral dose of 10 mg cetirizine capsule. The demographics and the age, weight, and height of each individual volunteer are shown in Appendix II. The inclusion/exclusion criteria are adequately explained; patients with mild or moderate renal impairment were accepted if they had normal clinical test values except those relating to renal disease.

Volunteers reported to the study site on the evening before dosing was to have commenced and they fasted for at least 8 hours prior to drug administration. The dose of cetirizine 10 mg capsule was administered with 180 ml of water and was given at 8 a.m. The volunteers fasted for another three hours after dosage administration after which breakfast was served (11 a.m.).

6. Sampling schedule: In normal subjects and in non-dialysis renal patients, five milliliters of blood samples were collected prior to dosing (0-hour), and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 36, and 48 hours. Additional samples were withdrawn at 72 and 96 hours for renal patients. Dialysis patients were scheduled for hemodialysis three hours after dosing (for 4 hours) and so their blood sampling times were: (0-hour), and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 7.25, 7.5, 7.75, 8, 12, 24, 36 and 48 hours. In addition to these samples, 10 ml of pre- and post-filter blood samples were taken at 4 and 6 hours after dosing to measure the effect of hemodialysis on the removal of cetirizine from the blood. The blood samples were centrifuged and the plasma samples so obtained were frozen at -20° C and maintained in the frozen state until assayed.

7. Analytical Methodology:

8. Adverse Drug Reactions: Six subjects reported mild drowsiness and two subjects reported a mild headache. The study was completed as planned by the firm.

9. Results: The individual plasma cetirizine concentrations are shown in Table 13 as are the values of the pharmacokinetic parameters (AUC, C_{max} and T_{max}) for each of the subjects. The individual urinary recovery values for cetirizine are shown in Table 14. The mean plasma concentration - time profiles for the four treatments are shown in Figure 9. The mean (s.d.) pharmacokinetic parameters are shown in Table 15; however, the mean (s.d.) parameters are also shown below.

<u>Parameter</u>	<u>Normals</u> (n=5)	<u>Mild</u> (n=5)	<u>Moderate</u> (n=5)	<u>Hemodialysis</u> (n=5)
AUC (0-t*) (ng*hr/ml)	2138 (320)	6352 (1230)	8328 (1982)	6084 (832)
AUC (0-inf) (ng*hr/ml)	2138 (320)	6536 (1358)	8726 (2211)	7611 (1786)
C max (ng/ml)	313 (46)	338 (70)	357 (172)	285(29)
Tmax (hours)	0.9 (0.2)	1.1 (0.2)	2.2 (1.1)	2.0 (0.7)
t 1/2 (hours)	7.0 (1.1)	19.4 (3.4)	20.9 (4.0)	19.8 (5.6)
Urinary Recovery (% unchanged drug) (0-t)*	63.5	31.9	16.4	

* t = 72 hours for normal subjects

t = 96 hours for mild and moderate groups

The results showed that renally impaired patients had approximately 3 - 4 times the AUC (mean: 6536 to 8726 ng*hr/ml) of normal volunteers (mean: 2138 ng*hr/ml). Among the renally impaired groups, there was a 33 % difference between the mild and the moderately impaired patients, and there was a 15 % difference between the moderately impaired patients and those on hemodialysis. Similarly, the t 1/2 values were almost three times greater (19-21 hours versus 7 hours) in the renal patients than in the normal subjects.

The parameters of Cmax and Tmax were quite proximal in their values between normal volunteers and the renally impaired volunteers. The mean Cmax values for the renally impaired subjects [mild and moderate groups] was about 7 - 12 % higher than for the normal subjects. The total amount of cetirizine removed by hemodialysis was less than 10 % of the administered dose suggesting that hemodialysis was not an effective method of clearing cetirizine from the blood.

Based on the results above it can be stated that as creatinine clearance decreases from normal [31-60 ml/min] to mild [7-30 ml/min] to moderately impaired subjects [< 7ml/min], cetirizine clearance (Dose/AUC) is also seen to decrease.

Urinary recovery of unchanged drug was about 64 % for the normal volunteers during the sample collection period of 0-72 hours, and was about 32 % and 16 % for the mild and moderate renally impaired groups, respectively, during the period of 0--96 hours.

10. Conclusion: Renally impaired patients had higher AUC values and longer half lives than normal subjects. Also, between renally impaired groups there was a 33 % difference between the mild and the moderately impaired patients, and there was a 15 % difference between the moderately impaired patients and those on hemodialysis. The study results indicate that creatinine clearance can be used to predict changes in cetirizine clearance.

IX. Study Number: 86-N-0002; (CPK-11)

1. Title: Clinical Pharmacokinetics of Cetirizine 5 mg PO in Pediatric Patients with Allergic Rhinitis.
2. Objective: To determine the pharmacokinetics of cetirizine in children with a history of allergic rhinitis.
3. Investigator
4. Formulation/Treatment:

Cetirizine 5 mg capsule — Lot No: C4056

5. Study Design and Dosing: This was an open, single dose study to determine the pharmacokinetics of cetirizine in a pediatric population. The study involved fourteen pediatric patients between the ages of 7 and 12 years (mean 10.1 ± 1.6 years), and all these children had a history of allergic rhinitis. The mean height and weight, $\pm$ s.d., were 56.7 ± 4.0 inches and 77.1 ± 17.4 pounds, respectively. With the exception of a history of allergic rhinitis, all patients were determined to be in good health and the inclusion/exclusion criteria are adequately explained. The patients had fasted for ten hours before they were administered a single dose of cetirizine 5 mg capsule at 8 a.m. The capsule was swallowed with 120 ml of water. The firm mentions that low-fat meals were served to each child at 10 a.m., 1 p.m., and 5 p.m.; the contents of the meals were not mentioned.

6. Sampling schedule: Five milliliters of blood were withdrawn into heparinized tubes at 0-hour (pre-dose), and at 0.5, 1, 1.5, 2, 4, 8, 12, 24, 48, and 72 hours after dosing. The blood samples were centrifuged and the plasma that was obtained was frozen till analyzed for the drug.

Urine samples were collected during the time intervals of 0-4, 4-8, and 8-12 hours post dosing. The total volume of each collection period was recorded and an aliquot of each urine sample was frozen at -20° C until analysis was performed.

7. Analytical Methodology:

8. Adverse Drug Reactions: No adverse reactions were reported during this study.

9. Results: Individual plasma concentration and time data for each child is shown in Table 16 as are the values of the pharmacokinetic parameters of AUC, C_{max} and T_{max}. The mean cetirizine plasma concentration - time data is shown in Figure 10. The mean pharmacokinetic parameters and their standard deviation are shown below:

<u>Parameter</u>	<u>Mean (s.d.)</u>
AUC (0-72), ng.hr/ml	2201 (280)
C max, ng/ml	275 (58)
T max, hr	1.1 (0.4)
t 1/2, hr	5.6 (1.1)
12 hour Urinary Recovery (mg unchanged drug)	2.1 (0.35)

This pharmacokinetic study brings forward the pharmacokinetics of cetirizine in pediatric (7 to 12 years old) patients. The mean urinary recovery was 2.1 mg ± 0.35 mg of cetirizine, and this shows that almost 50 % of the administered cetirizine was recovered unchanged in the urine in 12 hours after dosing.

A comparison of the above mentioned mean ± s.d. values for the pharmacokinetic parameters for children patients to those obtained for normal healthy adults - (study number CPK-3; 5 mg dose; age of subjects - 19 to 34 years), showed the following comparative features:

AUC: 1241.1 (249.9) ng*hr/ml adults versus 2201 (280) ng*hr/ml;

C_{max}: 140.4 (26.4) ng/ml adults versus 275 (58) ng/ml; and

T_{max}: 1.15 (0.4) hours adults versus 1.1 (0.4) hours.

It is therefore seen that both, the mean AUC and the mean C_{max} values for normal healthy adults were about 45 % less than the corresponding mean values in children after administering the same dose (5 mg) to both adults and children.

X. Study Number: 86-N-0034; CPK-12

1. Title: Pharmacokinetics and Metabolism of ^{14}C -Cetirizine in Male Human Subjects.
2. Objective: To obtain information on the pharmacokinetics and metabolism of cetirizine in humans.
3. Investigator:
4. Formulation/Treatment:

Doses were prepared by dissolving 100.0 mg of ^{14}C -cetirizine (batch PFZ/264/RP1) in 100 ml of distilled water. Individual doses of 10 ml (and representing 10 mg of ^{14}C -cetirizine; activity not mentioned), were placed in separate glass containers. Immediately after dosing the containers were each rinsed twice with distilled water, (2 X 50 ml), and these washings were also ingested.

5. Study Design and Dosing: The study involved six healthy adult male volunteers between the ages of 27 - 36 years. The subjects fasted for 12 hours prior to the commencement of the study and they continued to fast till four hours after the study began. A dose of 10 mg of ^{14}C -cetirizine, as a 10 ml aliquot, was administered to each subject and then the subjects consumed 2 X 50 ml rinsings of water.

6. Sampling schedule: Blood samples were withdrawn from each subject into heparinized tubes at 0-hour (pre-dose), and at 0.5, 1, 1.5, 2, 3, 5, 7, 10, 14, 18, 24, 30, 36, 48, 54, 60, 72, 96 and 120 hours after dosing. Five milliliters of each collected blood samples was stored at -20°C . The remaining portion of the blood samples were immediately centrifuged, and the plasma samples that were obtained were stored at -20°C till the drug assay was performed.

Urine samples were collected separately from each subject at pre-dose and during 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-36, 36-48, 48-72, 72-96, and 96-120 hours. Feces were collected separately from each subject during 0-24, 24-48, 48-72, 72-96, and 96-120 hours. Urine and feces samples were stored at -20°C also.

7. Analytical Methodology:

2 pages

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8. Adverse Drug Reactions: No adverse drug reactions were reported for this study.

9. Results:

A. Plasma and Whole-blood:

(i) Concentrations of radioactivity in plasma and whole-blood after oral administration of ^{14}C -cetirizine (10 mg) to human subjects:

Table 17 shows the mean plasma concentration in the plasma of six human subjects after oral administration of ^{14}C -cetirizine (10 mg) and it is seen that mean peak plasma concentrations of radioactivity as 359 ± 44 ng/ml, occurred after 0.5 hours. (Note: 0.5 hour was the first sampling time point). After the time of maximum concentration, radioactivity declined in an exponential fashion and Figure 11 shows the mean concentration - time profiles for the subjects in plasma and in whole-blood. The measured plasma AUC was $3.9 \text{ ug.hr/ml} \pm 0.6 \text{ s.d.}$ Mean concentration of radioactivity in whole blood was also maximal at 0.5 hours and this value was $250 \pm 30 \text{ ng/ml}$.

(ii) Concentrations of unchanged cetirizine in plasma after oral administration of ^{14}C -cetirizine (10 mg) to human subjects:

Concentrations of unchanged cetirizine in plasma were measured using a specific HPLC method as described above in the analytical section and it was seen that the maximal concentrations of cetirizine occurred between 0.5 - 1.0 hours after dosing with a mean peak concentration of 359 ng/ml ($\pm 25 \text{ ng/ml}$). The terminal half life was 7.4 hours ($\pm 1.0 \text{ hours s.d.}$).

A comparison between the concentrations of total radioactivity and unchanged cetirizine in plasma (h.p.l.c. assay) illustrates that up to at least 8 hours, cetirizine accounted for 90 % or more of plasma radioactivity (Figure 12); this concentration time profile covered 36 hours, i.e., adequately covering 4-5 half lives.

(iii) Profiles of radioactivity in extracts of plasma:

Thin-layer radiochromatography of plasma extracts indicated that the major radioactive component present in plasma was unchanged cetirizine based on the essentially identical chromatographic behaviour of the

^{14}C -cetirizine reference and the major radioactive plasma component, and on co-chromatography with authentic cetirizine. About 95-100 % of sample radioactivity was associated with unchanged cetirizine, and the remaining amount was associated with compound P026 based on co-chromatography evidence.

B. Urine and Feces:

(i) Excretion of ^{14}C -cetirizine after oral administration.

After oral administration of ^{14}C -cetirizine (10 mg) to six male subjects, a mean of 47.7 % ($\pm$ 7.3 %) was excreted in the urine during 12 hours, increasing to 60.5 % ($\pm$ 5.6 % s.d.) during 24 hours, and 70.1 % ($\pm$ 5.9 %) during 120 hours (i.e., 5 days) - (Table 18; Figure 13). In the same time periods, the mean % excretion of total radioactivity in feces were 4.1-, 6.0-, and 9.6 %. Thus, during a five day collection period, a (mean) total of 79.7 % $\pm$ 8.2 % s.d. of the dose was recovered in the urine and feces. Recovery of about 70 % of the dose in urine indicates that at least this proportion of the dose was absorbed.

Concentrations of cetirizine in urine were measured using a specific HPLC method as described in the analytical section. The corresponding total amounts of unchanged cetirizine excreted in urine samples are shown in Table 19. A total of 44.9 - 58.2 % of the dose was excreted as unchanged cetirizine in a period of five days.

Two minor radioactive components were detected in a few urine samples and were designated H1 and H2. Both of these components appeared to be relatively polar based on their chromatography behaviour of elution and they appeared in the later urine samples, and neither exceeded 5 % of total radioactivity. Thus it was seen that during 0 - 36 hours, (the period of almost all detectable cetirizine collection), that 51-61 % of the administered dose was excreted as cetirizine, 0.5-2.0 % was excreted as component H1, and 0.1-0.4 % was excreted as component H2. During this time the total dose excreted in urine ranged from 58-73 %.

Thin layer chromatography of methanolic fecal extracts proved generally difficult for the firm because of the very viscous nature of the final extract, and therefore, they mention that the results of fecal analysis would not provide for a quantifiable picture. Still based on the results, it is seen that radiochromatograms of fecal extracts indicated the presence of two components, viz., cetirizine and compound P026. There was considerable variation in these results: cetirizine accounted for 20-69 %, and compound P026 accounted for 11-24 % over a four day period.

10. Conclusion: Cetirizine was rapidly absorbed and was mainly excreted in the urine. Unchanged cetirizine accounted for essentially all the drug-related material in plasma. Cetirizine is metabolized to a very limited extent by oxidative O-dealkylation and the metabolite so formed is in very small amounts and is inactive. In short, it may be concluded that the main information obtained from this metabolism study is the presence of unchanged cetirizine particularly in urine. Therefore, all

biopharmaceutical and pharmacokinetic studies presented in this NDA can justifiably be approached by looking at the amount of unchanged cetirizine present in the biological fluids.

XI. Study Number: 86-N-0140; (CPK-12)

1. Title: The Influence of Repeated Administration of Cetirizine on the Antipyrine Clearance in Healthy Volunteers.

2. Objective: To investigate the possible enzyme inducing properties of cetirizine in humans.

3. Investigator:

4. Formulation/Treatment:

Antipyrine 250 mg dose (dissolved in 50 ml of water)

Cetirizine 10 mg tablet — Lot No: (not provided)

5. Study Design, Dosing and Sampling Schedule: The study was conducted with ten, healthy, adult male volunteers between the ages of 20 and 29 years of age and having an average weight of 74 Kg. The subjects fasted overnight and on the first day of the study they received 250 mg of antipyrine dissolved in 50 ml of water. An additional 50 ml of water was immediately swallowed after the dose had been administered. Blood samples were taken at 0, 3, 6, 8, 24 and 32 hours following drug administration. From three volunteers urine was also collected in three portions: 0-8 hours, 8-24 hours, and 24-32 hours; (collection into 32 hours meant day 2 of the study). On the night of study day 2 at 10 p.m., each of the subjects was given a 10 mg cetirizine tablet with 100 ml of water and the dosing (10 mg/day) continued for eight more days. On day eleven, the antipyrine dose similar to the one administered on day one was repeated and like day one the cetirizine dose was administered in the evening. The antipyrine clearance values for the first dose and for the last dose, were calculated and compared. Finally both the clearance values as well as plasma half life values before and after the cetirizine treatments were statistically compared utilizing the Wilcoxon test for paired observations.

7. Adverse Drug Reactions: No information was provided on adverse drug reactions in this study.

8. Results: The individual antipyrine clearance values and the antipyrine half life values before and after cetirizine treatment are shown in Tables 20 and 21. Application of the Wilcoxon test (a non-parametric test) for

paired observations of antipyrine clearance showed no statistical difference between the values for the treatments; in fact the mean antipyrine clearance values were very proximal and were about about 64 ± 12 ml/minute from either treatment. The same Wilcoxon test for the elimination half life values also showed no statistical difference for the paired observations of half life values. The mean $t_{1/2}$ values in the two treatments were about 11 hours.

Table 22 shows the cumulative excretion of the three metabolites of antipyrine - [namely, 4-hydroxyantipyrine (4-OH), norantipyrine (NA) and 3-hydroxymethylantipyrine (HMA)] - in urine before and after cetirizine treatment, and it is seen that the values are very similar. The mean values were:

92.0 mg of 4-OH versus 94.5 mg of 4-OH after;
34.6 mg of NA before versus 32.3 mg of NA after;
32.1 mg of HMA before versus 34.1 mg of HMA after.

The firm mentions that because of the very small number of subjects (n=3) for whom urine was collected, no statistical evaluation was applied and that the comparison of data is nominal and cursory.

9. Conclusion: When cetirizine was administered as a 10mg dose per day for nine days to healthy male volunteers, no change was observed in the antipyrine plasma clearance or in the antipyrine elimination half life. It is, therefore, reasonable to conclude that cetirizine does not alter the oxidative drug metabolizing enzyme activity in the liver.

B. Dissolution:

1. The firm has conducted dissolution testing of the three strengths of film coated tablets in water. Testing was conducted using USP Apparatus:

Samples were withdrawn at 20- and 45 minutes. Dissolution aliquots were analyzed for cetirizine by HPLC with a uv method of detection at:
The firm has not provided details of individual tablets and has simply submitted the mean $\pm$ s.d. results:

Results: The mean $\pm$ s.d. results are presented here.

<u>Dosage Form and Strength</u>	<u>Lot No.</u>	<u>% Label Claim (+ s.d.)</u>	
		<u>20 min.</u>	<u>45 min.</u>
Tablet 5 mg	C 6106		
Tablet 10 mg	C 6108		
Tablet 20 mg	C 6110		

It appears that the dissolution of cetirizine tablets is very rapid in water based on the mean results shown above.

The firm has also submitted the dissolution profiles of the three 'to be marketed' strengths of the tablets for 15-, 30-, 45-, and 60 minutes in water. No individual unit data are presented. The mean values (with the range in brackets) are as follows:

<u>Strength</u>	<u>15_min</u>	<u>30_min</u>	<u>45_min</u>	<u>60_min</u>
5 mg				
10 mg				
20 mg				

Dissolution profiles for cetirizine 10 mg tablets (Lot No: C6180 - same lot that was used in the bio-study) are also presented in three different media, viz., SGF without enzymes (pH 1.2), aqueous hydrochloric acid (pH 3.5), and SIF without enzymes (pH 7.5). No individual unit data are presented. The mean values (with the range) are as follows.

<u>pH</u>	<u>15_min</u>	<u>30_min</u>	<u>45_min</u>	<u>60_min</u>
1.2				
3.5				
7.5				

2. Dissolution results from Study CPK-1: Dissolution testing was conducted for the 10 mg strength of cetirizine tablets and capsules. (Lot numbers: C 5357 - capsule; C 6108 - tablet), using

Ten milliliters of the medium were withdrawn. The aliquots were filtered and were analyzed for cetirizine by HPLC using a uv method of detection at

The 10 mg capsule was tested at 20 minutes only and the results show a mean dissolution amount of . For the 10 mg tablets, it was seen that had dissolved in 20- and 45 minutes, respectively.

3. Dissolution results from study CPK-2: Dissolution testing was conducted for cetirizine 10 mg capsules (Lot number C 6021) and for 10 mg tablets (Lot number C 6180) using

At 20- and at 45 minutes intervals, dissolution aliquots were withdrawn, filtered, and analyzed for cetirizine using HPLC with a uv method of detection at . The mean dissolution (and s.d.) values for the capsule were in both 20- and in 45 minutes. From the tablet about of the drug had dissolved in 20- and in 45 minutes, respectively.

Table 1 a

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E Pharmacokinetic Parameters and Summary Statistics

10 mg Tablets

Subj.	AUC(0-∞) hr ng/ml	AUC hr ng/ml	T _{max} hr	C _{max} ng/ml	T _{1/2} hr

Mean	2903.4	2910.8	0.67	316.5	8.47
Std	704.8	720.2	0.57	64.5	1.21
Min	1738.3	1738.2	0.50	225.0	6.69
Max	4883.1	4687.0	2.00	456.0	10.01
C of V	24.3	24.7	58.9	26.8	14.3

10 mg Oral Solution

Subj.	AUC(0-∞) hr ng/ml	AUC hr ng/ml	T _{max} hr	C _{max} ng/ml	T _{1/2} hr

Mean	2784.1	2784.1	0.67	312.5	8.16
Std	650.0	680.0	0.54	72.3	1.09
Min	1624.6	1664.8	0.50	261.0	6.08
Max	4774.7	4774.7	1.50	578.0	10.03
C of V	23.3	23.3	51.4	22.3	13.3

10 mg Capsules

Subj.	AUC(0-∞) hr ng/ml	AUC hr ng/ml	T _{max} hr	C _{max} ng/ml	T _{1/2} hr

Mean	2918.8	2924.4	0.78	360.8	8.87
Std	712.8	718.8	0.51	86.3	1.51
Min	1493.8	1493.8	0.50	200	8.68
Max	4888.0	4888.0	1.50	600.0	11.14
C of V	24.4	24.5	40.8	27.2	17.6

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E Pharmacokinetic Parameters and Summary Statistics

Capsules

Subj.	AUC (0-∞) ng/ml	AUC ng/ml	Time hr	Time hr	Time hr

Mean	2614.0	1780.0	0.7	303.0	7.02
Std	553.6	176.4	0.3	70.5	1.00
Min	2028.0	1128.0	0.5	248.0	6.70
Max	4100.0	4051.0	1.5	490.0	9.43
CV	21.2	22.5	32.4	23.7	10.00

Tablets

Subj.	AUC (0-∞) ng/ml	AUC ng/ml	Time hr	Time hr	Time hr

Mean	2617.3	1751.3	0.6	368.0	7.60
Std	637.6	172.1	0.3	76.5	1.11
Min	2101.6	1101.6	0.5	227.0	6.36
Max	4521.8	4127.6	1.0	516.0	10.58
CV	24.3	22.9	32.6	22.9	14.28

Table 3. Mean (SD) Pharmacokinetic Parameters Following Administration of 10 mg Cetirizine Tablets and Capsules to Healthy Male Volunteers (N = 13)

Parameters	Capsule	Tablet	ANOVA p-Values
AUC (48 hr) (hr·ng/ml)	2915 (553)	2918 (623)	0.13
AUC (hr·ng/ml)	2946 (586)	2951 (672)	0.15
C _{max} (ng/ml)	334 (73)	347 (79)	0.34
T _{max} (hr)	5.9 (0.3)	5.9 (0.5)	0.59
T _{1/2} (hr)	7.9 (1.0)	7.8 (1.1)	0.56

B Plasma Concentrations and Summary Statistics

5 mg Tablets (ng/ml)

Subject	Period	Time in Hours							
		0 0	0 24	0 5	1	1 5	2	4	6
Mean		0.0	21.8	87.9	131.9	119.3	109.3	87.6	70.0
Std		0.0	38.6	52.1	28.1	22.9	15.3	13.0	10.5
Min		0.0	0.0	0.0	63.4	71.3	77.6	56.5	41.3
Max		0.0	135.0	180.0	194.0	166.0	133.0	105.0	84.6

Subject	Period	Time in Hours							
		8	12	16	24	36	48	60	72

Mean	55.3	34.1	23.5	12.4	4.5	0.3	0.0	0.0
Std	9.5	7.5	5.9	5.0	3.9	1.3	0.0	0.0
Min	30.1	14.9	10.4	0.0	0.0	0.0	0.0	0.0
Max	65.3	44.8	31.7	18.9	12.1	5.3	0.0	0.0

10 mg Tablets (ng/ml)

Subject	Period	Time in Hours							
		0.0	0.24	0.5	1	1.5	2	4	6
Mean		0.0	43.3	160.8	236.8	251.4	224.5	175.8	140.5
Std		0.0	82.6	109.2	52.1	36.5	31.8	25.3	24.9
Min		0.0	0.0	0.0	93.5	185.0	160.0	123.0	87.3
Max		0.0	325.0	372.0	341.0	302.0	292.0	211.0	184.0

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Subject	Period	Time in Hours							
		8	12	16	24	36	48	60	72

Mean		111.4	72.6	48.2	30.1	11.3	3.2	0.0	0.0
Std		21.7	19.6	14.5	14.4	6.6	3.5	0.0	0.0
Min		62.9	33.1	20.6	8.9	0.0	0.0	0.0	0.0
Max		140.0	110.0	76.9	66.9	23.7	8.0	0.0	0.0

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20 mg Tablets (ng/ml)

Subject	Period	Time in Hours							
		0 0	0 24	0.5	1	1.5	2	4	6
Mean		0 0	62.1	336.1	540.7	464.8	429.4	343.1	282.4
Std		0 0	97.4	220.7	138.8	54.6	50.2	47.5	42.3
Min		0 0	0 0	11.2	165.0	393.0	323.0	240.0	210.0
Max		0 0	361.0	696.0	706.0	576.0	500.0	410.0	349.0

A. The sample was insufficient for analysis

Subject	Period	Time in Hours							
		8	12	16	24	36	48	60	72

Mean	217.2	140.7	95.8	56.9	21.9	8.2	3.3	0.6
Std	41.6	34.3	28.5	20.4	9.9	6.2	3.8	1.7
Min	147.0	86.1	47.0	26.7	6.2	0.0	0.0	0.0
Max	293.0	199.0	134.0	101.0	36.9	16.9	9.0	5.0

D Pharmacokinetic Parameters and Summary Statistics

5 mg Tablets								
Sub	Per	AUC (72 hr)	AUC	AUC	C _{max}	C _{max}	T _{max}	T _{1/2}
		ng hr	ng hr	ng hr	ng ml	ng ml	hr	hr

Mean		1241.1	1241.1	1482.2	140.4	150.7	1.15	8.11
Std		249.9	249.9	477.7	26.4	32.8	0.43	2.40
Min		648.1	648.1	1056.2	90.0	180.4	0.50	4.68
Max		1522.2	1522.2	2056.4	194.0	388.0	2.00	12.47
C V		20.1	20.1	32.1	18.9	18.8	42.94	29.64

10 mg Tablets								
Sub	Per	AUC (72 hr)	AUC	AUC	C _{max}	C _{max}	T _{max}	T _{1/2}
		ng hr	ng hr	ng hr	ng ml	ng ml	hr	hr

Mean		2022.2	2022.2	2422.2	113	113	8.78	
Std		371.0	371.0	410	6.44	6.44	1.71	
Min		1481.6	1481.6	222.0	0.50	0.50	5.28	
Max		3552.7	3552.7	370.0	2.00	2.00	11.21	
C V		21.7	21.7	14.5	38.33	38.33	19.43	

20 mg Tablets

Sub	Per	ACC	ACC	NACC	CM _{max}	NC _{max}	T _{max}	T _{1/2}
		20 mg	20 mg	20 mg	20 mg	20 mg	hr	hr

Mean		5135.9	5135.9	2400.0	581.6	290.8	1.00	3.92
Std		1222.4	1222.4	513.2	86.6	43.3	0.45	1.50
Min		3202.4	3202.4	1651.2	421.0	210.5	0.50	6.34
Max		6548.8	6548.8	3274.4	706.0	353.0	2.00	10.99
C.V.		19.7	19.7	19.7	14.9	14.9	45.37	16.82

Table 3

Table 3. Mean (SD) Pharmacokinetic Parameters Following Administration of 5, 10 and 20 mg Cetirizine Tablets to Healthy Male Volunteers.

Parameters	5 mg Tablet	10 mg Tablet	20 mg Tablet	ANOVA p-Values
AUC (72 hr) (hr·ng/ml)	1241 (250)	2629 (571)	5196 (1023)	NC
AUC (hr·ng/ml)	1241 (250)	2629 (571)	5200 (1026)	NC
NAUC (hr·ng/ml)	2482 (500)	2629 (571)	2600 (513)	0.11
C _{max} (ng/ml)	140 (26)	282 (41)	582 (87)	NC
N C _{max} (ng/ml)	281 (53)	282 (41)	291 (43)	0.73
T _{max} (hr)	1.2 (0.5)	1.1 (0.4)	1.0 (0.5)	0.63
T _{1/2} (hr)	8.1 (2.4)	8.8 (1.7)	8.9 (1.5)	0.02

Table -

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B Plasma Concentration Data and Summary Statistics

Time hr	Subject											
	1	2	3	4	5	6	7	8	9	10	11	12

Table 7 (cont.)

86-N-0100, December 23, 1987

Plasma Cetirizine Concentrations (Continued)

Time	13	14	Subjects				Mean	Std	Min	Max	n
			15	16	17	18					

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Day 10, 0-24 Hours

Subject	AUC(24 hr)			C _{max} ng/ml	T _{max} hr
	hr	ng/ml	hr		

Mean	2502	...	...	...
Std	366.1	39.8	...	...
Min	1811.5	...	...	...
Max	3190.9	...	...	...
C of V	14.6	...	...	48.6

Day 1, 0-24 Hours

Subject	AUC(24 hr)			C _{max} ng/ml	T _{max} hr	T _{1/2} hr
	hr	ng/ml	hr			

Mean	2015.6	2513.9	227.3	0.9	8.07
Std	316.3	421.0	45.8	0.3	1.42
Min	1495.6	1753.9	188.0	0.5	6.02
Max	2528.4	3259.2	378.0	1.5	10.44
C of V	14.3	16.8	15.3	35.8	17.5

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C Cetirizine Recovered in Urine (mg)

		Day														
	Sub	0	1	2	3	4	5	6	7	8	9	10	11	12	13	Total
Mean	UU	46	54	50	48	48	59	51	49	46	44	06	01	00		554
Std	00	12	10	15	11	14	24	18	07	09	11	03	01	00		78
Min	00	17	38	21	22	21	19	29	30	28	26	03	00	00		335
Max	00	70	83	93	60	83	109	98	63	61	62	10	02	00		894
CV		25.4	19.4	29.2	22.7	28.5	40.8	30.7	14.7	20.6	24.4	33.8	59.2			14.9

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T-410 6

Mean ($\pm$ D) Pharmacokinetic Parameters on Day 1 and Day 10 Following Oral Administration of One 10 mg Cetirizine Capsule Daily for 10 Days (N=18)

Parameters	Day 1 (0 - 24 hr)	Day 10 (216 - 240 hr)	t-test p-values
AUC (24 hr) (hr·ng/ml)	2296 (316)	2502 (366)	0.01
AUC (hr·ng/ml)	2914 (421)	2856 (510)	0.01
C _{max} (ng/ml)	297 (46)	311 (40)	0.15
C _{min} (ng/ml)	27.5 (9.0)	29.9 (11.1)	0.32
T _{max} (hr)	2.9 (0.3)	1.0 (0.5)	0.55
T _{1/2} (hr)	5.1 (1.4)	8.3 (1.9)	0.47
Accumulation Index	-	1.14 (0.16)	
Fluctuation Index	-	2.8 (0.5)	
Urinary Recovery (% unchanged drug)	55	52	

B Plasma Concentrations and Summary Statistics

Subject	Period	Sequence	Time in Hours							
			0.0	0.25	0.5	1	1.5	2	4	5
Mean			0.0	54.0	205.0	338.1	328.3	338.0	180.1	144.7
Std			0.0	86.6	118.9	89.6	35.7	38.9	23.3	20.1
Min			0.0	0.0	0.0	65.6	179.0	168.0	146.0	119.0
Max			0.0	179.0	417.0	342.0	323.0	388.0	220.0	179.0
CV				162.0	58.2	26.7	14.8	12.6	12.4	13.9

Subject	Period	Sequence	Time in Hours					
			8	12	16	24	36	48

Mean			112.8	71.0	45.6	26.9	8.8	1.6	0.8
Std			17.4	16.0	11.5	7.3	4.7	3.3	3.5
Min			87.7	50.8	28.3	11.7	0.0	0.0	0.0
Max			140.0	90.0	68.9	40.8	16.5	10.1	10.8
CV			15.4	19.7	25.3	29.1	52.4	199.0	309.3

a: No sample was received.
 b: Standard excluded from curve due to interferences.

86-N-0106, November 13, 1987

8

Fed

Subject	Period	Sequence	Time in Hours							
			00	03	06	1	1.5	2	3	

Mean			0.0	4.4	35.0	88.8	142.8	188.1	191.1	188.0
Std			0.0	16.6	63.3	91.3	64.0	49.1	20.0	20.1
Min			0.0	0.0	0.0	0.0	0.0	18.5	165.1	127.0
Max			0.0	74.8	328.0	321.0	260.0	244.0	281.0	214.0
CV				388.8	194.4	102.0	42.0	25.8	12.7	10.8

Subject	Period	Sequence	Time in Hours							
			8	12	16	24	36	48	60	

Mean			121.2	78.1	68.7	37.2	10.1	2.8	0.4
Std			22.2	17.3	13.7	7.8	4.0	3.3	1.4
Min			91.0	61.0	30.3	19.3	0.0	0.0	0.0
Max			199.0	191.0	84.0	47.8	18.0	7.9	6.0
CV			18.3	22.0	28.8	20.8	48.0	199.1	282.7

Subj	Fed		T _{max} hr	C _{max} ng/ml	T _{1/2} hr
	AUC(0-60hr) hr ng/ml	AUC hr ng/ml			

Subj	Fasting				
	AUC(0-60hr) hr ng/ml	AUC hr ng/ml	T _{max} hr	C _{max} ng/ml	T _{1/2} hr

Mean	3468.0	3471.3	3.67	231.3	7.70
Std	418.0	422.5	1.24	33.5	1.18
Min	1780.7	1780.7	0.5	165.0	5.38
Max	3315.5	3345.3	4.0	321.0	9.87
CV	16.9	17.1	46.7	15.1	14.9

Mean	2550.3	2553.1	1.02	288.7	7.38
Std	450.4	453.8	0.48	46.4	1.07
Min	1738.9	1738.9	0.4	217.0	5.20
Max	3389.2	3349.2	2.0	417.0	9.39
CV	17.7	17.8	46.8	16.1	14.5

Table 8

Table Mean (SD) Pharmacokinetic Parameters Following Administration of a 10 mg Cetirizine Tablet to Healthy Male Volunteers Under Fasting and Fed Conditions.

Parameters	Fasting	Fed	ANOVA p-Values
AUC (0-24 hr) (hr·ng/ml)	2550 (450)	2468 (418)	0.22
AUC (hr·ng/ml)	2553 (454)	2471 (423)	0.23
C _{max} (ng/ml)	289 (46)	221 (34)	0.01
T _{max} (hr)	1.9 (0.5)	2.7 (1.2)	0.01
T _{1/2} (hr)	7.4 (1.1)	7.7 (1.2)	0.04

8 pages

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Table 12

Mean ($\pm$ S.D.) Pharmacokinetic Parameters in Adult and Geriatric Subjects
After Oral Administration of 10mg Cetirizine

Parameter	Age Group		ANOVA P-value
	Adult Subjects (N=14)	Geriatric Subjects (N=16)	
AUC (72 hr) (hr·ng/ml)	3317 (903)	5593 (1773)	0.01
AUC (hr·ng/ml)	3318 (903)	5653 (1824)	0.01
C _{max} (ng/ml)	384 (103)	450 (59)	0.02
T _{max} (hr)	1.0 (0.5)	0.9 (0.3)	0.55
t _{1/2} (hr)	7.4 (1.6)	11.0 (3.0)	0.01

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Mean (SD) Pharmacokinetic Parameters in Normal Volunteers, Patients with Mild and Moderate Renal Dysfunction and Hemodialysis Patients Following Ora. Administration of 10 mg Cetirizine Capsules

Parameter	Normals (N=5)	Mild (N=5)	Moderate (N=5)	Hemodialysis (N=5)
AUC (0-∞)* (ng·hr/ml)	2131 (300)	4050 (2170)	3108 (1970)	4004 (222)
AUC (0-96 hr)	2133 (300)	4036 (2153)	3026 (2010)	7610 (1154)
C _{max} (ng/ml)	313 (46)	338 (70)	357 (172)	235 (29)
T _{max} (hr)	0.9 (0.2)	1.1 (0.2)	2.2 (1.1)	2.0 (0.7)
T _{1/2} (hr)	7.0 (1.1)	19.4 (3.4)	20.9 (4.0)	19.3 (3.6)
Urinary Recovery (% unchanged drug)	63.5	31.7	16.4	-

- * t = 48 hr for normal and hemodialysis groups and 96 hr for mild and moderate groups.
- ** t = 72 hr for normal, and 96 hr for mild and moderate groups.

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Appendix I

2. Drug Product

a. Composition and Dosage Form

Composition

The quantitative composition of each dosage strength of cetirizine hydrochloride film coated tablets is presented in the following table:

<u>Components</u>	<u>mg/tablet</u>	
	<u>5 mg</u>	<u>10 mg</u>
Cetirizine Hydrochloride	5.00	10.00

INDUSTRIAL CHEMICALS COMPANY
Pharmaceutical Division

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PART II

BACKGROUND

The sponsor submitted on August, 19, 1993 the results of a single and multiple dose study (#88-N-0266) conducted in patients with varying degrees of renal impairment who were administered 10 mg cetirizine tablet once daily for 7 days.

The effects of hepatic diseases on the pharmacokinetics and pharmacodynamics of cetirizine were investigated in 2 publications by Y. Florsmans et al (J. Clin. Pharmacol. vol.33, pp. 929-932, 1993) and F. Simons et al (J. Clin. Pharmacol. vol.33, pp. 949-954, 1993) following single 20 and 10 mg oral doses respectively. These two publications were not submitted by the sponsor but were handed over by the Medical Officer.

The potential for interaction of cetirizine with either pseudoephedrine (PSE) or theophylline was examined in two studies (#89-N-0151 and #88-N-0218) conducted in healthy male volunteers. The results of these studies were submitted on July 7 and 8, 1993.

The electrocardiographic (ECG) effects of cetirizine alone and in combination with either erythromycin or ketoconazole and the possible pharmacokinetic interactions between either cetirizine and erythromycin or cetirizine and ketoconazole were evaluated in three multiple dose studies (#90CK16-0497, #92CK16-0603, and #92CK16-0604) conducted in healthy male volunteers. The results of these studies were submitted on September 28, September 30, and October 8 of 1993.

The possible aggravation of the antihistaminic effect of cetirizine and psychopharmacological effects of either alcohol or valium in cetirizine/alcohol and cetirizine/valium combinations was assessed in 3 studies. In these studies, only clinical data were included and no evaluation of the pharmacokinetic effects of the cetirizine/alcohol and cetirizine/valium combination was performed. Therefore, these studies have not been reviewed.

The analysis of pharmacokinetic data of cetirizine contained in the original NDA with respect to the demographic covariates of age, gender, and race were performed and the results of analysis were submitted on September 16, 1993.

A single dose study (#91-N-0182) was conducted to compare the bioavailability of 10 mg cetirizine tablet, manufactured by a commercial scale-up equipment, to a 10 mg cetirizine oral solution in healthy male volunteers. The results of this study were submitted on July 9, 1993.

The above mentioned studies and publications are being reviewed here by the Division of Biopharmaceutics.

Renal Impairment Study (#88-N-0266)

The pharmacokinetics of cetirizine were determined in patients with varying degrees of renal function following a single 10 mg dose and at steady state (10 mg once daily for 7 days). There were 7 normal subjects ranging in creatinine clearance (CLcr) from 89 to 128 mL/min, 8 patients with mild renal function ranging in CLcr from 42 to 77 mL/min, and 7 patients with moderate renal function, ranging in CLcr from 11 to 31 mL/min. Details of study protocol and results are presented in ATTACHMENT I

Mean (SD) Pharmacokinetic Parameters for Cetirizine Following Single-Dose Oral Administration of 10 mg Cetirizine HCL

Parameter	Normal (n=7)	Mild (n=8)	Moderate (n=7)
AUC _{0-∞} ng.h/mL	2818 (596)	4263 (2056)	11392 (5101)
C _{max} ng/mL	296 (33)	282 (51)	283 (54)
T _{max} hr	1.3 (0.4)	3.1 (2.3)	3.6 (0.9)
T _{1/2} hr	9.3 (2.3)	11.2 (6.6)	33.1 (16.2)
CL/F mL/min/kg	0.79 (0.21)	0.63 (0.21)	0.19 (0.06)
V _d /F L/kg	0.61 (0.11)	0.51 (0.08)	0.49 (0.09)

Following a single 10 mg oral dose (Day 1), AUC_{0-∞} of cetirizine increased by about 1.5-fold and 4-fold in mild and moderately renally impaired patients, respectively as compared to normal subjects. C_{max} was quite proximal among the three groups. However, T_{max} increased about 2.4-fold in mild renal group and by about 2.8-fold in moderate renal group as compared to the normal group (T_{max} = 1.3 hours). Oral clearance (CL/F) of the drug decreased from 0.79 mL/min/kg to 0.63 mL/min/kg (about 20% decrease) in mild group and to 0.19 mL/min/kg (about 75% decrease) in moderate group as compared to normal group. The terminal half-life (T_{1/2}) of cetirizine was prolonged from 9.3 hours in normal group to 11.2 hours (1.2-fold increase) in mild group and to 33.1 hours (3.6-fold increase) in moderate group. Apparent volume of distribution decreased from 0.61 L/kg in normal subjects to 0.51 L/kg (about 16% decrease) in mild renally impaired patients and to 0.49 L/kg (about 20% decrease) in moderate renally impaired patients.

Mean (SD) Pharmacokinetic Parameters for Cetirizine Following Oral Administration of 10 mg Cetirizine HCl, OD for 7 Days

Parameter	Normal (n=7)	Mild (n=8)	Moderate (n=7)
AUC _{0-24hr} ng.h/mL	2739 (617)	3895 (1393)	9512 (2174)
C _{max} ng/mL	301 (47)	355 (58)	545 (135)
T _{max} h:	1.5 (0.5)	2.8 (1.3)	3.1 (1.2)
T _{1/2} hr	10.2 (3.0)	13.9 (9.2)	30.4 (5.4)
CL/F mL/min/kg	0.81 (0.21)	0.65 (0.2)	0.23 (0.06)
V _{d/r} L/kg	0.71 (0.25)	0.67 (0.22)	0.56 (0.14)

At steady-state (Day 7), AUC_{0-24hr} of cetirizine increased by about 1.4-fold and 3.4-fold in mild and moderately renally impaired patients, respectively as compared to normal subjects. C_{max} was 18% and 81% greater in mild and moderate renal groups, respectively, than that in normal group. T_{max} increased about 1.8-fold in mild renal group and by about 2.1-fold in moderate renal group as compared to the normal group (T_{max}=1.5 hours). Oral clearance (CL/F) of the drug decreased from 0.81 mL/min/kg to 0.65 mL/min/kg (about 20% decrease) in mild group and to 0.23 mL/min/kg (about 72% decrease) in moderate group as compared to normal group. The terminal half-life (T_{1/2}) of cetirizine was prolonged from 10.2 hours in normal group to 13.9 hours (1.4-fold increase) in mild group and to 30.4 hours (3.0-fold increase) in moderate group. Apparent volume of distribution decreased from 0.71 L/kg in normal subjects to 0.67 L/kg (about 6% decrease) in mild renally impaired patients and to 0.56 L/kg (about 20% decrease) in moderate renally impaired patients. Accumulation ratio (R), calculated as: $R = 1 / (1 - e^{-0.693/T_{1/2} \times 24hr})$, was 1.4 and 2.3 in mild and moderate groups, respectively. Thus, accumulation of cetirizine is expected in moderate renally impaired patients.

It can be stated that absorption, distribution and elimination of cetirizine were affected by the degree of renal impairment. The effects on drug disposition was more pronounced in patients with moderate renal impairment having CL_{cr} values ranged from 11 to 31 mL/min. In these patients, it is recommended that a starting dose of 5 mg cetirizine be given once daily.

Effects of Hepatic diseases

The pharmacokinetics (PK) of cetirizine were evaluated after a single 20 mg oral dose in 5 patients with chronic hepatocellular liver disease ranging in age 39 to 45 yr (group A), in 5 patients with chronic cholestatic liver disease ranging in age from 40 to 66 yr (group B), and in 16 healthy volunteers ranging in age from 21 to 34 yr (Y. Horsmans et al, J.Clin. Pharmacol. vol. 33, pp. 929-933, 1993, ATTACHMENT II). All patients had normal measured creatinine clearance values (≥ 70 mL/min). Mean $\pm$ SD pharmacokinetic parameters are as follow:

Parameter	Group A	Group B	Healthy Volunteers
C _{max} ng/mL	678 $\pm$ 89	790 $\pm$ 226	775 $\pm$ 176
T _{max} hr	2.5 $\pm$ 1.5	3.1 $\pm$ 1.2	1.1 $\pm$ 0.27
T _{1/2} hr	14.3 $\pm$ 2.3	13.8 $\pm$ 3.1	9.4 $\pm$ 2.4
AUC _{0-∞} ng.hr/mL	12553 $\pm$ 4690	14157 $\pm$ 5008	7206 $\pm$ 2020
CL/F mL/min/kg	0.48 $\pm$ 0.23	0.41 $\pm$ 0.09	0.74 $\pm$ 0.19
CL _r ^a mL/min/kg	0.33	0.28	0.52
V _d /F L/kg	0.67 $\pm$ 0.46	0.47 $\pm$ 0.06	0.58 $\pm$ 0.16

(calculated by the reviewer as CL/F.^a)

There were no significant differences ($p > 0.05$) in PK parameters obtained in the two groups of hepatic patients. However, T_{max}, AUC_{0-∞}, T_{1/2}, CL/F of cetirizine were significantly different ($p < 0.01$) in each patient group as compared to healthy volunteers. T_{max} increased about 2.3-fold and 2.8-fold in groups A and B, respectively. Group A had about 52% increase in T_{1/2} and about 35% reduction in CL/F as compared to normals. Similarly, group B had about 47% increase in T_{1/2} and about 45% decrease in CL/F as compared to normals. Apparent volume of distribution did not significantly change between the hepatic patients and healthy volunteers.

It was noted that although the mean percentage recovered in urine as unchanged cetirizine did not change among the 3 groups (group A: 69 $\pm$ 15%, group B: 69 $\pm$ 13%, and healthy volunteers: 71 $\pm$ 7.8%), the calculated renal clearance was reduced by about 36% in group A and by about 46% in groups B as compared to normals. The more reduction of CL_r in group B than that in group A compared to normal group may be due the fact group B included some patients with age of more than 60 years old.

No adverse effect, particularly the sedative effect, was observed during the study.

The pharmacokinetic (PK) parameters and antihistaminic effects of cetirizine were determined in 6 patients with primary biliary cirrhosis after a single oral 10 mg dose. Patients had a mean age of 64 ($\pm$ Sd=8.0) years and a mean creatinine clearance of 74.7 ($\pm$ Sd=8.5) mL/min/1.73 m² (F. Simons et al, J.Clin. Pharmacol. vol. 33, pp. 949-954, 1993, ATTACHMENT II). The PK parameters obtained for cetirizine in biliary cirrhotic patients were compared to those obtained in 16 healthy volunteers (previous article). Mean $\pm$ SD PK parameters are as follow:

Parameter	Biliary Cirrhotic Patients	Healthy Volunteers [#]
C _{max} ng/ml	498 $\pm$ 118	387 $\pm$ 89 [⊙]
T _{max} hr	1.0 $\pm$ 0.4	1.1 $\pm$ 0.27
T _{1/2} hr	13.8 $\pm$ 1.8	9.4 $\pm$ 2.4
AUC _{0-∞} ng.hr/mL	6438 $\pm$ 1621	3603 $\pm$ 1010 [⊙]
CL/F mL/min/kg	0.44 $\pm$ 0.1	0.74 $\pm$ 0.19
CL _r mL/min/kg	0.15 $\pm$ 0.08	0.52 [*]
V _d /F L/kg	0.44 $\pm$ 0.04	0.50 $\pm$ 0.07

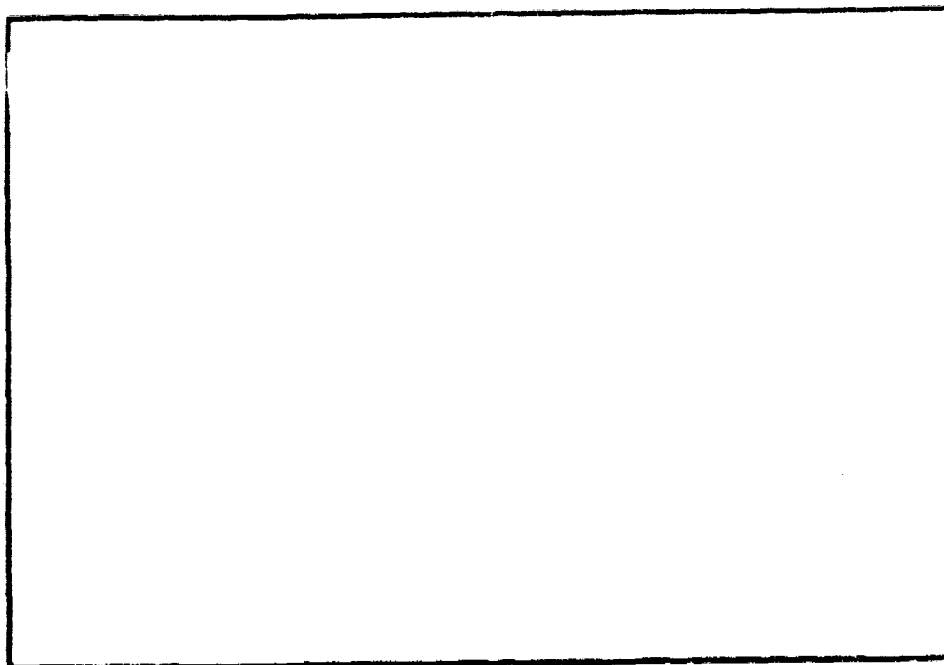
(Previous article)

⊙ (Normalized to 10 mg dose)

* (Calculated by the reviewer as CL/F_{cr})

Following a single oral dose of 10 cetirizine, C_{max} was about 29% higher in hepatic patients than that observed in normals. T_{max} remained unchanged among the two groups. Hepatic patients had about 47% increase in T_{1/2} and about 40% reduction in CL/F as compared to normals. AUC_{0-∞} was about 79% higher in hepatic patients than that in normal adults. Apparent volume of distribution did not significantly change between hepatic patients and healthy volunteers. The fraction of the dose excreted as unchanged cetirizine in the urine was 32 $\pm$ 14% in hepatic patients and was 71 $\pm$ 7.8% in healthy volunteers (Previous article). CL_r was reduced by about 71% in hepatic patients as compared to normals.

The following Figure shows the mean wheal and flare areas (produced after intradermal injection of histamine phosphate) before (0 hour) and at 1 to 96 hours after a single oral dose of 10 mg cetirizine in patients with primary biliary cirrhosis. A significant suppression in wheal area at 1 to 48 hours and in flare area at 1 to 72 hours from the baseline occurred after dosing ($p < 0.01$).



Adverse effects, particularly sedation was reported in all patients during the first 6 hours of the study. Four patients were fell asleep for a mean of 2.25 hours.

In conclusion, the results of these two studies demonstrated that hepatic diseases may have an impact on the pharmacokinetics of cetirizine. On overall, elimination half-life of the drug was prolonged by about 50% and its oral clearance was reduced by about 40% regardless of the type of hepatic disease. It is known that 60% of the cetirizine dose is excreted unchanged in urine within 24 hours and a small fraction of the dose is metabolized in the liver by oxidative-O-dealkylation of the side chain. Thus, the elimination of cetirizine was reduced because of the delay in the metabolic pathway of the drug in patients with hepatic diseases. Of interest, the renal elimination of cetirizine was also reduced on average by about 50% in hepatic patients, but this may be due to an age effect and not actually related to the effect of liver diseases. Although the $T_{1/2}$ was prolonged by about 50%, its value (on average 14 hours) was still less than the dosing interval for the drug (24 hours). Therefore, the accumulation of cetirizine upon multiple dosing and toxic effects are unlikely. However, a dosage adjustment is recommended.

Drug Interaction Studies

Pseudoephedrine (PSE):

A multiple-dose study (#89-N-0151) was conducted to determine the potential for interaction following co-administration of cetirizine (20 mg QD for 6 days) and PSE (120 mg Q12h for 6 days) as single entity, and in a combination, in 24 healthy male subjects. Details of study protocol and results are presented in ATTACHMENT III. Overall, steady state pharmacokinetics of either cetirizine or PSE did not change upon the concomitant administration of the other drug.

Theophylline:

A multiple-dose study (#88-N-0218) was conducted to assess the pharmacokinetics of cetirizine (20 mg QD for 3 days) and theophylline (400 mg QD for 3 days) when administered in the presence of each other to 25 healthy male volunteers. Details of study protocol and results are presented in ATTACHMENT IV.

It was noted that there was a 50% increase in the terminal half-life and a 27% decrease in the oral clearance of cetirizine when the combination treatment was given (either cetirizine+theophylline or theophylline+cetirizine) as compared to cetirizine alone treatment. The apparent volume of distribution of cetirizine did not change in presence of theophylline.

Mean (%CV) theophylline AUC_{0-24hr} values for theophylline alone treatment and the combination treatment (after cetirizine administration) were similar - 98.8 $\mu\text{g}\cdot\text{hr}/\text{mL}$ (26%) and 99.1 $\mu\text{g}\cdot\text{hr}/\text{mL}$ (29%), respectively. When the combination treatment (following theophylline treatment) was compared to theophylline alone treatment, the % change in AUC_{0-24hr} for theophylline was 11%; -- 109.6 $\mu\text{g}\cdot\text{hr}/\text{mL}$ (25%) and 98.8 $\mu\text{g}\cdot\text{hr}/\text{mL}$ (26%), respectively.

Electrocardiographic (ECG) Effects of Cetirizine Alone and in Combination with either Erythromycin or Ketoconazole

Cetirizine Alone:

The ECG effects and pharmacokinetics (PK) of cetirizine were investigated in an open-label (blinded for the cardiologist's reading of ECGs) randomized, placebo-controlled, multiple-dose, 3-way crossover study (90CK16-0497) in 24 healthy male volunteers (mean age=27.8 years, mean weight=76.5 kg). Each subject received placebo for the first 2 days of the study and then, either a 20 mg cetirizine QD, or 60 mg cetirizine QD, or a placebo QD, for 7 days on three different occasions with a 5-day washout period. QTc (calculated by Bazett's formula), RR, PR, and QRS intervals following cetirizine and placebo treatments and steady-state PK parameters following cetirizine (20 and 60 mg doses) treatment were determined. Details of study protocol and results are presented in ATTACHMENT V.

By examining the individual subject QTc intervals (Submission of September 28, 1993) following every treatment, and by using the criterion of QTc > 440 msec, subjects with abnormal values are as follow:

Subject #	Treatment	QTc > 440 msec

Thus, 6 subjects (2, 6, 11, 15, 16 and 22) had QTc intervals which exceeded the normal value (440 msec). The maximum QTc prolongations occurred in subject # 22 and were 470 and 481 msec following 60 mg cetirizine and 20 mg cetirizine treatments, respectively. Most values did not differ much from 440 msec.

It can be seen that from Table 4 (ATTACHMENT V) that there were no significant differences ($p > 0.05$) in the overall mean QTc, QT, RR, PR, and QRS values among the three treatments (viz. placebo, 20 mg cetirizine, and 60 mg cetirizine). Mean QTc intervals were 399.3, 397.6, and 397.2 msec following placebo, 20 mg cetirizine, and 60 mg cetirizine treatments, respectively.

There were also no significant differences ($p > 0.05$) in change (DELTA) from predose (baseline) of QTc, QT, RR, PR, and QRS (Table 5.1, ATTACHMENT V) among treatments. The overall mean DELTA QTc intervals were -3.1, -2.6, and -2.5 msec following placebo, 20 mg cetirizine, and 60 mg cetirizine treatments, respectively. There was a treatment by day effect in DELTA RR ($p < 0.001$) and in DELTA PR ($p = 0.015$) among the placebo, 20 mg and 60 mg cetirizine (Table 5.1). As it is seen in Table 5.2, the mean DELTA RR on Day 3 was significantly higher following 20 mg cetirizine treatment (47.87 msec) than that after the placebo (12.43 msec) and after 60 mg cetirizine treatment (21.4 msec). Similarly, on Day 5, mean DELTA RR was significantly higher after 20 mg cetirizine (26.91 msec) than that after the placebo (14.31 msec) and 60 mg cetirizine treatment (10.69 msec). Mean DELTA QTc was significantly different only on Day 5 after the 20 mg cetirizine treatment (6.55 msec) as compared to placebo (0.51 msec) and the 60 mg cetirizine treatment (-0.65 msec).

Prolongation of QTc interval of 10% or greater over the baseline occurred in 6 subjects after placebo, in 4 subjects after 20 mg cetirizine, and in 6 subjects after 60 mg cetirizine with a maximum value of 15.6%, 19% and 15.4%, respectively (Table 7, ATTACHMENT V).

Mean ± SD Steady-State Pharmacokinetic Parameters of Cetirizine:

Parameter	20 mg Dose (n=21)	60 mg Dose (n=21)	p-Value
AUC _{24hr} (ng.h/mL)	5595 ± 910	16943 ± 2702	--
*NAUC _{24hr} (ng.h/mL)	5595 ± 910	5648 ± 901	0.29
C _{max} (ng/mL)	528 ± 79	1587 ± 245	--
NC _{max} (ng/mL)	528 ± 79	529 ± 82	0.75
T _{max} (hr)	2.4 ± 1.1	2.7 ± 1.3	0.34
T _{1/2} (hr)	8.3 ± 1.0	8.4 ± 0.8	0.29
CL/F (mL/min/kg)	0.80 ± 0.13	0.79 ± 0.13	0.26

(Normalized to 20 mg Dose)

There were no significant differences ($p > 0.05$) in the dose-normalized AUC_{24hr} and dose-normalized C_{max} and in the other PK parameters of cetirizine following oral doses of 20 and 60 mg QD for 7 days. It can be stated that the kinetics of cetirizine are linear up to 60 mg dose, which is 3 times the maximum recommended dose (20 mg).

As requested by the Medical Officer, the firm has computed (Submission of October 29, 1993) Pearson correlation coefficients between average and the maximum change (from baseline) in Hodges QTc and C_{max} or CL/F of cetirizine. All correlations were not significantly different from zero ($p > 0.05$) as shown in Table 4A (ATTACHMENT V). Correlation coefficients relating C_{max}, obtained after 20 mg and 60 mg cetirizine, with the average change (from baseline) in Hodges QTc values were -0.205 and -0.319, respectively. The corresponding values, relating CL/F to average change (from baseline) in Hodges QTc values were 0.324, and -0.066, respectively.

Cetirizine and Ketoconazole:

The ECG effects and pharmacokinetics of cetirizine and ketoconazole were examined for each drug separately and in combination in an open-label (blinded for the cardiologist's reading of ECGs) randomized, placebo-controlled, multiple-dose, 2-way crossover study (#90CK16-0603) in 16 healthy male volunteers (mean age=30 years, mean weight=71.1 kg). There were 2 Phases involving a 3 week washout between each Phase. In each Phase subjects received placebo on first day, followed by 400 mg ketoconazole alone QD or placebo QD for 5 days, followed by combination (20 mg cetirizine+400 mg ketoconazole) QD for 10 days or 20 mg cetirizine alone for 10 days. QTc (calculated by Bazett's and Hodges' formulas) intervals following placebo, cetirizine alone, ketoconazole alone, and the combination treatments were determined. Steady-state PK parameters following cetirizine alone, ketoconazole alone and in combination were evaluated. Details of study protocol and results are presented in ATTACHMENT VI.

By examining the individual subject QTc intervals (Submission of September 30, 1993) calculated by Hodges' formula following every treatment, and by using the criterion of QTc > 440 msec, not a single subject had values that exceeded the normal interval. The maximum QTc was 439 msec and occurred in Subject # 2 after the combination treatment. However, based on Bazett's formula, the following subjects had abnormal QTc values:

Subject #	Treatment	QTc > 440 msec
6	Placebo	444
3,3,6,14	20 mg Cetirizine alone	445,456,444,441
	400 mg Ketoconazole alone	
3,3,3,3,14	Combination	445,447,444,443,442,444

Thus, only 3 subjects had experienced (3, 6 and 14) higher QTc prolongations. The maximum QTc prolongation was 456 msec (Subject # 3) and occurred after 20 mg cetirizine alone treatment. All QTc prolongations that occurred after the 400 mg ketoconazole treatment were below 440 msec.

The mean change from baseline in Hodges QTc for placebo, cetirizine alone, ketoconazole alone, and combination treatment are presented in Table 3 (ATTACHMENT VI). There was no significant ($p > 0.05$) drug interaction effect on the mean change from baseline in Hodges QTc. The mean difference between cetirizine alone and placebo was 7.07 msec and that between the combination and ketoconazole alone was 9.24 msec, giving a mean estimated drug interaction effect of 2.17 msec ($9.24 - 7.07 = 2.17$ msec). Similarly, a mean difference between ketoconazole alone and placebo was 7.23 msec and that between the combination and cetirizine alone was 9.40 which gave a mean estimated drug interaction effect of 2.17 msec ($9.40 - 7.23 = 2.17$ msec). The estimated drug interaction effect was not significantly different from zero ($p = 0.546$). The overall estimated drug interaction effects is 8.16 msec [$(7.07 + 9.24) / 2 = 8.16$ msec] for cetirizine and 8.32 msec [$(7.23 + 9.40) / 2 = 8.32$ msec] for ketoconazole, indicating that the presence of either component did not affect the other.

In Table 5 (ATTACHMENT VI), it can be seen that QTc prolongations of 10% or greater over the baseline occurred in 2 subjects after cetirizine alone, in one subject after ketoconazole alone, and in 5 subjects after the combination. Maximum prolongation was 10.7%, 12.1% and 14.3% after cetirizine alone, ketoconazole alone, and the combination, respectively.

Mean+SD Steady-State Pharmacokinetic Parameters of Cetirizine:

Parameter	Cetirizine Alone	Combination
AUC _{24hr} (ng.h/mL)	4950 ± 699	5325 ± 904
C _{max} (ng/mL)	496 ± 77	516 ± 99
T _{max} (hr)	2.7 ± 1.0	2.7 ± 1.0
CL/F (mL/min/kg)	0.96 ± 0.13	0.90 ± 0.16
Vd/F (L/kg)	0.67 ± 0.10	0.61 ± 0.17
T _{1/2} (hr)	8.1 ± 1.3	7.9 ± 1.4

Mean+SD Steady-State Pharmacokinetic Parameters of Ketoconazole:

Parameter	Ketoconazole Alone	Combination
AUC _{24hr} (mcg.h/mL)	82.2 ± 22.8	79.8 ± 19.5
C _{max} (mcg/mL)	10.05 ± 2.2	9.3 ± 2.0
T _{max} (hr)	3.1 ± 1.0	3.8 ± 1.0
CL/F (mL/min/kg)	1.23 ± 0.37	1.25 ± 0.36
Vd/F (L/kg)	0.49 ± 0.19	0.59 ± 0.30
T _{1/2} (hr)	4.7 ± 1.0	5.6 ± 2.3

Generally, there were no significant differences in PK parameters of either ketoconazole or cetirizine administered alone or in combination. There was about 20% increase in both T_{1/2} and volume of distribution of ketoconazole in presence of cetirizine; overall though the clearance of ketoconazole remained the same in both treatments.

As requested by the Medical Officer, the firm has computed (Submission of October 29, 1993) Pearson correlation coefficient between average and the maximum change (from baseline) in Hodges QTc and C_{max} or CL/F of cetirizine and ketoconazole administered alone or in combination. All correlations were not significantly different from zero ($p > 0.05$) as shown in Table 4B (ATTACHMENT VI). Correlation coefficients relating C_{max}, obtained in cetirizine alone and in combination, with the average change (from baseline) in Hodges QTc values were 0.192 and 0.053, respectively. The corresponding values, relating CL/F to average change (from baseline) in Hodges QTc values were -0.545, and 0.081, respectively.

Cetirizine and Erythromycin:

The ECG effects and pharmacokinetics of cetirizine and erythromycin were examined for each drug separately and in combination in an open-label (blinded for the cardiologist's reading of ECGs) randomized, placebo-controlled, multiple-dose, 2-way crossover study (#96-0604) in 16 healthy male volunteers (mean age = 30.6 years, mean weight = 73.5 kg). The study involved 2 study Phases with a 3 week washout between Phases. In each Phase subjects were assigned to one of the 2 treatments groups. Subjects received placebo for one day, followed by 500 mg erythromycin alone Q8h or 20 mg cetirizine alone QD for 5 days, followed by combination (20 mg cetirizine QD + 500 mg erythromycin Q8h) for 10 days. QTc (calculated by Bazett's and Hodges' formulas) intervals following placebo, cetirizine alone, erythromycin alone, and the combination treatments were determined. Steady-state PK parameters following cetirizine alone, erythromycin alone and in combination were evaluated. Details of study protocol and results are presented in ATTACHMENT VII.

By examining the individual subject QTc intervals (Submission of October 8) calculated by Hodges' formula following every treatment, and by using the criterion of QTc > 440 msec, the highest QTc prolongation was 441 msec which occurred in subject # 8 after the placebo treatment. Based on Bazett's formula, abnormal values are as follow:

Subject #	Treatment	QTc > 440 msec

Thus, 10 subjects (# 1,3,6,7,8,9,10,12,13,15) had QTc values over 440 msec. The maximum prolongation occurred after erythromycin alone treatment and was 469 msec.

The mean change from baseline in Hodges QTc for cetirizine alone, erythromycin alone, and combination treatment are presented in Table 3 (ATTACHMENT VII). The mean change from baseline in Hodges QTc due to cetirizine alone was -5.08 msec and was statistically significant (p=0.037). The estimated effect due to erythromycin was 3.03 msec and was not statistically significant (p=0.205). The estimated drug interaction effect was 0.03 msec and this was also not statistically significant (p=0.994).

In table 5 (ATTACHMENT VII), no subject had a QTc prolongation of 10% or greater over baseline following cetirizine alone treatment. QTc prolongations of 10% or greater occurred in 2 subjects with a maximum value of 13.1% after the combination treatment that followed 5 days of cetirizine alone treatment, and in 4 subjects with a maximum value of 12.7% after the combination treatment that followed 5 days of erythromycin alone treatment. Following the

erythromycin alone treatment, 2 subjects had QTc prolongation of 10% or greater with a maximum value of 17.8%.

Mean ± SD Steady-State Pharmacokinetic Parameters of Cetirizine:

Parameter	Cetirizine Alone	Combination (after 5 days cetirizine)
AUC _{24hr} (ng.h/mL)	4759 ± 913	5305 ± 1089
C _{max} (ng/mL)	439 ± 101	461 ± 101
T _{max} (hr)	2.0 ± 0.0	2.3 ± 0.7
CL/F (mL/min/kg)	0.98 ± 0.13	0.88 ± 0.18
V _d /F (L/kg)	0.64 ± 0.07	0.62 ± 0.11

Mean ± SD Steady-State Pharmacokinetic Parameters of Cetirizine:

Parameter	Cetirizine Alone	Combination (after 5 days erythromycin)
AUC _{24hr} (ng.h/mL)	4844 ± 952	5197 ± 1185
C _{max} (ng/mL)	437 ± 101	470 ± 100
T _{max} (hr)	2.0 ± 0.0	2.0 ± 0.0
CL/F (mL/min/kg)	0.97 ± 0.19	0.91 ± 0.20
V _d /F (L/kg)	0.62 ± 0.07	0.61 ± 0.09

Mean+SD Steady-State Pharmacokinetic Parameters of Erythromycin:

Parameter	Erythromycin Alone	Combination (after 5 days cetirizine)
AUC _{8hr} (mcg.h/mL)	7.9±4.4	9.2±5.3
C _{max} (mcg/mL)	2.1±1.2	2.2±1.0
T _{max} (hr)	2.0±0.0	2.0±0.0
CL/F (mL/min/kg)	17.8±7.9	15.5±7.3
T _{1/2} (hr)	2.4±0.6	2.5±0.7
V _d /F (L/kg)	3.7±1.9	3.3±1.6

Mean+SD Steady-State Pharmacokinetic Parameters of Erythromycin:

Parameter	Erythromycin Alone	Combination (after 5 days erythromycin)
AUC _{8hr} (mcg.h/mL)	7.7±4.3	7.7±3.8
C _{max} (mcg/mL)	2.0±1.2	2.0±0.9
T _{max} (hr)	2.0±0.0	2.0±0.0
CL/F (mL/min/kg)	18.3±7.9	18.1±8.3
T _{1/2} (hr)	2.5±0.6	2.4±0.5
V _d /F (L/kg)	3.8±2.0	3.5±1.3

There were no significant differences in PK parameters of either cetirizine or erythromycin administered alone or in combination.

Table 4C (ATTACHMENT VII) shows the correlation coefficients relating either C_{max} or oral clearance of cetirizine and erythromycin with the average and maximum change from baseline of Hodges QTc in following cetirizine alone, erythromycin alone or the combination as requested by the Medical Officer (Submission of October 29, 1993). A high correlation was found for C_{max} and CL/F of cetirizine, and, average change as well as maximum change in QTc after the combination that followed 5 days erythromycin alone treatment, 0.497, and -0.621, respectively. The correlation relating CL/F to the average or maximum change of QTc was significantly different from zero (p=0.018, 0.017, respectively). Other correlation

coefficients were not significantly different from zero ($p > 0.05$).

Overall, the results of the above three studies (90CK16 -0497, -0603, and -0604) demonstrated that there were no significant changes in QTc intervals following multiple-dose oral administration of cetirizine alone (20 and 60 mg QD), cetirizine (20 mg QD) + ketoconazole (400 mg QD), and cetirizine (20 mg QD) + erythromycin (500 mg q8h) for 5 to 10 days. The kinetics of cetirizine were linear up to 60 mg, which is 3 times the maximum recommended dose. The pharmacokinetics of cetirizine were not significantly altered by either ketoconazole or erythromycin. Also, the pharmacokinetics of either ketoconazole or erythromycin were not altered by cetirizine.

Analysis of Demographic Data

The analysis of pharmacokinetic data of cetirizine contained in the original NDA with respect to the demographic covariates of age, sex, and race were performed. Cetirizine data base included the pharmacokinetic parameters (C_{max} , CL/F , and $T_{1/2}$) for 110 males and 12 females (Total $N=122$) with a normal renal function ($CL_{cr} > 90$ ml/min). There were 103 White subjects, 11 Blacks and 8 others. Age was sorted into three groups: 6-12 years ($N=14$), 18-64 years ($N=107$), and > 64 years ($N=1$). Results are presented in ATTACHMENT VIII. It can be seen that (Table 1, ATTACHMENT VIII) no significant differences were observed in pharmacokinetic parameters obtained for White males, Black males and Others males (ages 18-64 yr), or, for White adult females and White adult males. The sponsor concluded that there were no significant racial, gender and age differences in the pharmacokinetics of cetirizine in subjects with normal renal function.

Bioavailability of Scale-Up 10 mg Tablet Versus 10 mg Oral Solution (Study #91-N0182)

(Submission dates of: July 9, 1993, February 17, 1994, and February 18, 1994)

The bioavailability of 10 mg cetirizine tablet (Batch #: C1325-22710, Batch size: tablets) was determined compared to an oral solution in an open-label, single-dose, randomized two-way crossover study in 24 healthy male volunteers. Batch # C1325-22710 was identical in qualitative and quantitative composition to the biobatch 10 mg #C6180 which was used in study #CPK-2. Batch # C1325-22710 was obtained from a commercial production lot (# J511-22710, which was manufactured by Pfizer, Brooklyn in November, 1991. Each subject received a single oral 10 mg dose of cetirizine tablet and solution (1 mg/mL) on two different occasions separated by a 6-day washout period. The ANOVA, and the 90 % confidence intervals obtained using the two one-sided tests procedure were determined on the untransformed C_{max} and AUC (using the solution as the reference formulation). Details

of study protocol, results and dissolution data for the scale-up lot are presented in **ATTACHMENT X**.

Mean ($\pm$ SD) C_{max} values of 305 (51) ng/mL and 316 (47) ng/mL were obtained for the tablet and solution, respectively. The 90% confidence interval (using the solution as a reference) was 89.2-103.8%, which is within the limit (80-120%). The mean ($\pm$ SD) AUC was 2778 (632) ng.h/mL after the tablet and 2679 (547) ng.h/mL after the solution. Mean relative bioavailability was 1.04. The 90% confidence interval interval (using the solution as a reference) was

The absorption from solution was faster than from tablet, T_{max} was 0.69 hour after solution and 1.08 hours after tablet; (a 24 minute difference). In conclusion, equivalence between the commercial scale-up 10 mg cetirizine tablet and the 10 mg oral solution was demonstrated. It appears that this batch can meet the dissolution criterion of dissolved in water in 30 minutes;

Dissolution data were submitted for the scale-up production batch (# J511-22710) using

ed.

NDA: 19-835**Submission Dates: November 29, 1989****Cetirizine Hydrochloride
REACTINE IR Tablets
5, 10 and 20mg tablets****Pfizer Pharmaceuticals
235 E. 42 St.
New York, N.Y. 10017****Type of Submission: Review of responses****Reviewer: Kusuma Mallikaarjun, Ph.D.**

BACKGROUND: Cetirizine hydrochloride is a H₁ receptor antagonist to be used in the treatment of urticaria and allergic rhinitis. The present submission is an amendment to the NDA (dated June 30 1988) and is a response to the deficiencies and comments conveyed to the firm, during a telephone conversation between the reviewer, Dr. Raman Baweja of the Division of Biopharmaceutics and Dr. Gabrinski of Pfizer, on October 15 1989. The deficiency and comments # 3 and 4 conveyed to the firm by Dr. Baweja are in Appendix II.

RECOMMENDATION TO BE SENT TO THE SPONSOR:

The dissolution specifications recommended by the Division of Biopharmaceutics in the present review of the November 29, 1989 amendment to NDA 19-835, are **interim dissolution specifications** since the original NDA for this product is currently under review. The interim dissolution specifications may therefore be amended appropriately at the time of approval of the product, based on the requested dissolution data (see comment 1), and the pharmacokinetic and bioavailability data currently under review in the original NDA. Please convey comments 1-2 and the above recommendation to the firm.

SUMMARY OF SUBMISSION: The present submission comprises the following:

Dissolution Data: The firm has submitted dissolution data for 12 tablets of 10 mg strength from a single lot, at different dissolution media pH (1.2, 3.5 and 7.5). Dissolution profiles have been included for this pH study (Appendix I, pages 1-5). The sponsor has not provided dissolution data for the 5 and 20 mg strengths as the three strengths vary only with respect to their fill weights, i.e. the three strengths are compositionally proportional. The firm has also provided formulation monographs for each strength of tablet evaluated, to support their statement that the only difference in formulation between the different strengths is in the tablet fill weights (Appendix I, pages 6-8).

The firm has reported dissolution of the three strengths of the tablets (5, 10 and 20mg) in water and provided the dissolution profiles of the same (Appendix I, pages 9-12). Only 6 tablets each, were used for the 5 and 20mg strengths and 12 tablets were used for the 10mg tablet (Appendix I, page 9).

Dissolution data at 30 and 45 mins. only in water, for three lots of the 5, 10 and 20mg strengths used in the pharmacokinetic and bioavailability studies has been included (Appendix I, pages 13-15). Only six tablets were tested from each lot except one 10mg and one 20mg lot, from which 12 tablets were used (Appendix I, pages 14 & 15). The lot #s and batch sizes of all the dissolution lots are provided on page 13 of Appendix I. The bio-lots are indicated in the same list.

Table #4: This Table from Study #CPK-8 provides the linear regression analysis of pharmacokinetic data with age, creatinine clearance and serum creatinine (Appendix II).

Plasma Data: Appendices 2 and 3 from Study #CPK-13 containing individual plasma concentration-time data are provided.

COMMENTS TO BE SENT TO THE SPONSOR:

1. The sponsor has not submitted individual and mean dissolution profiles of 12 tablets each, for bio-lots of the 5 and 20mg strengths in simulated gastric and intestinal fluids (without enzymes) as requested by the Division of Biopharmaceutics. The three strengths of the product proposed for marketing are compositionally proportional and also exhibit identical and adequate dissolution in distilled water at 30 mins sampling time and beyond. The 5 and 20 mg strengths of the product may be expected to behave in a similar fashion as the 10 mg strength on varying the pH of the dissolution media. However the 20 mg strength does exhibit slightly slower rate of dissolution in water up to 30 mins (Appendix I, page 12). Only six 20 mg tablets were utilized for dissolution testing in water (Appendix I, pages 9-12). **Therefore the sponsor should submit individual and mean dissolution profiles of 12 units of the 5 & 20 mg bio-lot tablets in water, simulated gastric and intestinal fluids (without enzymes).** The Division of Biopharmaceutics recommends the following interim specifications for dissolution testing of Cetirizine HCl tablets:

2. The sponsor should also submit a pH dissolution profile of the active ingredient, cetirizine HCl. Ideally the sponsor should also submit a pH dissolution profile of the highest strength of the formulation proposed to be marketed.

Kusuma Mallikaarjun
Kusuma Mallikaarjun, Ph.D.
Pharmacokinetic Evaluation Branch
October 11th 1991

RD/FT initialed by John Hunt on 10/11/91.

cc: NDA 19-835 Original, HFD-150, HFD-426 (Kusuma M.), Review, Drug and Chron files.

12 PAGES

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3. Dissolution Profiles on Three Lots of each Dosage Strength

Dissolution data on three lots each of the 5 mg, 10 mg and 20 mg dosage strengths are presented in Appendix IV Table 1. Production equipment and facilities were used in the manufacture of larger size batches. The lot numbers and batch sizes are as follows:

<u>Dosage</u>	<u>Lot Number</u>	<u>Batch Size</u> <u>No. of Tablets</u>
5 mg	C6106*	
5 mg	C6178	
5 mg	C6179	
10 mg	C6108*	
10 mg	C6180*	
10 mg	C6181	
20 mg	C6110*	
20 mg	C6182	
20 mg	C6183	

Lots that have * next to the lot numbers were used in Pharmacokinetics and Bioavailability Studies. The NDA Report No., Study No., Lot No., Dosage Strength, and Batch Size were included in the NDA Submission, Vol. 2, p. 102. A copy is enclosed in Appendix IV for ease of reference. Dissolution data for these lots at 20 and 45 minutes were included in the NDA report for each study.

Table 1 includes the 9 lots individual tablet dissolution data, mean, low, high, and standard deviation for 20 and 45 minute samples. The 45 minute data for non-asterisked lots had been previously submitted in our Chemistry, Manufacturing and Controls Section of the NDA, Vol. 3, p. 194. A copy is enclosed in Appendix IV for ease of reference.

Table 1

Cetirizine HCl Tablets Dissolution Data (% of Label Claim)

	5 mg Tablet	5 mg Tablet	5 mg Tablet	10 mg Tablet	10 mg Tablet	10 mg Tablet	20 mg Tablet	20 mg Tablet	20 mg Tablet
	Lot C6106	Lot C6178	Lot C6179	Lot C6108	Lot C6180	Lot C6181	Lot C6110	Lot C6182	Lot C6183
Table No./Sampling Time	20min 45min	20min 45min	20min 45min	20min 45min	20min 45min	20min 45min	20min 45min	20min 45min	20min 45min
1.									
2.									
3.									
4.									
5.									
6.									
7.									
8.									
9.									
10.									
11.									
12.									
Mean									
High									
Low									
Standard Deviation									



Table II

Cetirizine HCl Tablets Formulated Lots Information and Release Test Data

Bottle Tablet Lot No.	Date of Manufacture	Cetirizine HCl Bottle Lot No.	Batch Size (Approx. no. of Tablets)	Average Tab. Wt. (mg)	Cetirizine HCl			Dissolution (45 Minutes)		% of Water Content
					Potency	Dosage Uniformity (% of LC)	% Individual	% of Label Claim	Ave	
					mg/tab	Ave	HI	Low	MSD	

*Dissolution data is based on initial stability testing.

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Table 4. Regression Analysis of PK Parameters by Age, Creatinine Clearance (CCr) and Serum Creatinine (SrC)

Parameter	Intercept	Slope	R-square	Probability Slope=0
By Age				
AUC	-991	84	0.39	.01
Cmax	244	2.7	0.18	.02
Tmax	0.9	.00003	.0000	.996
T½	-0.81	0.16	0.24	.01
TBC	80	-0.67	0.38	.01
CLR	49	-0.46	0.48	.01
Vd	31	-0.07	0.03	.34
CCr	163	-1.43	0.61	.01
By CCr				
AUC	8187	-52	0.51	.01
Cmax	598	-2.5	0.50	.01
T½	15.4	-0.08	0.21	.01
TBC	5.2	0.45	0.58	.01
CLR	-3.0	0.31	0.72	.01
SrC	1.17	-0.002	0.08	.14
By SrC				
T½	-5.0	14	0.28	.01

The pharmacokinetics of cetirizine was also analyzed as a function of sex. Gender had no effect on AUC, Tmax, T½, TBC/F or CLR; Cmax was significantly higher and Vd/F was lower in females (467 ng/ml and 24.4 l) as compared to males (370 ng/ml and 29.8 l). When Cmax and Vd/F were adjusted for body weight, only the difference in Cmax remained significant (p=0.02). A tabulation of the pharmacokinetic parameters for each sex and t-test comparisons of these parameters are included in Appendix E.

B. Clinical Observations

One subject, 85-N-0073 #18, a 71 year old male, experienced mild drowsiness three hours after dosing, which resolved completely in four hours. The protocol for this study allowed concomitant drug therapy for existing medical ailments, and this subject was receiving oral Inderal 40 mg twice daily for hypertension. Since fatigue and lethargy are the most common central side effects reported for Inderal, the investigator designated the drowsiness as having an unknown relationship to the study drug. No other adverse experiences were reported during this study.

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Deficiency:

1. Dissolution information as provided by the firm is not adequate. The firm has only provided the mean $\pm$ s.d. values for the dissolution runs without submitting individual unit values. The firm should submit individual dosage unit data along with mean and % c.v. for all 'to be marketed' strengths of the dosage form. Dissolution profiles (percent dissolved versus time) should be generated from at least three production type lots, twelve dosage units per lot, including lots used in bioequivalence studies. Dissolution testing should be performed utilizing three different pH media such as SGF (without enzymes), water, and SIF (without enzymes). Samples should be obtained at 5, 10, 20, 30, 45 minutes and beyond until at least of dissolution is achieved.

Overall Comments:

1. Based on the results of a single dose study, (# CPK-1), it was shown that the 10 mg clinically studied cetirizine capsule and the 10 mg 'to be marketed' tablet are completely bioavailable relative to a solution (10 mg dose). This study also showed that:
the 10 mg cetirizine clinical capsule and the solution formulation (10 mg dose) were bioequivalent,
that the 10 mg cetirizine 'to be marketed' tablet and the solution formulation (10 mg dose) were bioequivalent,
and, that the 10 mg cetirizine 'to be marketed' tablet and the 10 mg cetirizine clinical capsule were bioequivalent.

Furthermore, another single dose study (CPK-2) also showed that the clinically studied 10 mg capsule and the 10 mg 'to be marketed' tablet are bioequivalent.

2. The dose proportionality study, (CPK-3), showed that the normalized mean values of both, AUC and C_{max} , for the 5 mg and the 20 mg 'to be marketed' tablets were comparable to the corresponding values of the 10 mg 'to be marketed' tablet, and that the three formulations (5, 10 and 20 mg tablets) were judged to be bioequivalent. Furthermore, the same study also showed correlation between the extent of absorption (AUC) and dose administered as well as C_{max} and dose administered (correlation coefficient ≥ 0.92) among the three doses.

3. It was noted that a Table (Table 4) containing creatinine clearance values (pertaining to study # CPK 8) was missing. The firm is requested to submit the Table.

4. There was a mention of individual plasma concentration - time data attached as Appendices to the antipyrine study, (study number CPK-13), but no such appendices were found in the study.

OCT 11 1995

**DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA**

Amendment Review

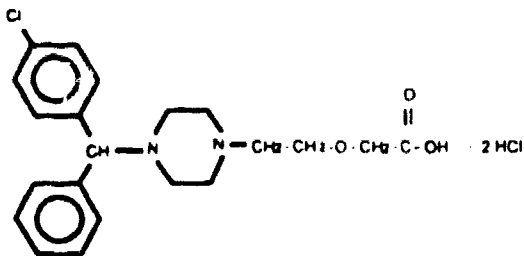
NDA No. 19-835
Dates of Submission: 13 January 1995 (1 volume) & 25 April 1995 (21 volumes)
Information for Sponsor: Yes (), No (X)
Reviewer: W. Mark Vogel, Ph.D.
Review Completed: 10 October 1995
Sponsor: Pfizer

Drug Names: *Generic Name:* Cetirizine HCl *Brand Names:* Zyrtec, Reactine

Chemical Name: (±)[2-[4-[(4-chlorophenyl) phenylmethyl]-1-piperazinyl]-ethoxy]- acetic acid, dihydrochloride.

CAS Numbers: CAS # 83881-52-1 (dihydrochloride salt); CAS # 83881-51-0 (acid)

Structure:



Molecular Weight and Formula: MW = 461.8; C₂₁H₂₅ClN₂O₃ · 2HCl

Related INDs/NDAs/DMEs:

Class: Antihistamine

Indication: Seasonal or perennial allergic rhinitis; Chronic idiopathic urticaria.

Clinical Formulation: Tablets 5, 10.

Route of Administration: Oral

Proposed Clinical Dose: 5 to 10 mg/day as single dose, increased to maximum of

20 if sufficient response is not obtained.

Previous Review(s), Date(s) and Reviewer(s):

Original review	04/11/89	Dou Huey Jean, Ph.D.
Statistical Review of carcinogenicity studies	03/06/89	Daphne Lin, Ph.D.
Original Amendment	02/09/90	Misoon Chun, Pharm.D.
Re-evaluation of mutagenicity studies	06/25/92	C. Joseph Sun, Ph.D.
Final Safety update	10/22/92	Alan S Taylor, Ph.D.
Amendment dated 3/22/93	10/18/93	C. Joseph Sun, Ph.D.
Amendments dated 7/22/93 & 8/11/93	10/18/93	C. Joseph Sun, Ph.D.
Note: Review of cardiovascular effects	02/23/94	C. Joseph Sun, Ph.D.
Amendment dated 2/24/94	04/21/94	C. Joseph Sun, Ph.D.
Amendments dated 1/6/95	01/13/95	C. Joseph Sun, Ph.D.

Relevant Studies Reviewed in This NDA

These studies were submitted in response to the NDA approvable letter of 21 February 1995.

General/Safety Pharmacology:

NDA Report NP-69: Acute Circulatory Tolerance of Cumulative Intravenous Doses of ucb 28557 in Anaesthetized Dogs. UCB Report RRLE93H0902, December 1993.

NDA Report NP-70: Acute Circulatory Tolerance of Cumulative Intravenous Doses of ucb 28556 in Anaesthetized Dogs. UCB Report RRLE93H0901, December 1993.

NDA Report NP-77: Hemodynamic Effects of ucb 28556 on Anesthetized Sprague-Dawley Rats. UCB Report RRLF92E0506, May 1992.

NDA Report NP-78: Hemodynamic Effects of ucb 28557 on Anesthetized Sprague-Dawley Rats. UCB Report RRLF92E0507, May 1992.

NDA Report NP-63: Study of the Effect of ucb 28556 on Hexobarbital-Induced Loss of Righting Reflex in Mice. UCB Report RRLE95A0505, April 1992.

NDA Report NP-64: Study of the Effect of ucb 28557 on Hexobarbital-Induced Loss of Righting Reflex in Mice. UCB Report RRLE95A0506, April 1992.

NDA Report NP-65: Effects of ucb 28556, ucb 28557 and Cetirizine on Hexobarbital-Induced Loss of Righting Reflex in the Mouse. UCB Report RRLE93D2901, April 29, 1993.

General Toxicology:

NDA Report T-44: ucb 28556 and ucb 28557. Toxicity to Rats by Oral Administration for Four Weeks, JCB Report RRLE92D0801, 24 September 1992.

[4/25/95 submission, vol 23, pg 11/3412]

NDA Report T-50: ucb 28556 and ucb 28557, Toxicity to Rats by Repeated Oral Administration for 4 Weeks. UCB Report RRLE95C1401, 15 March 1995. [4/25/95 submission, vol 22, pg 11/3014]

NDA Report T-46: ucb 28556, Toxicity to Rats by Repeated Oral Administration for 13 Weeks Followed by a 4 Week Recovery Period. UCB Report RRLE92G0902, 21 June 1993. [1/13/95 submission, vol 1, pg 17]

NDA Report NPK-34: ucb 28556, Pharmacokinetic Monitoring in the Course of a Toxicity Study to Rats by Repeated Oral Administration for 13 Weeks Followed by a 4-Week Recovery Period. UCB Report RRLE93B2201, 26 April 1993. [4/25/95 submission, vol 30, pg 11/5058]

NDA Report T-62: ucb 28556 and ucb 28557, Toxicity to Dogs by Repeated Oral Administration for 4 Weeks. UCB Report RRLE95C2004, 29 March 1995. [4/25/95 submission, vol 24, pg 11/3652]

NDA Report T-62 (Appendix A): ucb P071, Additional ECG Readings, Dog Toxicity Studies, Acute and 1-Month Oral Treatment. UCB Report LE90J051, 27 August 1990. [4/25/95 submission, vol 1, pg 61]

NDA Report T-45: ucb 28556 and ucb 28557, Toxicity to Dogs by Repeated Oral Administration for Four Weeks, UCB Report RRLE92D2103, 29 September 1992. [4/25/95 submission, vol 25, pg 11/4000]

NDA Report NPK-35: ucb 28556 and ucb 28557, Pharmacokinetic Monitoring in the Course of a 4-Week Toxicity Study to Dogs by Repeated Oral Administration. UCB Report RRLE93A2803, 29 April, 1993. [4/25/95 submission, vol 30, pg 11/5116]

NDA Report T-51: Ucb 28556, Toxicity to Dogs by Repeated Oral Administration for 13 Weeks. UCB Report RRLE92G1003, 12 January 1995. [4/25/95 submission, vol 25, pg 11/4075]

NDA Report NPK-36: ucb 28556, Pharmacokinetic Monitoring in the Course of a Toxicity Study to Dogs by Repeated Oral Administration for 13 Weeks. UCB Report RRLE93D0104, 27 May 1993. [4/25/95 submission, vol 31, pg 11/5265]

Genetic Toxicity:

NDA Report T-59: Ames Metabolic Activation Test to Assess the Potential Mutagenic Effect of ucb 26026. UCB Report DE88B172, February 11, 1988. [4/25/95 submission, vol 26, pg 11/4380]

NDA Report T-60: Study to Evaluate the Potential of Cetirizine Dihydrochloride (Ucb P017) to Induce Micronuclei in the Polychromatic Erythrocytes of CD-1 Mice. UCB Report RRLE94F0601, 09 August 1994. [4/25/95 submission, vol 26, pg 11/4399]

NDA Report NPK-38: UCB P071 Toxicokinetic Report, Study to Evaluate the Potential of Cetrizine Dihydrochloride (Ucb P071) to Induce Micronuclei in the Polychromatic Erythrocytes of CD-1 Mice. UCB Report RRLE94E0201, 20 May 1994. [4/25/95 submission, vol 31, pg 11/5395]

Note: Portions of this review were excerpted directly from the sponsor's submission.

PHARMACOLOGY

Acute Cardiovascular Effects of Intravenous Cetrizine Enantiomers in Dogs

NDA Reports NP-69 and NP-70

Methods: Acute cardiovascular tolerance studies were performed in beagle dogs pretreated with morphine and anaesthetized with intravenous chloralose. Cumulative intravenous doses of ucb 28556 or ucb 28557 (n=4/drug) ranging from 46 to 138 mg/kg with a half log step between doses were administered at twenty-minute intervals. Heart rate, systolic blood pressure and electrocardiograms were recorded three times at five minute intervals before treatment and at 1,2,5,10,15 and 20 minutes after injection of the test substance until death occurred.

Results:

Ucb 28556 caused dose-related decreases in heart rate at intravenous doses up to 4.6 mg/kg (-27%). Reflex tachycardia occurred from 14 mg/kg upward. At 46 mg/kg (1 dog) or 138 mg/kg (3 dogs) conduction and repolarization disturbances (ST-segment depression) occurred, ending with death (ventricular fibrillation in 2 dogs, asystole in 2). At 14 and 46 mg/kg ucb 28556 caused transient decreases in systolic and diastolic arterial blood pressure.

Ucb 28557 caused dose-related decreases in heart rate at intravenous doses up to 4.6 mg/kg (52%). At 46 mg/kg conduction disturbances occurred in all dogs (bundle blocks, atrial flutter, AV blocks, nodal tachycardia, and ST segment changes). One dog survived this dose and died 5 minutes after administration of 138 mg/kg. Ucb 28557 did not induce any changes in blood pressure at cumulative intravenous doses up to 14 mg/kg, after which transient drops in blood pressure were noticed.

Comment: The acute cardiovascular effects of the two cetrizine enantiomers are similar, with perhaps slightly greater potency for ucb 28557. Stock drug solutions at the highest doses were acidified (pH, 1.8) to prevent precipitation. This may have influenced the acute transient effects occurring with intravenous administration; control vehicle injections were not performed. The question of effects on QT interval was not directly addressed.

Acute Cardiovascular Effects of Cetrizine Enantiomers in Rats

NDA Reports NP-77 and NP-78 (Notarized translations with originals in French.)

Methods: Rats were anesthetized with sodium pentobarbital, a tracheotomy was performed and the animals were ventilated by respirator. Seven groups of male rats (n=6/group) were

administered vehicle (NaCl) or 4.6, 14.8, and 25.9 mg/kg of either ucb 28556 or ucb 28557. Diastolic arterial blood pressure and heart rate (from the arterial pressure pulse) were recorded at 6 and 60 minutes after intravenous drug administration.

Results: The results are summarized in table 1, below. Neither enantiomer had a significant effect at 4.6 mg/kg. At 14.8 mg/kg both enantiomers caused a decrease in heart rate which only partially recovered at 1 hr; both enantiomers caused an initial marked decrease in arterial pressure followed by a modest sustained increase. At 25.9 mg/kg effects of ucb 28556 were similar to those at the previous dose, with slight increases in the magnitude of the responses. At 25.9 mg/kg ucb 28557 caused complete collapse of arterial pressure and death in 5/6 rats.

Table 1. Cardiovascular Effects of Intravenous Cetirizine Enantiomers in Rats.

Dose(mg/kg)	Saline		ucb 28556						ucb 28557					
	0		4.6		14.8		25.9		4.6		14.8		25.9	
Time post-Rx	6 min	1 hr	6 min	1 hr	6 min	1 hr	6 min	1 hr	6 min	1 hr	6 min	1 hr	6 min	1 hr
Δ Heart rate (%)	0	-1	-3	-3	<u>-29</u>	-8	<u>-36</u>	<u>-18</u>	-3	-2	<u>-25</u>	<u>-10</u>	*	*
Δ Pressure (%)	+2	+3	-3	<u>-7</u>	<u>-55</u>	<u>+17</u>	<u>-58</u>	<u>+15</u>	-2	-5	<u>-64</u>	<u>+13</u>	*	*

* 5/6 rats died at this dose. Bold underlined values differ significantly from saline group.

Comment: The hemodynamic effects of the two cetirizine enantiomers in pentobarbital anesthetized rats are qualitatively similar, consisting of bradycardia and hypotension. Quantitatively, the effects were similar at 4.6 and 14.8 mg/kg. At the high dose of 25.9 mg/kg the effects of ucb 28557 were more severe.

Summary of Acute Cardiovascular Effects of Cetirizine Enantiomers in Dogs and Rats

The type of cardiovascular effects, hypotension and bradycardia, were similar in dogs and rats. Greater effects of the cetirizine enantiomers were seen at lower doses in rats compared to dogs. This could be because compensatory sympathetic reflexes are well preserved under the chloralose anaesthesia used in the dogs but not in the pentobarbital anesthesia used in the rats. For both species the effects of both enantiomers were similar at lower doses but the effects were more severe for ucb 28557 at the highest doses

Effects of Cetirizine Enantiomers on Hexobarbital-Induced Loss of Righting Reflex in Mice

NDA Reports NP-63, NP-64, and NP-65

Methods: Each compound was investigated in separate experiments. Cetirizine, and its enantiomers, ucb 28556, and ucb 28557, were administered intraperitoneally to groups of 10 mice at doses of 0, 25.9, 46.2 and 83.1 mg/kg 60 minutes before intravenous administration of hexobarbital at a dose of 30 mg/kg. Immediately after injection of hexobarbital, the animals were placed on their backs and were observed until they regained their righting reflex.

Results: Results are summarized in table 2 below. Cetirizine and its enantiomers at the highest dose (83 mg/kg) all prolonged the hexobarbital sleeping time. No substantive difference between the enantiomers was seen. The ability to prolong barbiturate sleeping time may relate to the effect of sedation in humans.

Table 2. Effects of Cetirizine Enantiomers on Hexobarbital Sleeping Time in Mice.

	Vehicle	25.9 mg/kg	46.2 mg/kg	83.1 mg/kg
Cetirizine	2.9 ± 0.9	4.4 ± 1.4*	4.2 ± 2.3	17.6 ± 9.2*
ucb 28556	2.8 ± 0.5	3.0 ± 0.9	4.1 ± 2.9	18.1 ± 11.5*
ucb 28557	2.8 ± 0.5	4.9 ± 3.3	5.0 ± 3.7	16.0 ± 8.8*

Values are means ± SD. * P < 0.05 vs vehicle control.

Overall Summary of Pharmacology Studies

Acute effects of cetirizine enantiomers on cardiovascular function and hexobarbital sleeping time were measured. There was no substantive difference between the enantiomers or between the enantiomers and previously or concurrently observed effects of racemic cetirizine.

TOXICOLOGY

4-Week Oral Study of Cetirizine Enantiomers with 4-Weeks Recovery in Rats

NDA Report T-44: UCB 28556 and UCB 28557, Toxicity to Rats by Oral Administration for Four Weeks, UCB Report 417/920312, 24 September 1992.

NDA Report T-50: UCB 28556 and UCB 28557, Toxicity to Rats by Repeated Oral Administration for 4 Weeks. UCB Report RPLE95C1401, 15 March 1995.

Study Dates: 23 September 1991 to 22 November 1991

Testing Lab: Main study- UCB S.A., Pharma Sector, Chemin du Foriest, Belgium.

Test Articles: Cetirizine (+) enantiomer, ucb 28556, Batch D 005

Cetirizine (-) enantiomer, ucb 28557, Batch D 005

GLP: There were signed GLP statements for both studies.

Methods:

Sprague Dawley OFA rats received the drugs orally once a day for four weeks. Seven groups (12/sex/group) received: 0, 25, 75, or 225 mg/kg/day of the cetirizine (+) enantiomer, ucb 28556; or the same doses of the cetirizine (-) enantiomer, ucb 28557. Three additional groups (6/sex/group) received: 0 or 225 mg/kg/day ucb 28556, or ucb 28557 for four weeks followed by a four week recovery period. The following observations were made:

Check for dead/moribund animals daily

Clinical signs	daily
Body weight	weekly
Food consumption	twice weekly
Ophthalmoscopy	pre-study; week 4 in control and high dose groups only
Hematology/Clinical chemistry	after week 4 or end recovery
Urinalysis	after week 4 or end recovery
Necropsy	terminal
Histopathology	liver and kidney in all animals, specified tissues in zero and high dose groups (see Histology Inventory), unscheduled deaths or macroscopically abnormal tissues in all groups.
P450 enzyme activity	terminal (4/sex/group)
Plasma sample for drug levels	day 23 at 1.5, 3, 6, & 9 hr post-dose (1/sex/data point)

Results:

Mortality: Possible treatment-related deaths occurred for both enantiomers at 225 mg/kg/day, and for ucb 28556 at 75 mg/kg/day. Deaths were more frequent in rats treated with ucb 28556. Mortality data are summarized in table 1 below. Many of the deaths appeared to be the result of accidental tracheal intubation during dosing (occurring with labored or noisy breathing and blood-like nasal discharge). However, these deaths were also dose-related, suggesting that drug treatment made the rats more susceptible to injury during handling.

Clinical Signs: Clinical signs were presumed to result from the impaired condition of rats in the high dose groups (these included: reduced activity, soiled uro-genital area, ptosis, stability problems, and hair loss). The incidence of decreased motor activity is shown in table 3 below for illustration. Other signs, such as noisy breathing and blood-like nasal discharge were interpreted as trauma resulting from accidental tracheal intubation. Since these signs were clearly more frequent in the higher dose groups the investigators suggest that some drug effect (e.g. altered muscle tone or increased irritability and defensive reactions) might have made the rats more susceptible to injury during drug dosing. Hypersalivation was dose-related but occurred at all doses. Except for hypersalivation, the 25 mg/kg/day dose level was free of drug-related adverse clinical signs for both enantiomers. The incidence of these clinical signs was similar for both enantiomers but slightly higher incidence for the (+) enantiomer, ucb 28556.

Table 3. Clinical observations in rat 4-wk oral toxicity study of cetirizine enantiomers.

Treatment	Control		ucb 28556 (+)						ucb 28557 (-)					
	0		25		75		225		25		75		225	
Dose (mg/kg/day)	0		25		75		225		25		75		225	
Sex	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Total subjects	18	18	12	12	12	12	18	18	12	12	12	12	18	18
Total deaths	0	1	0	0	0	2	5	8	0	0	1	3	1	4
Unexplained deaths	0	0	0	0	0	1	3	6	0	0	0	0	0	3
Noisy breathing	0	0	0	0	1	0	9	6	0	0	0	0	2	4
Blood-like nasal discharge	2	1	0	0	1	1	5	4	1	0	2	1	3	2
Hypersalivation	0	0	0	6	2	2	7	10	0	3	0	2	5	4
Decreased motor activity	0	0	0	0	0	0	7	5	0	0	0	0	1	4

Ophthalmology: No significant drug-related effects.

Body Weight Gain: Weight gain tended to decrease with increasing dose of either enantiomer in both males and females. This was statistically significant for males in the high dose group of either enantiomer, as shown in table 4 below. During the recovery period, the differences compared to controls disappeared rapidly and were not significant from day 43 onwards.

Food Consumption: In the first weeks of the study, food consumption was decreased in males from the high dose groups of both enantiomers. Toward the end of the 4-week study food consumption in these groups returned to normal. These results are shown in table 4 below. During recovery, food consumption was increased in high-dose males for both enantiomers.

Table 4. Treatment effects in rat 4-week oral toxicity study of cetirizine enantiomers.

Treatment	Control		ucb 28556 (+)						ucb 28557 (-)					
	0		25		75		225		25		75		225	
Dose (mg/kg/day)	0		25		75		225		25		75		225	
Sex	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Body weight gain (g)	122	57	123	56	116	48	95	46	111	52	131	52	89	48
Food consumption (g/day)														
days 1 - 3	32	23	31	23	30	22	27	21	32	23	33	22	27	20
days 25 - 27	33	24	33	26	31	26	33	24	32	24	34	26	31	24
Serum Chemistry														
ALT (U/l)	24	19	27	19	26	19	48	41	26	18	23	18	40	26
BUN (mM)	5.6	5.9	6.1	6.4	6.1	6.4	6.7	7.8	6.0	6.0	5.4	5.8	6.0	6.7
Creatinine (mM)	50	56	48	53	51	54	51	53	51	55	46	51	50	53
alpha2-Globulin (g/l)	7.7	6.7	7.8	5.8	8.4	5.9	9.2	7.9	7.8	7.4	8.7	7.4	9.9	8.6
beta-Globulin (g/l)	8.8	8.8	8.6	9.0	8.7	8.9	10.0	9.6	9.6	9.1	9.4	10.0	10.0	10.7
Triglycerides (mM)	0.99	0.77	1.30	0.81	0.88	0.86	0.60	0.88	0.72	0.68	1.013	0.64	0.38	0.81
Phospholipids (mM)	1.7	2.2	1.9	2.2	1.8	2.4	2.0	2.4	1.9	2.2	1.7	2.1	1.3	2.1
Urine volume (ml/24 hr)	11	7	14	10	13	8	12	11	11	10	10	6	11	10
Urine pH	8.2	7.4	8.3	7.2	8.2	7.2	7.5	6.6	8.1	7.6	8.0	7.3	7.5	6.6
Liver weight (% body)	3.0	2.9	2.9	3.0	3.3	2.9	4.2	3.3	2.9	3.0	3.4	3.0	4.6	3.7
Kidney weight (% body)	0.73	0.74	0.68	0.73	0.72	0.73	0.80	0.78	0.72	0.72	0.73	0.73	0.85	0.75

Bold underlined values differ significantly from control group.

Clinical Chemistry: Significant alterations are summarized in table 4 above. Increased ALT (40-100%) indicated liver toxicity at the highest dose of both enantiomers in both sexes. There was a tendency for increased BUN after treatment with ucb 28556, reaching statistical significance only in males at the highest dose. The increase was only slight (20-30%) and was not accompanied by increased mean serum creatinine. In one female rat treated with 225 mg/kg/day of ucb 28556 BUN was 16.7 mM, a value which would suggest impaired renal function. Serum creatinine was increased in this individual. (This animal died on day 32; microscopy revealed fat deposits in the renal cortical tubules) Increased BUN might also have resulted from tissue catabolism rather than from impaired renal function. There were alterations in serum proteins and lipids that appear to be treatment-related but do not suggest specific organ toxicity. These

include increased alpha₂- and beta-globulins, and decreased triglycerides. Phospholipids were increased slightly with ucb 28556 but decreased slightly with ucb 28557. These effects were confined mainly to the highest dose. The decreased alpha₂-globulin found in rats treated with 25 mg/kg/day ucb 28556 appears to be an aberrant observation. All changes observed at 225 mg/kg/day of either enantiomer were absent after a 4-week treatment-free period.

Hematology: The only substantial alteration in hematology was increased platelet count (+27%) in females treated with ucb 28556 at the highest dose. It is not clear whether this was treatment-related or an incidental finding.

Urinalysis: Results are shown in table 4 above. Urine pH was decreased at the highest dose of both enantiomers in males and females. This may be due to presence of the drug in the urine. Urine volume was greater in female rats in the high-dose group for each enantiomer. Increased urine volume in the drug-treated groups was not clearly dose-related and may be due to a relatively low value in the control group. Semiquantitative analysis indicated trace or small amounts of increased protein, bile salts, and epithelial cells in urine from males and females treated with 225 mg/kg/day of both enantiomers. The increases of urinary proteins and bile salts were believed to be artifactual due to analytical interference by the test substances. After four weeks recovery there were no significant differences between treated and control groups.

Organ Weights: Significant alterations are shown in table 4 above. Relative liver weight was increased in males ($\approx$ 40-60%) and females ($\approx$ 16-30%) at 225 mg/kg/day of either enantiomer and in males at 75 mg/kg/day of either enantiomer. Relative kidney weight was increased in males at 225 mg/kg/day of either enantiomer. After 4-weeks recovery organ weights returned toward normal, although liver weight in males receiving 225 mg/kg/day of ucb 28556 was still slightly higher than control (8.5%).

Hepatic P450 Enzymes: Significant alterations are summarized in table 5 below.

Table 5. Hepatic P450 activity in rat 4-week oral toxicity study of cetirizine enantiomers.

Treatment	Control		ucb 28556 (+)						ucb 28557 (-)					
	0		25		75		225		25		75		225	
Sex	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Cytochrome P450 (nmol/g)	11	11	16	15	29	10	63	14	17	11	34	11	75	22
aniline 4-hydroxylase	4.3	5.2	5.9	4.5	6.2	4.9	6.2	6.5	5.4	4.4	5.5	6.1	6.2	9.3
7-ethoxyresorufin O-deethylase	0.2	0.4	0.3	0.3	0.8	0.3	1.0	0.4	0.4	0.3	0.7	0.4	1.2	0.8
ethylmorphine N-demethylase	40	13	59	24	70	14	72	31	37	12	54	17	59	34
p-nitroanisole O-demethylase	1.2	1.0	1.4	1.2	2.0	1.4	3.0	1.9	1.3	1.2	2.2	1.6	3.7	3.2

enzyme activities expressed as nmol product/min/g liver

Liver cytochrome P450 content increased in males at all doses of ucb 28557 and all but the lowest dose of ucb 28556. Cytochrome P450 content increased in females at the highest dose of ucb 28557. Various enzyme activities were increased in males treated with 75 or 225 mg/kg/day of either enantiomer. The induction of 7-ethoxyresorufin O-deethylase exhibited the

greatest increase (+400-500%) and occurred at the lowest dose of ucb 28556. The amount of enzyme induction was similar for each enantiomer. Females were less sensitive than males to enzyme induction. Enzyme induction was not observed after the 4-week recovery period.

Gross Pathology: No significant drug-related effects.

Histopathology: Treatment-related abnormalities were found in the liver and kidneys. The observations are summarized in table 6 below.

Hepatocyte enlargement and vacuolation were observed in male rats treated with 75 and 225 mg/kg/day of either ucb 28556 or ucb 28557. Females were less sensitive, with liver changes occurring only in a few females at the highest dose. Only one animal from the recovery group exhibited residual hepatocyte enlargement, suggesting that the changes are largely reversible.

Renal abnormalities attributable to drug treatment included wedges and rays of cortical tubular basophilia or cortical scarring and also small areas of tubular basophilia. These lesions were observed in males and females treated with 75 and 225 mg/kg/day of ucb 28556 or with 225 mg/kg/day of ucb 28557. Deposition of small amounts of fat in the cortical tubules was observed in several animals, with a somewhat higher incidence in females. The significance of this finding is questionable since it was not clearly dose-related and occurred spontaneously in 3 control animals. Histologic abnormalities were absent after 4 weeks of recovery, except for centrilobular hepatocellular enlargement in one male treated with 225 mg/kg/day of ucb 28556.

Table 6. Histologic observations in rat 4-week oral toxicity study of cetirizine enantiomers.

Treatment	Control		ucb 28556 (+)						ucb 28557 (-)					
	0		25		75		225		25		75		225	
Sex	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Liver (number examined)	[12]	[13]	[12]	[12]	[12]	[12]	[14]	[15]	[12]	[12]	[12]	[12]	[14]	[15]
Centrilobular vacuolation	0	0	0	0	0	0	4	0	0	0	0	0	0	0
Centrilobular enlargement	0	0	0	0	3	0	5	1	0	0	4	0	1	3
Centrilobular + midzonal enlargement	0	0	0	0	1	0	8	0	0	0	1	0	12	0
Centrilobular fat deposition	0	0	0	0	2	0	3	0	0	0	0	0	0	0
Kidneys (number examined)	[12]	[13]	[12]	[12]	[12]	[12]	[14]	[15]	[12]	[12]	[12]	[12]	[14]	[15]
Areas of tubular basophilia		0	0	0	1	0	2	0	0	0	0	0	0	0
Wedges/rays of cortical tubular basophilia	0	0	0	0	1	1	0	0	0	0	0	0	3	2
Cortical tubular fat deposition	0	3	0	7	3	2	4	7	0	0	0	0	0	2

Toxicokinetics: Toxicokinetic parameters are summarized in table 7 below. C_{max} and AUC values were higher for ucb 28556 compared to ucb 28557 in both sexes at all doses. There were no consistent sex related differences in plasma concentrations for either enantiomer. Renal excretion of both enantiomers was much lower for males than for females and the renal clearance of ucb 28556 was lower than that of ucb 28557. No conversion between enantiomers *in vivo* was observed.

Table 7. Toxicokinetics in rat 4-week oral toxicity study of cetirizine enantiomers.

		ucb 28556 (+)						ucb 28557 (-)					
Dose (mg/kg/day)		25		75		225		25		75		225	
	day	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Cmax (µg/ml)	23	17	12	81	45	81	128	3	5	16	16	52	29
AUC ₀₋₂₄ (µg·hr/ml)	23	89	41	38	19	100	101	5	9	91	66	348	205
Urinary excretion	17	12	38	27	58	43	59	2	33	21	54	21	51

Summary of Rat 4-Week Oral Toxicity:

Treatment-related deaths occurred at 225 mg/kg/day of both enantiomers; a few deaths at 75 mg/kg may have been drug-related. At the high dose of both enantiomers there were clinical signs related to impaired general condition or to gavage problems. Hypersalivation occurred at all doses. Induction of hepatic P450 enzyme activities occurred in males at all doses of both enantiomers. At 225 mg/kg/day both enantiomers caused decreased body weight gain, hepatic, and renal toxicity. At 75 mg/kg/day renal histopathology was observed for ucb 28556. The NOAEL dose was 25 mg/kg/day for ucb 28556 and 75 mg/kg/day for ucb 28557. Systemic exposure was greater for ucb 28556 than for ucb 28557. All of the adverse effects were absent or substantially returned toward normal after 4-weeks recovery.

13-Week Oral Study of (+) Enantiomer with 4-Weeks Recovery in Rats

NDA Report T-46: UCB 28556, Toxicity to Rats by Repeated Oral Administration for 13 Weeks Followed by a 4 Week Recovery Period. UCB Report RRLE92G0902, 21 June 1993.

NDA Report NPK-34: UCB 28556, Pharmacokinetic Monitoring in the Course of a Toxicity Study to Rats by Repeated Oral Administration for 13 Weeks Followed By a 4-Week Recovery Period. UCB Report RRLE93B2201, 26 April 1993.

Study Dates: 30 December 1991 to 27 April 1992
Testing Lab:
Test Articles: Cetirizine (+) enantiomer, ucb 28556, Batch D 006
GLP: There were signed GLP statements for both studies.

Methods:

Rats of the CrI: CD (Sprague Dawley) BR strain received the cetirizine (+) enantiomer orally. Four groups received: 0, 25, 75, or 225 mg/kg/day (12/sex/group). Two recovery groups (5/sex/group) received 0 or 25 mg/kg/day for 13 weeks followed by 4-weeks recovery. Toxicokinetics were measured in a satellite study. The following observations were made:

Check for deaths twice daily
Clinical signs daily for 4 weeks, weekly thereafter

Body weight	weekly
Food consumption	weekly
Water consumption	daily visual appraisal, daily by weight in week 12
Ophthalmoscopy	pre-study, 13 wk and recovery
Hematology	during week 13 or end recovery
Clinical chemistry	during week 13 or end recovery
Urinalysis	during week 13 or end recovery
Necropsy	terminal
Histopathology	liver examined in all animals, specified tissues in zero and high dose groups, macroscopically abnormal tissues in low and mid dose groups.
P450 enzymes	terminal (5/sex/group)
Toxicokinetics	
plasma samples	week 13 at 0, 1.5, 3, 9, and 12 hr post-dose (2/sex/data point)
urine samples	24 hr samples in week-1, week-6, and week-13

Results:

Statistically significant, treatment-related effects are summarized in table 8 below.

Table 8. Treatment related effects of ucb 28556 administered orally to rats for 13 weeks

Dose (mg/kg/day)	13 Wk p.o. Administration										4 Wk Recovery			
	0		4		8		25		75		0		75	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Salivation (% incidence)	0	0	0	0	0	0	0	0	29	10	—	—	—	—
Body weight gain (g)	327	132	317	120	319	126	301	115	303	118	350	156	364	139
AST = GOT (U/l)	62	52	55	56	61	75	58	61	59	62	60	54	60	58
Urine pH	7.3	6.3	7.2	6.4	7.2	6.5	7.1	6.4	7.1	6.1	7.4	7.0	7.4	6.3
Urine protein (mg/dl)	99	70	103	74	125	67	117	82	130	102	110	72	115	93
Adjusted liver weight (g)	19.1	9.6	19.3	9.6	20.5	10.3	22.0	10.9	21.9	10.3	20.7	10.0	21.8	11.7
Cytochrome P450 (nmoles/g liver)	12.4	9.7	13.5	6.6	11.5	8.2	15.2	7.1	19.5	8.4	11.6	11.4	12.4	9.3
7-Ethoxyresorufin O-deethylase (nmoles/min/g liver)	1.3	2.8	1.8	2.1	1.8	2.5	4.9	3.5	6.5	3.6	1.3	2.4	1.6	2.9

Bold underlined values indicate statistically significant difference vs relevant zero dose

Mortality:	There were no deaths in this study.
Clinical Observations:	The incidence of salivation increased progressively during the study.
Body Weight:	Weight gain was decreased (11-13%) in females at higher doses.
Food/Water Consumption:	No significant drug-related effect.

Clinical Chemistry: AST (GOT) activity was increased in females at doses from 8 to 75 mg/kg/day. The increase was small (20-40%) and not clearly dose-related. The mean value in females was 52 U/l (S.D. = 8; mean + 3SD = 76), one female had a value of 150 and two had values of 80 at 8 mg/kg/day; one female had a value of 75 at 25 mg/kg/day; one female had a value of 116 at 75 mg/kg/day. Animals with high AST values also had ALT (GPT) values

somewhat higher than normal. Total bilirubin was not increased in these animals. Thus, several female rats in the drug-treated groups had abnormally high liver enzymes in plasma, but it is not clear that this was treatment-related. AST was normal in all males.

Hematology: No significant drug-related effect.

Urinalysis: Data are summarized in table 8 above. Urinary pH was decreased in males and females receiving 75 mg/kg/day of ucb 28556. Urinary protein concentration increased (17-30%) in males at doses from 8 to 75 mg/kg/day and in females at the highest dose (46%). This was considered an artifact due to presence of drug in the urine. A similar finding was reported in a 13-week oral toxicity study in dogs (NDA Report T-51, 4/25/95 submission, vol 25, pg 11/4075). That report states "Investigation of these findings showed that the presence of the test material in the urine affected the quantitative urinary protein assay used for this study." The data supporting this conclusion were not reported.

Organ Weights: Liver weight was increased ($\approx 15\%$) in males at 25 and 75 mg/kg/day; this abnormality was reversible in the recovery group. Data are summarized in table 8 above.

Hepatic Drug Metabolizing Activity: Cytochrome P450 content increased in males at the highest dose (57%) but decreased slightly in females at doses from 8 to 75 mg/kg/day. Four microsomal enzyme activities of liver homogenates were increased ($\approx 100-400\%$) in males from the 25 and 75 mg/kg/day treatment groups: 1) aniline 4-hydroxylase, 2) p-nitroanisole O-demethylase, 3) ethylmorphine N-demethylase, and 4) 7-Ethoxyresorufin O-deethylase. The treatment effect was greatest for the latter activity, which is shown in table 8 above for illustration.

Gross Pathology: No significant drug-related effects.

Histopathology: The observations are summarized in table 9 below.

Table 9. Histologic abnormalities in rat 13-week oral toxicity study of ucb 28556

	13 Wk p.o. Administration (mg/kg/day)										4 Wk Recovery			
	0		4		8		25		75		0		75	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Liver (total number examined)	[10]	[10]	[10]	[10]	[10]	[10]	[10]	[10]	[10]	[10]	[5]	[5]	[5]	[5]
Centrilobular vacuolation	2	0	1	1	1	0	5	0	8	0	1	0	0	0
Centrilobular enlargement	0	0	0	0	0	0	4	0	7	0	0	0	0	0
Centrilobular fat deposition	0	0	0	0	0	0	0	0	8	0	0	0	0	0
Kidneys (total number examined)	[10]	[10]	[2]	[0]	[0]	[0]	[0]	[0]	[10]	[10]	[5]	[5]	[5]	[5]
No abnormalities detected	9	10	2	0	0	0	0	0	10	10	5	5	5	4
Tubular dilation	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Dilatation of renal pelvis	1	0	0	0	0	0	0	0	0	0	0	0	0	1
Cystically dilated cortical tubules	0	0	1	0	0	0	0	0	0	0	0	0	0	0

Changes secondary to enzyme induction were found only in the livers from male rats. The incidence of centrilobular hepatocyte enlargement and vacuolation were increased in males from the 25 and 75 mg/kg/day groups. Centrilobular fat deposition was observed in the high dose

group. These observations correlate with the increased liver weight found in males from these dose groups. Hepatic changes were not observed in the recovery group. No treatment-related abnormalities were observed in other tissues; negative findings for kidney are summarized for comparison with the previous 4-week study (table 6).

Reversibility: In the 4-week recovery groups no drug-related effects were observed, suggesting that abnormalities observed after 13-week's treatment were reversible.

Toxicokinetics: Toxicokinetic parameters are summarized in table 10 below. Systemic exposure to the drug as measured by C_{max} and AUC increased with increasing doses. Systemic exposure was similar in males and females. The C_{max} values may be somewhat underestimated because the first blood level, taken at 1.5 hours, was usually the highest; previous studies with the racemate measured a T_{max} of 0.5 hours (see original Pharmacology/Toxicology review). Metabolism of the drug may be saturated at higher doses because the percent recovered unchanged in the urine increases at higher doses. Urinary excretion was greater in females than in males.

Table 10. Toxicokinetic parameters after daily oral dosing with ucb 28556 in rats

	wk	4 mg/kg		8 mg/kg		25 mg/kg		75 mg/kg	
		♂	♀	♂	♀	♂	♀	♂	♀
C_{max} ($\mu\text{g/ml}$)	13	1.7	1.2	5.5	3.6	21	17	72	89
T_{max} (hr)	13	1.5	1.5	3.0	1.5	1.5	1.5	1.5	1.5
AUC_{0-24} ($\mu\text{g} \cdot \text{hr} \cdot \text{ml}^{-1}$)	13	3.1	2.0	32	11	107	47	441	386
Urinary excretion, 24 hr (% of administered dose)	1	0.04	3.1	0.31	22.6	6.9	29	22.3	31.1
	6	0.49	1.5	0.81	26.1	15.4	28.4	26.4	36.5
	13	0.24	5.3	1.7	28.9	23.7	23.7	27.9	36.7

Summary of Rat 13-Week Oral Toxicity With (+)Enantiomer, ucb 28556:

No deaths occurred in this study. Hypersalivation at 75 mg/kg/day was the only treatment-related clinical abnormality. Body weight gain was decreased in females at 25 and 75 mg/kg/day. Plasma AST (SGOT) activity increased in female rats at doses from 8 - 75 mg/kg/day. This small increase was not clearly dose-related, making the toxicological significance questionable. Liver weight increased in males at 25 and 75 mg/kg/day. This correlated with liver P450 enzyme induction and centrilobular hepatocyte enlargement and vacuolization at 25 and 75 mg/kg/day; with centrilobular fat deposition at 75 mg/kg/day. All abnormalities were reversible as determined by their absence in the 4-week recovery groups. The NOAEL dose for serious adverse effects was 25 mg/kg/day.

Summary of 4-Week and 13-Week Rat Oral Toxicity Studies

Increased plasma ALT (SGPT), suggesting liver toxicity, was observed at 225 mg/kg/day of both enantiomers in the 4-week study; it was not observed up to 75 mg/kg/day in the 13-week study. The NOAEL for this effect was 75 mg/kg/day. Altered hepatic histology in rats was observed

after 4-weeks treatment with both enantiomers or 13-weeks of treatment with the (+) enantiomer; the (-) enantiomer was not studied at 13 weeks. The changes included centrilobular and midzonal hepatocyte enlargement, centrilobular hepatocyte vacuolization, and centrilobular fat deposition. These alterations occurred predominantly in males, at doses of 25 mg/kg/day or greater. The changes were associated with increased liver weight and induction of P450 enzyme activity. The changes were reversible during 4-weeks recovery. These changes are typical of enzyme induction and do not represent an adverse effect. Furthermore, other studies indicate that this effect is peculiar to rodents and does not occur in dogs or monkeys.

The other target organ for toxicity in these studies was the kidney. In the 4-week studies, reversible lesions were found at 75 and 225 mg/kg/day of ucb 28556 and 225 mg/kg/day of ucb 28557. In the 13-week study no renal lesions were observed at 75 mg/kg/day. This does not represent a major discrepancy between the two studies. Renal abnormalities were observed in only a few animals at 75 mg/kg in the 4-wk study so this can be considered a threshold dose for the effect. The studies had several differences that might contribute to variability: they were done at different times, using different strains of rats, and the slides were evaluated by different pathologists. Lethality was observed at 75 mg/kg/day in the 4-week but not the 13-week study. The mild proteinuria measured in the 4-week and 13-week studies is considered artifactual and was not accompanied by changes in blood urea nitrogen or creatinine.

4-Week Oral Study of (+) and (-) Cetirizine Enantiomers in Dogs

NDA Report T-62: UCB 28556 and UCB 28557, Toxicity to Dogs by Repeated Oral Administration for 4 Weeks. UCB Report RRLE95C2004, 29 March 1995.

NDA Report T-62 (Appendix A): Ucb P071, Additional ECG Readings, Dog Toxicity Studies, Acute and 1-Month Oral Treatment. UCB Report LE90J051, 27 August 1990.

NDA Report T-45: Ucb 28556 and Ucb 28557, Toxicity to Dogs by Repeated Oral Administration for Four Weeks, UCB Report RRLE92D2103, 29 September 1992.

NDA Report NPK-35: UCB 28556 and UCB 28557, Pharmacokinetic Monitoring in the Course of a 4-Week Toxicity Study to Dogs by Repeated Oral Administration. UCB Report RRLE93A2803, 29 April, 1993.

Study Dates: 04 November 1991 to 18 December 1991

Testing Lab: Main Study - UCB S.A., Pharma Sector, Braine-l'Alleud, Belgium
Histology

Test Articles: Cetirizine (+) enantiomer, ucb 28556, Batch D 005
Cetirizine (-) enantiomer, ucb 28557, Batch D 005

GLP: The reports were accompanied by signed GLP statements.

Methods:

Six groups of beagle dogs (n=3/sex/dose) were treated with ucb 28556 or ucb 28557 at 15, 45

or 135 mg/kg/day, a single control group received no drug. Drug was administered orally in gelatin capsules. Because severe toxicity was observed in dogs receiving 135 mg/kg/day of ucb 28556, dosage was reduced to 90 mg/kg/day from day 8 of treatment onwards. Duration of treatment was 35 to 44 days. The following observations were made:

Check for dead animals	daily
Clinical signs	daily
Body weight	weekly
Food consumption	daily
Electrocardiography	pre-study, week 1, and week 4 (0, 1, & 4 hr post-dosing)
Ophthalmoscopy	pre-study; week 4
Clinical chemistry	weeks -4, -2, and during week 5
Hematology	weeks -4, -2, and during week 5
Urinalysis	weeks -4, -2, and during week 5
Necropsy	terminal
Histopathology	liver and kidney examined in all animals, specified tissues in zero and high dose groups, any unscheduled deaths or macroscopically abnormal tissues in low and mid dose groups.
P450 enzyme activity	terminal, all animals except unscheduled deaths
Drug Monitoring	
plasma	days 1 & 23 at 0, 1.5, 3, 6, 9, & 24 hr post-dose
urine	days 1 & 23, 24-hr sample
other	contents of gall and urinary bladder during necropsy

Results:

Mortality: One male and two females treated with 135 mg/kg/day of ucb 28556 died. Death was associated with: tremors, prostration, hypersalivation, nausea and emesis, decreased body weight, and intestinal impaction of fecal material. Ileal ulceration contributed to the death of one animal; tracheitis in a second animal may have been due to inhalation of vomitus. Certain abnormal clinical chemistry and pathologic findings were attributed to the generally impaired condition. Hepatocellular vacuolation was seen in two dogs with elevated alkaline phosphatase at the time of death. One dog had a long QT interval before death (16% increase). A cause of death could not be determined, but the gastrointestinal tract was a target of toxicity.

Clinical Observations: The incidence of clinical signs is summarized in table 11 below. The most frequent adverse effect was emesis, which occurred at similar frequencies with both enantiomers. Hypersalivation occurred at all dose levels of both enantiomers, with a higher frequency for ucb 28556. Tremors were observed sporadically with both enantiomers at low and intermediate doses but with a marked increase in dogs treated at the high dose of ucb 28556. Reduced motor activity and labored breathing were indicative of a generally impaired condition; these signs were observed for mid and high doses of ucb 28556 and in one female at the high dose of ucb 28557. Coughing may have been related to tracheitis observed in some animals, possibly secondary to aspiration of vomitus. Other symptoms such as abnormal posture, palpebral ptosis, ocular discharge, abnormal stools were observed with a low incidence, mainly in high dose groups. They were considered secondary to the impaired condition of the dogs.

Table 11 Clinical signs in dog 4-wk oral toxicity study of cetirizine enantiomers.

Treatment	Control		(+) enantiomer ucb 28556						(-) enantiomer ucb 2857					
	0		15		45		135/90*		15		45		135	
Dose (mg/kg/day)	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Tremors	0	0	0	0	0	1/4	3/21	3/15	0	1/4	0	1/1	0	0
Reduced activity	0	0	0	0	1/2	1/7	3/7	1/2	0	0	0	0	0	1/1
Hypersalivation	0	0	1/1	0	1/2	1/4	3/37	3/11	1/1	0	1/1	0	1/9	1/1
Emesis	0	1/1	2/4	3/4	3/17	3/9	3/14	3/11	2/5	2/2	3/13	2/21	3/38	3/49
Labored breathing	0	0	0	0	0	1/1	2/2	2/2	0	0	0	0	0	0
Cough	0	0	0	0	1/2	1/3	1/7	0	0	0	1/1	0	0	0

Only frequent or serious clinical signs are tabulated. Incidence = number of animals/number of days. * Dose was reduced from 135 to 90 mg/kg/day on day 8.

Ophthalmoscopy: Minor redness or congestion of the conjunctiva or scleral blood vessels were observed in a few dogs from the medium and high dose groups receiving either enantiomer. The finding occurred in five animals treated with ucb 28556 and in one treated with ucb 28557.

Body Weight: There was no consistent effect on bodyweight gain. Occasional decreases in individual animals were probably related to emesis.

Food Consumption: There was no consistent effect on food consumption. Occasional decreases in individual animals were probably related to emesis and nausea.

Electrocardiography: The report concludes that no electrocardiographic abnormalities were detected. However, evaluation of the data indicates that both enantiomers caused a modest, but reproducible increase in the time for repolarization, as measured by the QT interval corrected for heart rate (QT_C). The sponsor submitted a reevaluation of the EKG data from the original 1-month oral toxicity study of cetirizine in dogs including calculation of QT_C; data from males and females were combined for statistical evaluation. (UCB Report LE901051, 27 August 1990.) The data from that reevaluation are summarized in figure 1, below. On days 10 and 11, calculated QT_C before dosing and at 4 and 6 hours after dosing was significantly increased in the high-dose group (135 mg/kg/day) vs controls. QT_C at 4 and 6 hours after dosing was significantly increased in the mid-dose group (45 mg/kg/day). The magnitude of increase in QT_C was about 10-20%. This effect on QT_C was not found consistently; a statistically significant effect on QT_C was not observed at 2 or 4 weeks in the same study.

In the enantiomer study QT_C corrected for heart rate was not calculated. (The authors did calculate a predicted QT interval which they abbreviated "QT_C" but this was not a value corrected for heart rate in the usual sense.) From the individual data submitted in the report for QT and RR intervals, a heart-rate corrected QTC was calculated by the reviewer, using the formula $QT_C = QT - (0.115 \cdot (RR - 0.54))$. Here, QT is the absolute QT interval in seconds; RR is the absolute RR interval in seconds; 0.115 is a slope constant relating RR and QT, previously established by the testing laboratory in a population of 71 male and 72 female

Effect of Cetirizine on QTc in Dogs

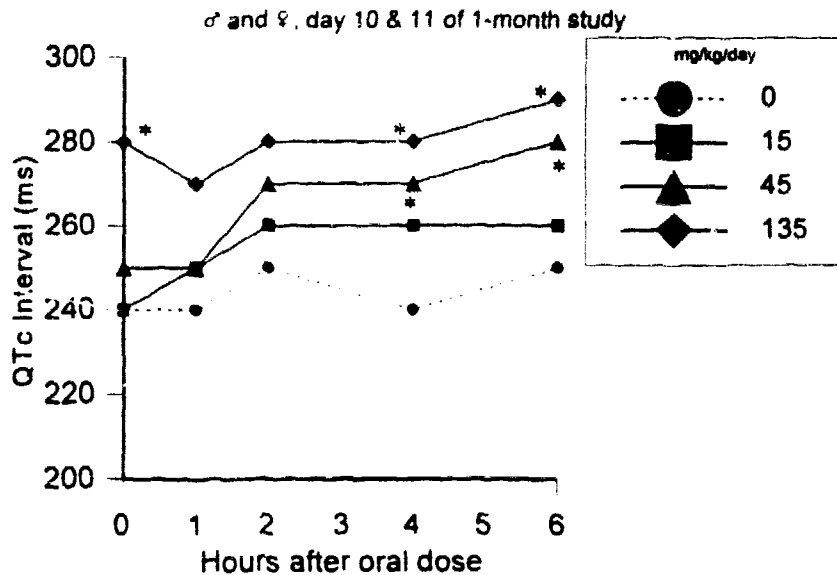


Figure 1. Data were abstracted from sponsor's re-evaluation of electrocardiography data in one-month oral toxicity study of cetirizine in dogs. * P < 0.05 vs 0 mg/kg/day at same time point.

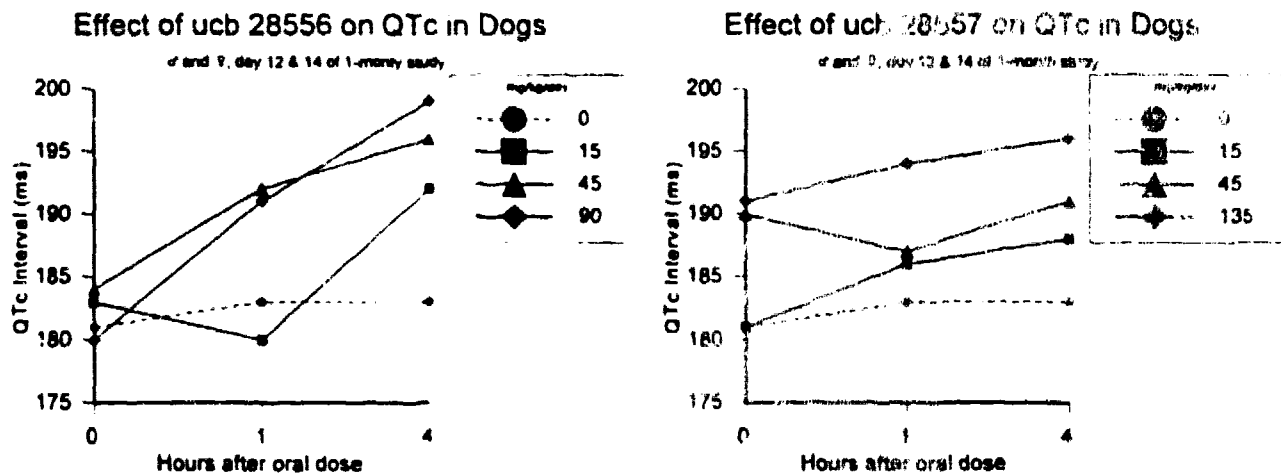


Figure 2. Data were calculated by reviewer from individual data for heart rate and QT interval from 1-month study of oral cetirizine enantiomers in dogs. No statistical analysis was performed.

untreated beagle dogs from the UCB breeding facility; 0.54 is the average overall RR value on the day of observation in the present study (during week 4). As in the cetirizine data submitted by the sponsor, values for males and females were similar and were averaged together. Results of this analysis are illustrated in figure 2 above. The results with either cetirizine enantiomer were similar to those with the racemate; there was a modest, time and dose-related increase of QT_c after dosing with ucb 28556 or ucb 28557. Baseline values of QT_c from the racemate and enantiomer studies differ because different formulas were used to calculate QT_c . Heart rate tended to increase after dosing; this was not statistically significant. In conclusion, there was no difference among racemic cetirizine and either enantiomer in their effect on QT_c interval.

Clinical Chemistry: In one high-dose ucb 28556 male and one high-dose ucb 28557 female plasma CPK activity was increased. Because LDH was not increased, the CPK was thought to come from muscle rather than from imperceptible hemolysis. In the high-dose ucb 28557 group alkaline phosphatase activity was increased in one male (50%) and one female (170%).

Hematology: No significant drug-related effects. Bone marrow smears were not evaluated.

Urinalysis: There was a trend for slightly increased urine volume in males (70%) and females (30%) in the high-dose ucb 28557 group. Slight increases of bile salts in the urine were considered artifacts due to interference of the test substance with the assay.

Organ Weights: No significant drug-related effects.

Gross Pathology: No significant drug-related effects.

Histopathology: There was no evidence of organ specific toxicity in survivors. Sporadic instances of tracheal or esophageal inflammation with both compounds were attributed to reflux/vomiting of the test substances.

Hepatic Drug Metabolizing Activity: No significant drug-related effects.

Toxicokinetics: Toxicokinetic parameters are summarized in table 12 below. Plasma levels were similar in both sexes. Plasma levels at 90 mg/kg/day of ucb 28556 were similar to those at 135 mg/kg/day of ucb 28557. There was drug accumulation such that C_{max} and AUC increased from day 1 to day 23, particularly at higher doses. Urinary excretion was substantial and increased from day 1 to day 23. Both enantiomers were concentrated in bile, with bile concentrations > 8 times peak plasma concentrations. Ucb 28557 was concentrated in bile to a somewhat greater extent than was ucb 28556. At the highest doses, C_{max} and AUC were lower than expected from the progression of doses. This may be due, at least partially, to the emetic effects of both enantiomers. Urine samples from dogs treated with each enantiomer were tested, with a chiral assay, for the presence of the other enantiomer. There was no evidence of interconversion of the enantiomers. Plasma half lives for both enantiomers were about 12 to 15 hours.

Table 12. Toxicokinetics in dog 4-week oral toxicity study of cetirizine enantiomers.

Parameter	Day	ucb 28556 (mg/kg/day)			ucb 28557 (mg/kg/day)		
		15	45	135/90*	15	45	135
C_{max} ($\mu\text{g/ml}$)	1	33 $\pm$ 8	83 $\pm$ 12	113 $\pm$ 38	28 $\pm$ 6	62 $\pm$ 10	67 $\pm$ 36
	23	39 $\pm$ 10	100 $\pm$ 10	160 $\pm$ 19	32 $\pm$ 5	73 $\pm$ 17	175 $\pm$ 39
Trough ($\mu\text{g/ml}$)	23	13 $\pm$ 2	41 $\pm$ 10	51 $\pm$ 20	12 $\pm$ 3	29 $\pm$ 8	78 $\pm$ 27
AUC ₀₋₂₄ ($\mu\text{g} \cdot \text{hr/ml}$)	1	297 $\pm$ 43	856 $\pm$ 240	1432 $\pm$ 563	277 $\pm$ 29	827 $\pm$ 141	1108 $\pm$ 698
	23	493 $\pm$ 41	1503 $\pm$ 155	2413 $\pm$ 445	429 $\pm$ 40	1062 $\pm$ 184	2941 $\pm$ 930
Urinary Excretion (%)	1	21 $\pm$ 6	20 $\pm$ 5	11 $\pm$ 6	28 $\pm$ 3	28 $\pm$ 2	11 $\pm$ 5
	23	39 $\pm$ 4	39 $\pm$ 7	33 $\pm$ 3	46 $\pm$ 5	42 $\pm$ 3	34 $\pm$ 9
Bile Conc. ($\mu\text{g/ml}$)	terminal	214 $\pm$ 31	896 $\pm$ 228	1473 $\pm$ 363	312 $\pm$ 99	1100 $\pm$ 242	2770 $\pm$ 782

Values are means $\pm$ SD; data from males and females combined; n = 3/sex/dose.

* Dose was reduced from 135 to 90 mg/kg/day on day 8.

Summary of Dog 4-Week Oral Toxicity:

Toxic effects were similar for both enantiomers but the degree of toxicity was greater for ucb 28556 than for ucb 28557. Toxicity was similar in both sexes. Deaths occurred in 3/6 dogs treated with 135 mg/kg/day ucb 28556; therefore the dose was lowered to 90 mg/kg/day. A cause of death was not determined but animals that died exhibited gastrointestinal and hepatic toxicity. Plasma concentrations of ucb 28556 at 90 mg/kg/day were similar to those of ucb 28557 at 135 mg/kg/day. Some animals lost weight, probably due to nausea and emesis. There was modest prolongation ($\approx$ 10-20%) of the QT_c interval of the electrocardiogram at the high doses of racemic cetirizine and both enantiomers. There was no organ specific toxicity other than gastro-intestinal. At 45 mg/kg/day there were some clinical signs and mild QT_c prolongation. The profile of toxicity is similar for the racemate and both enantiomers. The NOAEL dose for both enantiomers was 15 mg/kg/day.

13-Week Oral Study of (+) Cetirizine Enantiomer in Dogs

NDA Report T-51: Ucb 28556, Toxicity to Dogs by Repeated Oral Administration for 13 Weeks. UCB Report RRLE92G1003, 12 January 1995.

NDA Report NPK-36: Ucb 28556, Pharmacokinetic Monitoring in the Course of a Toxicity Study to Dogs by Repeated Oral Administration for 13 Weeks. UCB Report RRLE93D0104, 27 May 1993.

Study Dates: 07 January 1992 to 09 April 1992

Testing Lab:

Test Article: ucb 28556 batch D006

GLP: The study was accompanied by a signed GLP statement.

Methods:

Four groups of beagle dogs (n=4/sex/dose) were treated with ucb 28556 at 0, 8, 25 and 75 mg/kg/day. Drug was administered orally in gelatine capsules. Duration of treatment was 13 weeks. The following observations were made:

Check for dead animals	daily
Clinical signs	daily
Body weight	weekly
Food consumption	daily
Electrocardiography	pre-study, week 6, and week 13 (pre- & 3 hr post-dosing)
Ophthalmoscopy	pre-study; week 13
Hematology	pre-study, week 6, and week 13
Clinical chemistry	pre-study, week 6, and week 13
Urinalysis	pre-study, week 6, and week 12
Bone Marrow	terminal
Necropsy	terminal
Histopathology	specified tissues examined in all animals (see Histology Inventory)
Drug Monitoring	
plasma	day 1, week 13: 0, 1.5, 3, 6, 9, & 24 hr post-dose
urine	day 1, week 6, week 13: 24-hr sample
other	terminal: contents of gall and urinary bladder

Results:

Mortality: None

Clinical Observations: Emesis was the only treatment-related clinical observation. The incidence of emesis is summarized in table 13 below.

Electrocardiography: Heart rate increased 3 hours after dosing; this was statistically significant at 75 mg/kg/day for both males and females at 6 weeks, but only males at 13 weeks. The QT interval of the electrocardiogram did not differ among treatment groups. However, one would expect the QT interval to decrease with an increase of heart rate. This implies that relative QT interval was prolonged in the drug-treated animals. QT corrected for the influence of heart rate "QT_c" was not calculated.

Ophthalmoscopy: No toxicologically significant drug-related effects.

Body Weight: No toxicologically significant drug-related effects.

Food Consumption: No toxicologically significant drug-related effects.

Clinical Chemistry: No toxicologically significant drug-related effects.

Hematology: There was a slight decrease (-10%) in hemoglobin concentration with no change in red cell number or hematocrit. Data are summarized in table 13 below.

Urinalysis: No toxicologically significant drug-related effects. Increased protein measurement

was considered to be an artifact of test material in the urine interfering with the protein assay.

Organ Weights: There were increases of spleen weight (64% in males, 10% in females) and adjusted kidney weight (28%). Pooled data for males and females are summarized in table 13 below. Because there were no histopathological or functional correlates to these findings, they were not considered to be toxicologically significant.

Gross Pathology: No toxicologically significant treatment-related effect.

Table 13. Treatment effects during 13-week oral toxicity study of ucb 28556 in dogs.

Dose (mg/kg/day)	0	8	25	75
Incidence of emesis	6/13	8/24	6/34	8/65
Heart rate (bpm): 0hr/3hr	116/120	112/123	119/135	129/148*
QT interval (sec): 0hr/3hr	0.22/0.22	0.22/0.21	0.22/0.21	0.21/0.21
Hemoglobin (g/dl)	14.7	13.9	14.4	13.3*
Spleen weight (g)	62.6	70.6	78.7*	82.4*
adjusted Kidney weight (g)	51.5	54.7	59.2*	58.5*

Incidence = number of animals/number of days; n = 4/sex/group; total animal days = 728.
MCHC = mean corpuscular hemoglobin concentration; *P < 0.05 vs control; EKG data are from week 6, pre-dose/3hr post-dose.

Histopathology: No toxicologically significant treatment-related effect.

Toxicokinetics: Toxicokinetic parameters are summarized in table 14 below. Systemic exposure increased with increasing dose. There was significant accumulation of drug from day 1 to week 13; AUC in week 13 was about twice that on day 1. Urinary excretion increased from day 1

Table 14. Toxicokinetic parameters from dog 13-week oral toxicity study of ucb 28556.

Parameter	Time	Dose of ucb 28556 (mg/kg/day)		
		8	25	75
C _{max} (µg/ml)	Day 1	17	39	101
	Week 13	22	79	167
Trough (µg/ml)	Day 1	2	3	13
	Week 1	3	8	22
AUC ₀₋₂₄ (µg·hr/ml)	Day 1	114	308	923
	Week 13	191	808	2154
Urinary excretion	Day 1	13	14	16
	Week 6	20	27	32
	Week 13	21	28	32
Bile conc. (µg/ml)	Week 13	63	319	1785

to week 6; urinary excretion increased slightly with increasing dose. Drug was markedly concentrated in bile. There was no evidence for conversion to the opposite enantiomer.

Summary of dog 13-week oral toxicity study:

At 75 mg/kg/day heart rate increased but QT interval was not affected, QT interval was not corrected for the increase of rate. Emesis occurred at all dose levels. Spleen and kidney weight were increased at 25 and 75 mg/kg/day but neither was associated with histopathological abnormalities. The NOAEL was 8 mg/kg/day.

Overall Summary of Toxicology Studies

In rats the liver was the primary target for treatment effects. Effects included: increased liver weight, elevated plasma AST or ALT, induction of P450 enzyme activities, hepatocellular enlargement, vacuolization, and fat deposition. Effects were much more marked in males than in females. The extent of abnormalities was similar for either cetirizine enantiomer. Systemic exposure was considerably less for the (-) enantiomer, ucb 28557, compared to the (+) enantiomer, ucb 28556. Systemic exposure was similar in males and females. Renal excretion was substantially greater in females than in males; this may contribute to the lesser degree of liver alterations in females. Liver abnormalities occurred at 75 and 225 mg/kg/day in the 4-week study and at 25 and 75 mg/kg/day in the 13-week study. The dose-effect relation is similar to that of racemic cetirizine in previous 1- and 6-month studies (NDA reports T-7 and T-12).

Renal toxicity was observed in rats in the 4-week study. Kidney weight was increased in males from the 4-week study at 225 mg/kg/day of both enantiomers. Occasional animals of either sex in the 75 and 225 mg/kg/day groups showed microscopic evidence of renal tubular basophilia. Renal lesions were not observed in the 13-week study of ucb 28556 or in previous studies in any species. Increased kidney weight was reported in: the 6-month oral toxicity study of cetirizine in rats (NDA report T-12); the present 13-week oral toxicity study of ucb 28556 in dogs; the 1-month oral toxicity study of cetirizine in dogs (NDA report T-14); and in a 1-month oral toxicity study of cetirizine in monkeys (NDA report T-17). This suggests that cetirizine and its enantiomers can cause sporadic renal effects at high doses. Only in the 4-week study of cetirizine enantiomers in rats was there histologic evidence of renal injury. Signs of renal failure, such as substantially increased BUN or creatinine have not been observed.

There was no liver toxicity in dogs; the gastro-intestinal tract was the main target for toxicity. Effects included nausea, emesis, and salivation. Ileal ulceration was observed in one dog treated with 135 mg/kg/day of ucb 28556. Modest prolongation of the QT_c interval ($\approx$ 10-20%) was observed for both enantiomers and the racemate at 45 and 75 mg/kg/day. QT prolongation was observed previously in the 1-yr oral toxicity study of cetirizine at 60 mg/kg/day. One dog that died during treatment with 135 mg/kg/day ucb 28556 exhibited QT prolongation of $\approx$ 16% at a plasma level of 225 μ g/ml. The NOAEL dose for QT_c prolongation was 15 mg/kg/day. The C_{max} and AUC values for either enantiomer at this dose ($\approx$ 30 μ g/ml and 450 μ g-hr/ml) were 40-60 times those attained in humans after oral administration of 20 mg (0.7 μ g/ml and 7.4 μ g-hr/ml). This indicates an acceptable safety margin and does not present a safety concern.

SPECIAL TOXICITY STUDIES

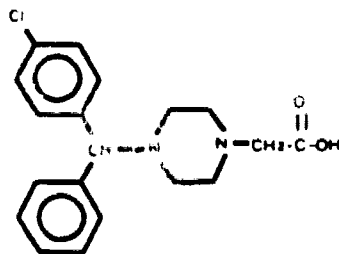
Genetic Toxicity

Ames Test of Cetirizine Metabolite (ucb 26026):

NDA Report T-59: Ames Metabolic Activation Test to Assess the Potential Mutagenic Effect of ucb 26026. UCB Report No. DE88BI72, February 11, 1988.

Study Dates: 15 January 1988 to 27 January 1988
Testing Lab:
Test Articles: ucb po26 = ucb 26026, batch # A003, 98.8% purity
GLP: The study was accompanied by a signed GLP statement.

This study tested the mutagenic potential of ucb 26026, a metabolite of cetirizine, in a bacterial reverse gene mutation assay (Ames test). The chemical structure of ucb 26026 is shown below:



Methods: ucb 26026 was examined for mutagenic activity in five strains of *Salmonella typhimurium*: TA 1535, TA 1537, TA 1538, TA 98 and TA 100, with and without metabolic activation (rat liver S-9 mix). Plates were prepared in triplicate; each test, in each strain, was conducted on two separate occasions. The solvent served as control, and 2-aminoanthracene, 2-nitrofluorene, 9-aminoacridine and N-ethyl-N'-nitro-N-nitrosoguanidine were positive controls. Ucb 26026 was tested at concentrations of 15, 50, 150, 500, and 1500 $\mu\text{g}/\text{plate}$. The maximum concentration was selected following a preliminary toxicity test using ucb 26026 at concentrations of 5, 50, 500, and 5000 $\mu\text{g}/\text{plate}$ in the five tester strains. Ucb 26026 was toxic towards the tester strains at a concentration of 5000 $\mu\text{g}/\text{plate}$. A statistically significant, dose related increase in revertant colony count of at least twice the control value in two separate experiments was considered a positive outcome.

Results: At exposure levels of 15 to 1500 $\mu\text{g}/\text{plate}$, ucb 26026 did not increase revertant colony numbers over control counts for any of the strains tested. Positive controls all produced the expected positive results. Thus, under these conditions, ucb 26026 exhibited no mutagenic activity.

Micronucleus Test of Cetirizine in Mice:

NDA Report T-60: Study to Evaluate the Potential of Cetirizine Dihydrochloride (ucb P071) to Induce Micronuclei in the Polychromatic Erythrocytes of CD-1 Mice. UCB Report No. RRLE94F0601, August 9, 1994

NDA Report NPK-38: ucb P071 Toxicokinetic Report. Study to Evaluate the Potential of Cetirizine Dihydrochloride (ucb P071) to Induce Micronuclei in the Polychromatic Erythrocytes of CD-1 Mice. UCB Report No. RRLE94E0201, May 20, 1994.

Study Dates: 22 December 1993 to 17 February 1994
Testing Lab:
Test Articles: Cetirizine dihydrochloride (ucb P071), batch 2080
GLP: Both studies were accompanied by a signed GLP statement.

Methods: Dose ranging studies were carried out in 8 groups of mice receiving cetirizine on two consecutive days at doses from 139.2 to 2840 mg/kg/day (8 dose levels, 3 mice/sex/dose). The calculated LD₅₀ value was 630 mg/kg/day. A dose of 470 mg/kg was chosen as the upper dose for the main study. For the micronucleus test, 4 groups (10/sex/group) received cetirizine orally, as a solution in purified water, at doses of 0, 117.5, 235 and 470 mg/kg/day for 2 days. Mice were killed 24 or 48 hours after treatment on the second day. An excess number of mice were treated at the high dose to replace any deaths. Bone marrow slides prepared from both femurs were analyzed blindly for the frequency of multinucleated polychromatic erythrocytes (MPCE). Additional groups (3/sex/group) were similarly treated and blood samples were taken at 1, 3, 6, 12 or 24 hours after treatment on the second day to determine cetirizine plasma concentrations. Purified water was the negative control; cyclophosphamide, single oral dose of 80 mg/kg, was the positive control (n=5/sex). The test was considered positive if a statistically significant increase in the frequency of MPCE occurred for at least one dose at one kill time, exceeding the historical vehicle control range, with corroborating evidence of increased frequency of MPCE at other doses or kill times (though not necessarily statistically significant).

Results: At 470 mg/kg, one mouse was killed in extremis and other animals showed signs of toxicity (piloerection, irregular breathing, lethargy). Observed frequencies of MPCE and plasma drug concentrations are summarized in table 15 below. Cetirizine had no effect on MPCE

Table 15. Cetirizine in mouse micronucleus test.

Dose (mg/kg)	Vehicle		Cetirizine HCl						Cyclophosphamide	
	♂	♀	117.5 x 2		235 x 2		470 x 2		80 x 1	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
24 hr MPCE frequency /1000	0.6	0.4	0.4	0.9	0.3	0.5	0.4	0.5	23.4	19.3
48 hr MPCE frequency /1000	0.6	0.4	0.1	0.5	0.5	1.0	0.3	0.5	---	---
Cmax (µg/ml)	---	---	68	71	130	97	150	119	---	---
AUC ₀₋₂₄ (µg·hr/ml)	---	---	549	501	1224	849	2147	1295	---	---
MPCE = multinucleated polychromatic erythrocytes.										

frequency nor on the ratio of normochromatic to polychromatic erythrocytes; values were within the range of historical vehicle controls. Cyclophosphamide, the positive control, significantly increased MPCE frequency. Systemic exposure to cetirizine, measured as C_{max} and AUC did not increase in proportion to dose at the highest dose level; females had less systemic exposure than males at any dose level. For comparison, in a previous clinical pharmacokinetic study (NDA Report, CPK-4), the plasma C_{max} and AUC in humans after a 10 mg dose was 0.31 $\mu\text{g/ml}$ and 2.7 ($\mu\text{g}\cdot\text{hr/ml}$), respectively. Thus, the C_{max} and AUC in male mice from the high dose group were 484 and 795 times greater than those observed in humans at the recommended dose.

SUMMARY AND RECOMMENDATIONS

Toxicity and "side effects" (eg. QT_c prolongation and increased hexobarbital sleeping time) of both cetirizine enantiomers are similar to that observed for the racemic compound. There is no rationale for developing a particular enantiomer for human use.

The occasional occurrence of reversible renal lesions in rats at relatively high doses of 75 and 225 mg/kg/day (observed only in the 4-week study of rats) does not warrant special monitoring in humans or inclusion in the labelling.

The modest prolongation of cardiac repolarization, measured as an increase of the electrocardiographic QT_c interval, does not present a safety concern. The magnitude of the effect was relatively small ($\approx 10\text{-}20\%$ increase) and occurred only at high doses (45 mg/kg/day and greater). Prolongation of the QT_c was not consistently observed in different studies. This may be due, in part, because the extent of prolongation is near the limit of resolution for the measurement (≈ 10 ms). The effect seems to reach a plateau; absolute QT interval was increased only 16% in one dog dying after oral administration of 135 mg/kg/day of the (+) cetirizine enantiomer. The NOAEL dose of 15 mg/kg/day in dogs was associated with plasma concentrations about 40 times those measured in humans after 20 mg cetirizine.

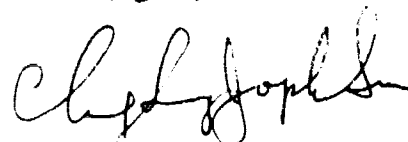
No concerns for genetic toxicity were raised by these data.

c.c. Original NDA 19-835
HFD-155/Division File
HFD-155/C. J. Sun
HFD-155/A. M Saavedra-Delgado
HFD-155/W. M. Vogel



W. Mark Vogel, Ph.D.
Pharmacologist/Toxicologist

10.10.95



Oct 11, 1995

Histopathology Inventory for NDA # 19-835

Study	3 wk oral	13 wk oral	4-wk oral	13-wk oral		
Species	rat	rat	dog	dog		
Adrenals	✓	✓	✓	✓		
Aorta		✓	✓	✓		
Bone Marrow						
Bone (femur)	✓		✓	✓		
Brain	✓	✓	✓	✓		
Cecum	✓	✓	✓	✓		
Cervix		✓				
Colon	✓	✓	✓	✓		
Duodenum	✓	✓	✓	✓		
Epididymis		✓	✓	✓		
Esophagus	✓	✓	✓	✓		
Eye	✓		✓	✓		
Fallopian Tubes	✓					
Gali Bladder			✓	✓		
Harderian Gland						
Heart	✓	✓	✓	✓		
Ileum	✓	✓	✓	✓		
Injection Site						
Jejunum	✓	✓	✓	✓		
Kidneys	✓	✓	✓	✓		
Lachrymal Gland						
Larynx						
Liver	✓	✓	✓	✓		
LNodes, cervical	✓	✓	✓	✓		
LNodes, mandibu-						
LNodes, mesen-		✓	✓	✓		
Lungs	✓	✓	✓	✓		
Mammary Gland	✓		✓	✓		
Nasal Cavity						
Optic Nerves	✓					
Ovaries	✓	✓	✓	✓		
Pancreas	✓	✓	✓	✓		
Parathyroid		✓	✓	✓		
Peripheral Nerve						
Pharynx						
Pituitary Gland	✓	✓	✓	✓		
Prostate	✓		✓	✓		
Rectum		✓		✓		
Salivary Gland	✓		✓	✓		
Sciatic Nerve	✓	✓	✓	✓		

Seminal Vesicles	✓					
Skeletal Muscle	✓		✓	✓		
Skin	✓	✓	✓	✓		
Spinal Cord	✓			✓		
Spleen	✓	✓	✓	✓		
Sternum		✓		✓		
Stomach	✓	✓		✓		
Testes	✓	✓	✓	✓		
Thymus	✓	✓	✓	✓		
Thyroid	✓	✓	✓	✓		
Tongue	✓			✓		
Trachea	✓	✓	✓	✓		
Urinary Bladder	✓	✓	✓	✓		
Uterus	✓	✓	✓	✓		
Vagina				✓		
Zymbal Gland						

OCT 18 1993

Pharmacologist Review of NDA 19670
(Amendment of May 20, 1993)

REVIEWER: C. Joseph Sun, Pharmacologist (HFD-155)
SPONSOR: Schering Corp.
DRUG: Claritin-D (5 mg loratadine and 120 mg Pseudoephedrine) Slow Release Tablets 125 mg
Date of review: Oct. 13, 1993

SUBMISSION CONTENT: Proposed labeling

COMMENT: The proposed labeling conforms to the format specified under CFR 21.Part201.subpart B dated April 1, 1993. It generally reflects the preclinical data with one exception. In the Pregnancy B category section, oral dose of combination should be specified. Thus, the first sentence should be modified as below:

"There was no evidence of animal teratogenicity in reproduction studies performed on rats and rabbits with the combination product at oral doses up to 150 mg/kg (885 mg/m² or 5 times the maximum recommended human dosage (250 mg or 185 mg/m²) and 120 mg/kg (1416 mg/m² or 8 times the maximum recommended human dosage), respectively."

RECOMMENDATION:

The above-mentioned modification for pregnancy B category section should be incorporated for the labeling.



C. Joseph Sun, Ph. D.

Oct 18, 1993

Orig. NDA
HFD-155/Division file
HFD-155/Dr. Sun
HFD-155/Dr. Honig
HFD-155/CSO

272, 10-18-93

Handwritten signature

Pharmacologist Review to NDA 19835
(Amendments of July 22 and Aug. 11, 1993)

OCT 12 1993

REVIEWER: C. Joseph Sun , Pharmacologist (HFD-155)

SPONSOR: Pfizer

DRUG: Cetirizine

DRUG CATEGORY: antihistamine (H₁ receptor antagonist)

DATE OF RECEIPT BY HFD-155: July 26 and Aug 18, 1993

Date of review: Oct. 12, 1993

SUBMISSION CONTENT: Revised labeling

Comment:

The sponsor has not incorporated the modifications, which have been conveyed to the sponsor on March 15, 1991, for the labeling recommended by Dr. Jean in the original NDA review of April 11, 1989. Thus, Dr. Jean's recommended changes for the labeling in carcinogenesis, mutagenesis, and impairment of fertility and pregnancy category sections as indicated in the review should be incorporated for final labeling with an exception in the carcinogenesis section.

Dr. Jean concluded that the incidence of thyroid follicular adenoma in male rats was statistically significant and should be mentioned in the carcinogenesis section. However, incidence rate of 12 % for the tumor in the high dose group was within sponsor's historical control range of 0-12%. Moreover, since this tumor type is a common one (average incidence for this tumor type was 3.9% based on 15 historical control groups), p value of trend analysis of 0.039 (see statistical analysis by Dr. Lin on 3/6/89) did not consider statistically significant. Thus, we conclude that incidence of thyroid follicular adenoma in male rats was not biologically significant.

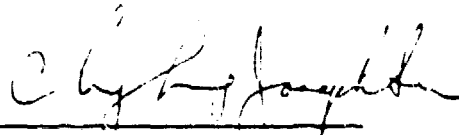
Cetirizine was not shown to be mutagenic in four tests (Ames test, clastogenic assay in human lymphocytes, mouse lymphoma forward mutation assay and in vivo micronucleus test in rats. These four in vitro and in vivo tests should be specified in the mutagenesis section as well.

Identified target organs of toxicity of liver and stomach in rodents should be inserted in the overdosage section. The minimal lethal oral dose in mice was 237 mg/kg (711 mg/m²) in rodents, which is equivalent to 48 times the recommended clinical dose (0.4 mg/kg or 14.8 mg/m²).

Reactine was not teratogenic in mice, rats and rabbits. Other effects of Reactine on

NDA 19835
Page 3

Due to the possible relevance of H₁ receptor antagonist and its adverse cardiovascular events in humans, study the effect of cetirizine and its metabolite, PO26, on specific channels and action potential of cardiac tissues is recommended.



C. Joseph Sun, Ph. D.

Oct 12, 1993

Orig. NDA
HFD-155/Division file
HFD-155/Dr. Sun
HFD-155/CSO
HFD-155/Dr. Saavedra-Delgado

WJS 10-12-93

Division of Oncology and Pulmonary Drug Products
Pharmacology and Toxicology Review

OCT 22 1992

Reviewer: Alan S. Taylor, Ph.D.
Completed : October 22, 1992

NDA 19-835: Final safety update
Submission dated 1/30/92

Sponsor: Pfizer Inc.

Drug: Reactine (ceterizine HCl) Tablets

Nonclinical toxicology studies
Summary and evaluation

This submission consists of 4 study reports detailing data provided to the FDA and the Pulmonary-Allergy Drugs advisory committee meeting on June 14, 1991. All studies deal with aspects of liver changes associated with chronic administration in rodents. Report numbers and titles are attached.

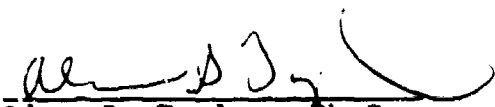
Studies T-35 and T-36 report electron micrographic examinations of livers from control and drug treated rats and mice respectively after 4 weeks of ceterizine administered via the diet. The EMS indicated that liver changes consisted of minimal to moderate proliferation of the smooth endoplasmic reticulum (SER) and associated decrease in the amount of rough endoplasmic reticulum in male mice, 5/10 at 9 mg/kg/d and 10/10 at 27. Similarly minimal proliferation was observed in 3/10 male rats at 18 mg/kg/d. Similar changes were not observed in female mice or rats.

Report T-37, measured changes in hepatocyte size associated with dietary administration of ceterizine in the two year rodent bioassays. There was a significant increase in centrilobular hepatocyte cell size in both sexes of mice and rats the high doses tested of 16 mg/kg/d and 20 mg/kg/d, respectively.

Histological assessment of cytoplasmic staining characteristics of the benign liver cell tumors in male mice from the two year bioassays (Report-T38) revealed no differences between tumors from control or treated mice. (ie, the proportion of basophilic, eosinophilic, normochromic and mixed staining tumors were roughly comparable between groups.)

Recommendations

1. This NDA is considered approvable based on Pharmacology and Toxicology considerations.


Alan S. Taylor, Ph.D.

10/22/92

SECTION L
Individual Study Reports/Published Literature

3. Non-Clinical Study Reports

TABLE OF CONTENTS

<u>Title</u>	<u>Regulatory Filing Status</u>	<u>NIA Report</u>		
		<u>No.</u>	<u>Vol.</u>	<u>Page</u>
Overview				
Electron Microscopy (EM) of Livers of Rats from Control and Cetirizine 18 mg/kg/day Dose Level in the Diet for Four Weeks. EHC Report No. UCB 186/91530, August 8, 1991.	Not Filed	T-35	30	12 4295
Electron Microscopy of Livers of Mice from Control and Cetirizine 9 mg/kg/day and 27 mg/kg/day Dose Levels in the Diet for Four Weeks. EHC Report No. UCB 187/91518, August 8, 1991.	Not Filed	T-36	30	12 4311
A Quantitative Assessment of Liver Cell Size Changes in mice and Rats from the Dietary Tumorigenicity Studies. EHC Report No. UCB 215/199/91779, October 11, 1991.	Not Filed	T-37	30	12 4328
A Histological Assessment of the Cytoplasmic Staining Characteristics of Benign Liver Cell Tumors from Male Mice. EHC Report No. UCB 215/911049, November 11, 1991.	Not Filed	T-38	30	12 4342

12 4292

JUN 25 1992

Memorandum

Date: June 25, 1992

From: C. Joseph Sun, Ph. D.
Pharmacologist (HFD-150) *C. Joseph Sun 6/25/92*

Thru: Alan Taylor, Ph.D. *A. Taylor 6-25-92*
Supervisory Pharmacologist
HFD-150

To: Gregory Burke, M.D., Ph. D.
Division Director
Division of Oncology and Pulmonary Drug Products
HFD-150

SUBJECT: Re-evaluation of mutagenicity studies of ceterizine (P071)
NDA 19835 & IND 24084

Evaluation of carcinogenicity studies by the CAC concludes that ceterizine possesses an equivocal increase in the incidence of benign hepatocellular adenoma in male mice but not in female mice nor in rats. However, both studies appeared to have not been performed at the maximally tolerated doses (MTDs) but at 1/2.7 -1/5 of MTDs. It was considered likely that tumor signals would be increased if the studies were repeated at higher doses. Thus, a re-evaluation of the mutagenicity should be undertaken to examine ceterizine's mutagenic potential more closely and to determine its genotoxic involvement in the mechanism of action on its carcinogenicity.

Following mutagenicity tests submitted in the NDA 19835 on 6/30/88 are re-evaluated: (1) Ames test, (2) in vivo micronucleus test in rats, (3) clastogenic assay in human lymphocyte and (4) TK forward mutation assay in L5178Y mouse lymphoma.

Ames Test
(Report no. DE84A113)

Testing laboratory:

Date of the study: March 22, 1982 to April, 1982

Methods: Five histidine-dependent strains of *Salmonella typhimurium*, TA981535, 1537, 1538, 100 and 98 were treated with P071 (Batch no. D003) at concentrations of 8-5000 ug/plate by Ames plate incorporation test. Treatment was carried out with or without metabolic activation (hepatic microsome form rats that had been treated with Aroclor

1254). 2-Aminoanthracene (5 ug/plate in the presence and absence of S-9), 9-aminoacridine (50 ug/plate in the absence of S-9), 2-nitrofluorene (5 ug/plate in the absence of S-9), benzopyrene (5 ug/plate in the presence and absence of S-9) and N-methyl-N'-nitro-N-nitrosoguanidine (2 ug/plate, in the absence of S-9 mix) were used as the positive controls. Concentration selection was based on a preliminary toxicity test in that cytotoxicity was shown at concentration of 5 mg/plate. Criteria for positive response were not stated. All plates were prepared in triplicate and incubated at 37°C for 48 hours. Numbers of revertant colonies were counted.

Results: Inhibition of growth observed as thinning of the background lawn of non-revertant cells at a level of 5000 ug/plate, indicating cytotoxicity. No increases in revertant colony numbers over control were reported with all five stains following exposure to P071 at levels from 8 to 5000 ug/plate. Positive controls yield typical positive results.

In conclusion, ceterizine at concentration of 5 mg/plate was negative in the Ames test.

Clastogenic Assay in Human Lymphocytes
(Report no. DE84A112)

Testing laboratory:

Date of the study: March 23, 1988 to Aug. 6, 1988.

Methods: Whole blood culture were treated with P071 (Batch no. D003) for 48 hours at concentration of 20, 100 and 500 ug/ml in the absence or presence of metabolic activation. Distillate water was used as negative solvent control. Cyclophosphamide (6 ug/ml) was used as the positive control. Three hours before termination, cell division was arrested by the addition of colcemid (0.4 ml of 10 ug/ml). A preliminary toxicity test at concentration dose range of 1.6-5000 ug/ml was conducted to establish a top dose level for the test. No metaphase were observed from slides prepared from cultures exposed to P071 at concentration of 1000 or 5000 mg/ml. Criteria for positive response were not stated.

Results: In the absence of metabolic activation, there were increases in % cells with aberrations other than gaps at concentration of 500 u/ml (3.95% vs 1.5% in the negative control) but the increases were not statistically significant. Furthermore, mitotic index was markedly decreased (94%) at this concentration, therefore, the effect at this toxic

level should not be considered valid. No increase in aberrations was observed in the presence of metabolic activation: Positive control, cyclophosphamide, did not increase the incidence of aberrations in the absence of metabolic activation, however, it caused an increase in chromosome aberration other than gaps in 9.5% of cells in the presence of metabolic activation.

In conclusion, ceterizine at concentration of 500 ug/ml did not produce significantly increased incidence of chromosomal aberrations. Positive controls other than cyclophosphamide which will induced positive response in the absence of metabolic activation should be chosen for the study.

In Vivo Micronucleus Test in Rats
(Report no. DE84A176)

Testing laboratory:

Date of the study: Nov. 5, 1982 to Dec. 20, 1983.

Methods: Five groups of CD-1 mice each consisting of 5 males and 5 females were given orally P071 (Batch no. D003) dissolved in water at constant volume of 10 ml/kg at dose levels of 0, 14, 70 and 350 mg/kg/day for 2 days. Positive control animals were given chlorambucil (30 mg/kg). Animals were sacrificed six hours after administration of final dose. Bone marrow slides were prepared. The resultant data were used to calculate the number of micronucleated cells per 1000 erythrocytes. The frequency of micronuclei in polychromatic cells provides an index of induced genetic damage. Dose selection was based on an oral LD50 of 600 mg/kg and a preliminary toxicity study in that no evidence of severe toxicity was reported. Criteria for positive response were not provided.

Results:

At 350 mg/kg, eight out of ten animals lost weight (1-2 g) and one animal exhibited slight piloerection, indicating a MTD was employed. Animals receiving positive control showed more marked evidence of toxicity: all animals lost 2-4 g body weight and all had slight piloerection.

Incidence of micronucleated cells: There were no statistically significant increases in the incidence of micronucleated polychromatic erythrocytes between control and drug-treated

groups. Positive control, chlorambucil, produced a statistical significant increase in micronucleated cell (46 per 1000 polychromatic erythrocytes).

In conclusion, oral administration of compound at doses up to 350 mg/kg did not induce any mutagenic potential. However, duration between the last treatment of drug and sacrifice of animals was not sufficiently long to permit full assessment of mutagenic potential. Therefore, the results of this study are not considered definitive. It is recommended that if two treatments are employed sampling times of 20 and 48 hours after the last dose would be suitable for detection of most chemicals currently known to induce micronuclei (Mutation Research, 189:103,1987). Thus, in the study two samples should be taken 20 to 48 hr after the last dose to allow full expression of the effect in mutagen in the erythrocytes.

L5178Y Mouse Lymphoma Forward Mutation Assay
(Report no. DE86F126)

Testing laboratory:

Date of the study: January 15, 1986 to July 1, 1986.

Methods: P071 (Batch no. 11) dissolved in water at concentrations of 260-460 ug/ml in the absence of metabolic activation (S-9 fraction from Aroclor-treated rats liver) and at concentrations of 100-400 ug/ml in the presence of metabolic activation was tested. Concentrations selection was based on a preliminary toxicity study using range of 19.5-5000 u/ml. Ethylmethane sulfonate (500 ug/ml) and cyclophosphamide (5 ug/ml) were used as the positive controls in the absence and presence of metabolic activation, respectively. Water was used as the solvent negative control. After growth in suspension had been monitored for a 24 hr and 48 hr periods following treatment, the most appropriate treatment groups were chosen for subsequent cloning in agar and assessment of mutant colony numbers. The criteria for a positive response were (1) the induction of at least two-fold increase in mutant frequent relative to the control, (2) the demonstration of a statistically significant response, (3) evidence of a dose-related response, and (4) response must be reproducible.

Results:

Treatment with concentrations between 300 and 460 ug/ml in the absence of S-9 and 150-300 ug/ml in the presence of S-9 induced dose-related cytotoxicity with acceptable level

Memo
Ceterizine
Page 5

of 10-90 % suspension growth of control. No significant increase in mutant frequency were induced after treatment with P071 to the solvent controls. EMS (in the absence of S-9) and cyclophosphamide (in the presence of S-9) induced significant increases of 9 and 4 times the solvent controls, respectively.

In conclusion, ceterizine at concentrations of 300-420 ug/ml did not induce any utagenicity in the test.

SUMMARY AND EVALUATION:

Ceterizine at concentrations up to 5 mg/plate was negative in the Ames test. At concentration of 500 ug/ml, it did not produce significantly increased incidence of chromosomal aberrations. Oral administration of ceterizine at doses up to 350 mg/kg did not induce any mutagenic potential in the micronucleus test in mice. However, duration between the last treatment of drug and sacrifice of animals was not sufficiently long to permit full assessment of mutagenic potential. Ceterizine at concentrations of 300-420 ug/ml did not induce any mutagenicity in the L5178Y mouse lymphoma forward mutation assay.

RECOMMENDATION:

Additional in vivo mutagenicity screen including DNA adduct formation should be considered to better evaluate mutagenic potential. In addition, unscheduled DNA synthesis assay may be considered as an additional highly sensitive assay.

NDA 19835
IND 24084
HFD-150/Division file
HFD-150/Dr. Sun
HFD-150/Dr. Leonard
HFD-150/Dr. Taylor
HFD-100/Dr. Temple

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NDA 19-835

Date: February 9, 1990

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Amendment, Dated May 24, 1989

DRUG: Cetirizine HCl Tablet
(5, 10, and 20 mg Tablets)

SPONSOR: Pfizer Pharmaceuticals
Pfizer Inc. 835 E. 42nd St
New York, N.Y. 10017

CATEGORY OF DRUG: Antihistamine

INDICATION: Seasonal Allergic Rhinitis; Perennial Allergic Rhinitis;
and Chronic Idiopathic Urticaria

ROUTE OF ADMINISTRATION: Oral

REASON FOR THE SUBMISSION:

This submission contains three reports (NP-58, T-33, NPK-29) from UCB, Brussels, Belgium which describe some pharmacologic, toxicologic, and pharmacokinetic properties of the enantiomers of cetirizine.

In addition, the sponsor states that this submission answers the question 2.(d) in a letter from FDA, dated February 7, 1989 with regard to the pharmacological properties of each enantiomer.

SUMMARY OF THE REPORTS:

1. The Report NP-58 characterizes the antihistaminic and behavioral effects of the two isomers of cetirizine in mice and guinea pigs.
2. Report T-33 describes data comparing the acute toxicity of the isomers and the racemic compound in mice.
3. Report NPK-29 presents information on the pharmacokinetic properties of the two isomers in dogs.

EVALUATION OF THE REPORTS:

1. Study NP-58: General Behavioral Effects and Antihistaminic Activity of Cetirizine and Its Enantiomers

- a) The activity of the two enantiomers of UCB P071 (UCB 28556 and UCB 28557) on the histamine-induced respiratory spasms in guinea pigs were studied and the results obtained then compared with those produced by UCB P071.

Results

	<u>iv. Dose</u> <u>(umol/kg)</u>	ED ₅₀ (1)	ED ₅₀ (2)	ED ₅₀ (3)	ED ₅₀ (median)
UCB 28556 (+)	0.1 0.32 1.0	0.53	0.39	0.33	0.5 umol/kg
UCB 28557 (-)	0.1 0.32 1.0	0.43	0.39	0.31	0.4 umol/kg
UCP P071 (+)	0.1 0.32 1.0	0.20	0.20	0.24	0.20 umol/kg

Conclusions

The sponsor concluded that, when given intravenously, UCB P071 and its two enantiomers all appeared to have a similar antihistaminic action on the histamine-induced respiratory spasms in guinea pigs, although the racemic mixture seemed to have lower ED₅₀ than either enantiomer.

- b) The effect produced by both enantiomers on the cutaneous reaction to histamine was studied in female NMRI mice, aged 6-8 weeks. UCB 28556 and UCB 28557 were given orally to mice two hours prior to an intradermal injection of histamine (10 ul of either a 100 or 200 ug/ml solution). The skin reactions were monitored by giving an iv injection of Evans blue immediately after the intradermal injection of histamine.

Results

Both isomers produced significant inhibition of histamine-induced skin reactions in mice at doses as low as 0.032 umol/kg. The ED₅₀ of the two isomers were identical and were similar to the ED₅₀ for cetirizine (ED₅₀ = 0.1 umol/kg).

Conclusion

When given orally, the antihistaminic action of UCB P071 and its two enantiomers is the same on the skin reaction to histamine in mice.

- c) The effects of UCB 28556, UCB 28557 and cetirizine on the general behavior of male NMRI mice (18-22 g) was studied using the Irwin test. Animals were administered test drug by either the intraperitoneal or oral route in a dose volume of 15 ml/kg each to 3 mice and the behavioral, neurological and autonomic patterns were observed at 5, 15, 30, 60 and 120 minutes post-dosing.

Results

<u>Observations</u> <u>Minimum Doses</u>	<u>UCB PO71</u> <u>(mg/kg)</u>	<u>UCB 28556</u> <u>(mg/kg)</u>	<u>UCB 28557</u> <u>(mg/kg)</u>
<u>Intraperitoneal administration</u>			
No effect of behavior	46	14	14
Onset of sedation	92	46	46
Decreased motor activity	92	46	46
Piloerection	138	46	46
Decreased muscle tone	138	46	92
Marked decrease motor activity slight transient tremor		92	92
Onset of stimulation	138		
Onset of irritation of CNS	138	138	138
Decreased righting reflex	138	138	138
Lethality (within 24 hrs) (Number of animals dead)	138 (2/3)	138 (3/3)	138 (3/3)
Death within 1 hr	462 (3/3)		
<u>Oral administration</u>			
No effect on behavior	46	46	46
Slight increased spontaneous activity	138		
Slightly decreased body tone		138	138
Piloerection	138	138	1384
Reddening of skin	138	138	462
Onset of stimulation but decreased spont. activity	462		
Decreased righting reflex	462 (slight)	462	462
Onset of sedation	1384	462	462
Tremor	1384	462	462
Lethality (within 24 hrs) (number of animals dead)	1384 (3/3)	1384 (3/3)	1384 (2/3)

Conclusions

When administered by the ip route, UCB PO71 (racemate) appeared to have no significant effect on the behavioral, neurological and autonomic patterns of NMRI mice, up to a dose of 46 mg/kg (0.1 mmol/kg) and up to 14 mg/kg for the isomers. Sedation became evident at a dose of 92 mg/kg (0.2 mmol/kg) for the racemate and 46 mg/kg for the isomers. Higher doses of racemate (138 mg/kg) first induced a stimulation and irritation of the CNS, followed by hypoactivity with decreased muscle tone. The marked decrease motor activity and muscle tone appeared at 92 mg/kg of the isomers. The righting reflex was impaired at the lethal dose of 138 mg/kg (0.3 mmol/kg) for all three compounds.

When administered by the oral route, UCB P071 produced stimulation at a dose of 462 mg/kg (1.0 mmol/kg), sedation became evident at the lethal dose of 1384 mg/kg (3.0 mmol/kg); whereas the isomers produced similar effects at 138 mg/kg and 462 mg/kg, respectively.

At all doses, whether administered orally or intraperitoneally, the effects produced by the two enantiomers were comparable to those of the racemic compound but the effects by the two enantiomers appeared at lower doses than the racemate.

2. Study T-33: Acute Toxicity Studies in Mice with Cetirizine and Its Enantiomers

Testing Laboratory:

April 1987

Procedure

Compounds: UCB P071, UCB 28556, UCB 28557
 Test species: NMRI mice (males and females)
 Single administration by the intravenous route.
 Observation time: 14 days

Results

Mortalities: All animals died at 420 mg/kg and higher
 some animals at dose levels of 180 and 240 mg/kg.

Dose (mg/kg)	Total Number of Death				UCB 28557		UCB P071	
	UCB 28556		UCB P071		(M)	(F)	(M)	(F)
	(M)	(F)	(M)	(F)				
180					0/5	1/5		
240	1/5	0/5	1/5	0/5	2/5	1/5	0/5	0/5
320	0/5	1/5	1/5	4/5	5/5	5/5	2/5	1/5
420	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5
560	5/5	5/5						

LD₅₀ Values:

Compounds	LD ₅₀ (males and females) (mg/kg)
UCB 28556	353
UCB P071	314
UCB 28557	252
UCB P071	337

Clinical signs:

Clinical signs were essentially the same for the three compounds. The most common symptoms were: dyspnea, decrease of motor activity, side lying and jerks or jumps.

Macroscopic examination of organs:

The most common findings among dead animals were white spots on the liver, coagulated blood around liver and intestine, and distended intestine with high doses of all three compounds. There were presence of blood in the urinary bladder and intestine containing yellow to orange liquid.

Conclusion:

The acute toxicity, investigated on mice (M/F) by the intravenous route, is of the similar magnitude in terms of lethality with similar clinical signs for the three compounds tested. However, the LD₅₀ for the isomer UCB 28557 (levo) is lower and seems slightly more toxic than UCB 28556 (dextro).

3. Study NPK-29: Comparative Pharmacokinetics in the Beagle Dog with UCB 28556 and UCB 28557

Testing Laboratory:**Procedure**

Compounds: UCB 28556 (batch D003), UCB 28557 (batch D002)

Test species: 12 Adult Beagle dogs (6 males and 6 females)

(Age: 15.8 months ± 1.0, Mean Body Weight: 9.1 kg ± 0.8)

Single administration by the intravenous route, 1 mg/kg dose

After dosing, blood samples (5 ml) were collected at 0, 5, 10, 20,

40, 60, 90 minutes, 2, 3, 4, 6, 8, 12, 24, 32, 48 hours. Urine

samples were collected before dosing and 0-2, 2-4, 4-6, 6-8, 8-12,

12-24, 24-48 hours after dosing.

The racemic compound, UCB P071 was used for calibration procedures.

Results**Parameters (Plasma)**

	<u>Unit</u>	<u>UCB 28556</u> (Means ± SD)	<u>UCB 28557</u> (Means ± SD)
Terminal rate constant (k)	1/h	0.085 ± 0.008	0.072 ± 0.008
Terminal half-life ($t_{1/2}$)	h	8.20 ± 0.75	9.74 ± 1.12
Area under curve (AUC)	ug.h/ml	36.4 ± 8.8	26.7 ± 4.0
Volume of distribution ($V_{d_{ss}}$)	l/kg	0.32 ± 0.07	0.51 ± 0.07
Clearance (D/AUC)	ml/min/kg	0.487 ± 0.134	0.638 ± 0.103
Mean Residence Time (MRT)	h	11.2 ± 1.3	13.3 ± 1.5

1. After intravenous administration (1 mg/kg), the data indicated that the plasma levels of UCB 28556 and UCB 28557 could be described by a two-compartment open model.
2. The plasma kinetic parameters are summarized above. Variance analysis indicates that terminal half-life, MRT, $V_{d_{ss}}$ and total body clearance of UCB 28556 are statistically different from those of UCB 28557.

page

PURGED

NDA 19-835

Pfizer Pharmaceuticals
New York, NY 10017

Date of Submission: June 30, 1988
Date of Original Review: April 11, 1989

Date of Review: March 6, 1990

ADDENDUM TO PHARMACOLOGY REVIEW OF APRIL 11, 1989

- (1) The trade name has now been established as Reactine which was not available at the time the application was submitted (June 30, 1988).
- (2) In Pharmacology Review of April 11, 1989, the following statements were noted by this reviewer on pages 16 and 102:

I. PHARMACOLOGY:

Primary activity: as an antihistamine or H1 receptor antagonist.

- (A) In vivo studies: (Note: the ED₅₀ values on pages 2 38-2 39 are different from those listed under individual studies, e.g. NP-2, NP-4, NP-8, NP-10 on pages 5 31-5 139. The following summary is based on the results from individual studies. The applicant is to be requested to clarify the discrepancies)

In response to this reviewer's request to clarify the discrepancies on the ED₅₀ values, Dr. Patricia Young called (2-26-90). She indicated that the ED₅₀ values from the individual reports were the correct ones whereas those under "Summary" were erroneous due to typographic error.

As indicated in the original review, the ED₅₀ values from individual reports rather than those under "Summary" were used by this reviewer.

- (3) Dr. Patricia Young also provided the correct dosage for Study NP-13: 10 mg/monkey, instead of 10 mg/kg (see Pharmacology Review of 4-11-89, pages 17 and 102).

Conclusion:

The addendum provides additional information and/or clarification that do not affect the conclusion and recommendations in the original pharmacology review of April 11, 1989.



Dou Huey Jean, Ph.D.
Pharmacologist

CC.
NDA 19-835
HFD-150
CSO-Ledet
R/D DHJean 3/6/90
R/D Init. by WCoulter

DRAFT LETTER TO THE SPONSOR:

Please submit the optical purity data and analysis of UCB 28556 and UCB 28557 used in reports NP-58, T-33 and NPK-29. Also please comment on whether interconversion (racemization) occurs in animals or humans.

cc: NDA 19-835
HFD-150/Div. File
HFD-150/CSO
HFD-150/MChun/
HFD-502/JWeissinger

R/D Init. by *W. G. ...* 2/2/90

Misoon Y. Chun

Misoon Y. Chun; Pharm. D.
Pharmacologist

3. The urinary excretion parameters are summarized below. The data indicates that the half-excretion time, cumulated urinary excretion and renal clearance of UCB 28556 are lower and statistically different from those of UCB 28557.

Parameters (Urinary)

	<u>Unit</u>	<u>UCB 28556</u> (Means $\pm$ SD)	<u>UCB 28557</u> (Means $\pm$ SD)
Excretion half-life (T-1/2)	h	7.80 $\pm$ 1.76	8.25 $\pm$ 1.68
Total excreted fraction (Au)	% dose	25.6 $\pm$ 2.1	38.1 $\pm$ 3.4
Renal clearance (Au/AUC)	ml/min/kg	0.123 $\pm$ 0.029	0.243 $\pm$ 0.044

Conclusion

Data indicated that the plasma levels decline in a biphasic fashion in all animals. The differences in parameters (T-1/2, $V_{d_{ss}}$ and Cl) for two isomers are statistically significant ($p < 0.01$). The most different parameter is the volume of distribution. The difference in the cumulated excreted amounts (Au) and renal clearance of two isomers are statistically significant ($p < 0.01$). No statistically significant difference is obtained for the excretion half-life.

SUMMARY AND CONCLUSION:

UCB P071 (Cetirizine) and its two enantiomers at all doses, whether administered orally, intravenously, or intraperitoneally, all appeared to have a similar antihistaminic action on the histamine-induced respiratory spasms in guinea pigs, the same antihistaminic action on the skin reaction to histamine in mice, and comparable behavioral and neurologic effects in mice.

The acute toxicity, investigated on mice (M/F) by the intravenous route, is of the similar magnitude in terms of lethality with similar clinical signs for the three compounds tested. However, the LD₅₀ for the isomer UCB 28557 (levo) is lower and seems slightly more toxic than UCB 28556 (dextro).

Pharmacokinetic data indicated that there are differences in parameters (T-1/2, $V_{d_{ss}}$ and Cl) for two isomers which are statistically significant ($p < 0.01$). The most different parameter is the volume of distribution being greater with UCB 28557. The difference in the cumulated excreted amounts (Au) and renal clearance of two isomers are statistically significant ($p < 0.01$), but the difference obtained for the excretion half-life is not statistically significant.

JAN 16 1995

DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
NDA 19835

Date of submissions: January 6, 1995 (2 submissions)

Reviewer: C. Joseph Sun, Pharmacologist (HFD-150)

Date of review completed: January 13, 1995

Sponsor: Pfizer

Drug name: Cetirizine HCl Tablets

Submission contents: Comments on two toxicological issues (Impairment of fertility and embryocidal effect) presented in the labeling

Evaluation and comments:

Impairment of fertility: Although slightly lower pregnancy rate (90%) as compared to that of the control group (100%), it was within historical control range of the testing laboratory (87-100%, 95.4 %) as provided by the amendment. Thus, the marginal lower pregnancy rate at 64 mg/kg is considered not biologically significant.

Segment II study in rats: Pre- and post-implantation losses were slightly higher but not statistically significant at 225 mg/kg. Slightly lower fetal weights were observed at 225 mg/kg. However, it exhibited marked maternal toxicities (mortality, clinical signs of toxicity and severe reduction in body weight gain) at this dose. These minor embryocidal toxicity (lower fetal weight) was probably a consequence of the marked maternal toxicity and may not be biologically significant.

Recommendation:

Impairment of fertility was not observed in the mouse segment I study. The sentence referred to impairment of fertility could be modified as revised.

Lower fetal weight at maternal toxic dose level (225 mg/kg/day) does not constitute any embryocidal effect because it was probably a consequence of the marked maternal toxicity in rats. Thus, "Zyrtec had an embryocidal effect in rats at maternal toxic dose of 225 mg/kg/day (180 times the human dose)" could be deleted in the Pregnancy Category B Teratogenic Effect section.

C. Joseph Sun
C. Joseph Sun, Ph. D.

Jan 16, 1995

Orig. NDA 19-835
HFD-150/Division file, HFD-150/Dr. Sun, HFD-150/Dr. DeGeorge
HFD-150/R. Lee

[Signature] 1/14/95

FEB 23 1994

Pharmacologist's Note to NDA 19835

REVIEWER: C. Joseph Sun, Pharmacologist (HFD-155)

DRUG: Cetirizine

Date of review: Feb. 23, 1994

Comment:

Cardiovascular effects of hydroxyzine and its metabolite, cetirizine, in animals are summarized below.

Hydroxyzine

Based on reviews of several published articles, cardiovascular effects of hydroxyzine are given below:

Species or Tissue	Dose or Concentration	Effect	Reference
Dog	3 mg/kg, i.v.	Prolongation of QT interval, Prolongation and depression of ST Segment, Large diphasic T wave	(1)
Isolated cat auricle	1 mg/50 ml (53 uM)	Prolongation of refractory period (100%)	(2)
Perfused dog heart	0.1-1.5 mg/ml (0.267-4 mM)	Bradycardia	(3)
Isolated cat papillary muscle	$0.68-2.7 \times 10^{-5}$ g/ml (20-70 uM)	Decreased contractile force (20-40%) & increased threshold (11-14%).	(4)
Isolated cat auricle	$4.4-8.8 \times 10^{-5}$ g/ml (117-234 uM)	Decreased amplitude (28-89%) and frequency (11-19%) of contraction	
Isolated cat heart (Langendorff method)	125-500 ug	Decreased amplitude of contraction (7-31%) and heart rate (3-17%)	
Anesthetized cat	1.25-20 mg/kg, i.v.	Hypotension (17-61%)	

(1): American Surgeon 26,492-493,1960

(2): Arch. Intern. Pharmacol 141,239-253,1963

(3): J. Thoracic and Cardiovascular Surgery, 8:610-617,1959

(4): JPET. 118,451-460,1956

Cetirizine

In the pharmacology section of NDA (see original NDA review of 4/11/89 by Dr. Jean), hypotension was reported in anesthetized rats given iv. dose of cetirizine (26 mg/kg). In anesthetized dogs, tachycardia, hypertension, lower ST segment and conduction block were observed at iv dose of 14.7 mg/kg. Lowering ST segment and increased T wave were reported at id (intraduodenal) dose of 46 mg/kg. In addition, tachycardia and hypotension were found in dog at higher id dose of 148 mg/kg. In conscious dogs, no effects on EKG pattern were reported at iv doses up to 11.9 mg/kg except tachycardia and hypertension. The above-mentioned effects are summarized below:

Species	Dose (mg/kg)	Heart Rate	Blood Pressure	EKG
Rat anesthetized	14.8 (iv)	NE	NE	
	26 (iv)	NE	-25%	
	46 (iv lethal dose)			
Dog anesthetized	4.6 (iv)	inc	inc	
	14.7 (iv)	inc	inc	lowering ST conduction block
	67.7 (iv lethal dose)			
	14.8 (id)	inc		
	46.1 (id)			lowering ST
	148 (id)	inc	dec	inc T
675 (id lethal dose)				
Dog conscious	1.2 (iv)			
	3.8 (iv)		+10%	
	11.9 (iv)	inc	+10%	

In toxicity studies, EKG and BP were normal in monkeys at oral doses up to 45 mg/kg/day (C_{max} = 32ug/ml; AUC of 134 ug.hr/ml; C_{24h} = 0.6 ug/ml) in the one year oral toxicity study. EKG and BP were normal at oral doses up to 150 mg/kg (C_{24h} = 2.2 ug/ml) in the one month toxicity study.

In dogs, prolongation of QTC in males was observed at 60 mg/kg/day. However, it was

within normal range and not considered biological significant. In females, increase of systolic blood pressure in females was observed at 15 and 60 mg/kg/day. PK data for the study were: 60 mg/kg; C_{max} = 101.5 ug/ml, AUC = 1456 ug.hr/ml, C_{24h} = 38.8 ug/ml and 15 mg/kg/day; C_{max} = 30 ug/ml, AUC = 325 ug.hr/ml. In the 6 month oral toxicity study, no EKG effects were reported at doses up to 75 mg/kg/day.

Thus, based on the preclinical studies in monkeys and dogs, no effect doses on EKG of 150 and 60 mg/kg 24 hours after dosing were established, respectively. At these dose levels, plasma cetirizine concentrations (provided by the sponsor in telephone conference call of 1/31/94) at time of EKG monitoring were 2.2 and 38.8 ug/ml, which are equivalent to 3 and 55 times, respectively, the human exposure at the proposed recommended dose of 20 mg.

Hepatic toxicity in rats and dogs and GI toxicity in dogs (vomiting and reduced food consumption and weight gain but without any histopathological findings) and monkeys (salivation but without any histopathological findings) were reported in toxicity studies. The AUCs at the no effect doses in dogs and monkeys were 8.8 and 1.3 times, respectively, the human AUC at the recommended dose of 20 mg. Observed clinical signs of GI disturbance in the one year dog and monkey toxicity studies were not accompanied by any histopathological findings. Therefore, they would not impose any safety concern for clinical trial of short term. Thus, the doses of 60 and 45 mg/kg/day in both studies would be the tolerated dose in dogs and monkeys, respectively. The AUCs at these doses were 200 and 18 times, respectively, the human AUC at the recommended dose of 20 mg.

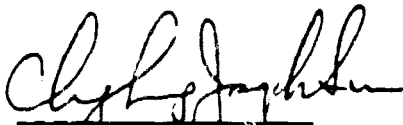
Linearity of PK was demonstrated in humans at oral doses of 20 mg (C_{max} = 0.7 ug, AUC = 7.4 ug.hr/ml) and 60 mg (C_{max} = 2.2 ug/ml, AUC = 22 ug.hr/ml). The T_{max} and T_{1/2} of dogs were more comparable to humans than those of monkeys. Moreover, the C_{max} and AUC were scaled reasonably well between dog and human based on mg/kg and monkey and human based on mg/m² as shown below:

	Human	Dog	Monkey	Dog/human Ratio	Monkey/Human Ratio
AUC					
(ug.hr/ml/mg/kg)	13.5	24.3	2.9	1.31	0.15
(ug.hr/ml/mg/m ²)	0.5	1.21	0.25	2.42	0.5
C _{max}					
(ug/ml/mg/kg)	1.75	1.7	0.7	0.97	0.40
(ug/ml/mg/m ²)	0.05	0.085	0.06	1.70	1.20

RECOMMENDATION:

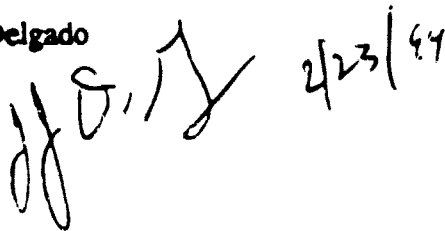
The NDA is approval from a pharmacology perspective.

The estimated safe dose for a 10 day escalating clinical study is up to 55 times the proposed recommended human dose of 20 mg based on the drug plasma levels from the one year toxicity study in dogs at which no effects on EKG (including prolongation of QTc interval) and no other significant toxicities were observed. However, safety of a escalating dose of more than 3 times the recommended human dose of 20 mg based on the drug plasma in monkeys is unknown because no additional plasma data beyond three times the human dose was available in monkeys with concurrent recording of EKG. Peak levels of 40 times the human Cmax were achieved in monkeys but were unaccompanied by EKG assessment.


C. Joseph Sun, Ph. D.

Orig. NDA
HFD-155/Division file
HFD-155/Dr. Sun
HFD-155/Dr. Savedra-Delgado

Feb. 23, 1994

 J.S. 2/23/94

Pharmacologist review of NDA 19835
(Amendment of March 22, 1993)

OCT 18 1993

REVIEWER: C. Joseph Sun, Pharmacologist (HFD-155)

SPONSOR: Pfizer

DRUG: Reactine (Cetirizine)

DRUG CATEGORY: Antihistamine (H₁ receptor antagonist)

Date of review: Oct. 18, 1993

SUBMISSION CONTENTS: The amendment contains the reports of the following studies :
(1) Pharmacological study of two enantiomers (UCB 28556 and 28557) of cetirizine (2) acute toxicity study of two enantiomers, (3) 4 week histopathology study of two enantiomers, (4) mutagenicity study of UCB 28556 and (5) pharmacokinetics study of two enantiomers,

Pharmacological study:

Effect on isolated guinea pig ileum contraction induced by acetylcholine, serotonin, histamine or nicotine: Both enantiomers inhibited histamine-induced contraction in a dose-dependent manner with comparable IC₅₀ values (UCB 28556, 2×10^{-6} M; UCB 28557, 4.7×10^{-6} M) but higher than that of cetirizine (1.7×10^{-6} M). Both enantiomers, like cetirizine, demonstrated a lack of significant activity in blocking contractions induced by acetylcholine, serotonin or nicotine.

Effect of guinea pig trachea contraction induced by histamine: UCB 28556 is a non-competitive inhibitor (IC₅₀ of 3.1×10^{-8} M) as cetirizine (IC₅₀ of 6.2×10^{-8} M). UCB 28557 was a competitive inhibitor.

Effect on Irwin test in mice: UCB 28556 produced no overt behavioral modification at oral dose of 46.1 mg/kg and at intraperitoneal dose of 1.3 mg/kg. UCB 28557 produced no overt behavioral changes at oral dose of 46.1 mg/kg or at ip dose of 13.8 mg/kg. Thus, both enantiomers produced similar behavioral changes at comparable oral doses in mice. UCB 28556 exhibited more behavioral changes than UCB 28557 when given intraperitoneally.

Acute toxicity study

Results of the acute toxicity studies are summarized below:

Species	Route of administration	Compound	LD50	minimal lethal dose	Highest non-lethal dose	Clinical signs
Mouse	p.o.	UCB 28556	804	560	240	(1)
	p.o.	UCB 28557	608	560	200	(2)
	i.v.	UCB 28556	244	270	190	(3)
	i.v.	UCB 28557	187	190	130	(4)
Rat	p.o.	UCB 28556	472	560	240	(5)
	p.o.	UCB 28557	542	240	100	(6)
	i.v.	UCB 28556	52	68	32	(7)
	i.v.	UCB 28557	40	32	22	(8)
Dog	p.o.	UCB 28556	*	*	320	(9)
		UCB 28557	*	*	320	(10)

(1) Ventral lying, quiet behavior, half-closed eyelids, muscular weakness, jerky breathing and dyspnea. Necrotic stomach, congested intestine and necrotic liver.

(2) ventral lying, muscular weakness, half-closed eyelids and jerky breathing. Congested and hemorrhagic stomach and intestine.

(3) dyspnea, tachypnea, jerky breathing, ventral lying, agitation, exophthalmia and spread hind limbs. necrotic tail and blood in urinary bladder.

(4) ventral lying, extension of posterior paws, exophthalmia and dyspnea. Necrotic tail and blood in urinary bladder.

(5) Half-closed eyes, jerky breathing, bradypnea, quiet behavior, ventral lying and muscular weakness. Target organs of toxicity: Stomach and kidney.

(6) Same as (5)

(7) unsteady gait, jumps, dyspnea, jerky breathing, tachypnea, ventral lying, spread hind paws. Necrotic tail.

(8) unsteady gait, jump, dyspnea, jerky breathing, ventral lying. Necrotic tail.

(9) salivation, vomiting and diarrhetic stool.

(10) Same as (9).

*: No higher dosage were tested.

Histopathology study

4 Week Oral Histopathology Study in Rats (Report no. T-44)

Date of the study: Sept. 24, 1993

Testing laboratory: .

Methods: Seven groups of rats (strain was not specified) each consisting of 12 males and 12 females were given by gavage of UCB 28556 or 28557 at dose levels of 0, 25, 75 and 225 mg/kg/day for 4 weeks. Additional 6 males and 6 females were assigned to each of two high dose groups for a recovery period of 4 weeks.

Results:

Liver: enlargement and/or vacuolation of hepatocyte were observed in mid and high dose groups. Localized necrosis was noted in the high dose groups. These changes were observed less frequently in the recovery groups.

Kidney: Some changes (dilation of affected tubules and deposition of fat in the cortical tubules were reported in both compound at high and mid dose levels with higher incidence and severity in the UCB 28556 groups. They were absent in the recovery groups.

In conclusion, both enantiomers produced toxicity profile in liver and kidney with higher incidence in the UCB 28556 group.

4 Week Oral Histopathology Study in dogs (Report no. T-45)

Testing laboratory:

Date of the study: Sept 29, 1992.

Methods: Seven groups of dogs each consisting of 3 males and three females were given UCB 28556 or UCB 28557 by gavage at dose levels of 0, 15, 45 and 135 mg/kg/day for 4 weeks. Dose levels for the UCB 28556 135 mg/kg group were changed to 90 mg/kg/day from day 8.

Results:

Tracheitis and thymus atrophy were seen in the UCB 28556 mid and high dose groups. There was no specific target organ of toxicity with UCB 28557.

Mutagenicity study

Ames test: UCB 28556 at concentrations of 50-5000 ug/plate was tested in Salmonella at typhimurium strains (TA 1535, 1537, 1538, 98 and 100) in the presence or absence of metabolic activation. NO evidence of mutagenicity was seen.

Mouse lymphoma L5178Y TK locus assays: UCB 28556 at concentrations of 50-350 ug/ml in the absence of metabolic activation or 25-350 ug/ml in the presence of metabolic activation did not induce any increase in mutant frequency.

Mouse micronucleus test: UCB 28556 at oral dose of 800 mg/kg did not produce any significant increase in the frequency of micronucleated polychromatic erythrocytes in mice.

Pharmacokinetics study

Rats: Pharmacokinetics parameters collected on day 23 of the 4 week oral study in rats are given below (extracted from sponsor's table on page 674):

Dose	ucb 28556			ucb 28557		
	25 mg/kg	75 mg/kg	225 mg/kg	25 mg/kg	75 mg/kg	225 mg/kg
Male						
Cmax (ug/ml)	17.3	80.8	80.7	2.82	16.0	51.5
Cmax norm (ug/ml)	0.69	1.08	0.36	0.11	0.21	0.23
Tmax (hours)	1.5	1.5	3.0	1.5	1.5	3.0
AUC trap (ug h/ml)	88.8	386.8	1004.6	5.0	90.6	347.5
AUC trap norm	3.55	5.16	4.46	0.20	1.21	1.54
TBC/F (ml/min/kg)	4.7	3.2	3.7	83.3	13.8	10.8
As (% dose)	11.7	27.4	42.7	1.5	20.9	20.9
Renal clear. (ml/min/kg)	0.5	0.9	1.6	1.2	2.9	2.3
Female						
Cmax (ug/ml)	12.4	44.8	127.8	5.33	16.3	29.1
Cmax norm (ug/ml)	0.80	0.80	0.57	0.21	0.22	0.13
Tmax (hours)	1.5	1.5	3	1.5	1.5	1.5
AUC trap (ug h/ml)	40.7	188.9	1010.0	8.9	83.9	204.7
AUC trap norm	1.83	2.88	4.48	0.38	0.88	0.57
TBC/F (ml/min/kg)	10.2	6.3	3.7	48.8	19.0	18.1
As (% dose)	38.1	57.7	58.9	32.6	53.5	50.9
Renal clear. (ml/min/kg)	3.9	3.8	2.2	15.3	10.1	9.3

Both compound were rapidly absorbed. Systemic exposure, based on Cmax and AUC, was much higher for UCB 28556 than for 28557. No relevant concentrations of UCB 28557 (UCB 28556) was measured in urine samples collected from animals dosed with UCB 28556 (UCB 28557). Thus, it was concluded that no evidence of in-vivo inversion occurred for both enantiomers.

Dogs: UCB 28556 and 28557 were measured in plasma following a single oral administration at doses of 32, 100 and 320 mg/kg. Samples were collected 0.5-48 hours post dosing. The results are summarized below:

	UCB 28556			UCB 28557		
	32	100	320	32	100	320 mg/kg
Cmax (ug/ml)	69	50	126	48	118	79
Tmax (hr)	1	2	2	1	4	2
AUC ₀₋₄₈ (ug.hr/ml)	830	968	2613	773	2732	1720

Overall, the PK parameters indicated that both compounds were fairly absorbed with no gender difference. Emesis could be attributable to the non-linear relationship in the UCB 28557 groups.

Pregnant rabbits: UCB 28566 was measured in plasma on day 6 and day 18 of pregnancy following repeated oral (gavage) administration of UCB 28566 at doses of 23, 45 and 90 mg/kg in the pregnant rabbits. Urine samples were collected on day 15 of pregnancy. Plasma pharmacokinetics data are given below (extracted from sponsor's table on p 818):

	23 mg/kg		45 mg/kg		90 mg/kg	
	Day 1	Day 13	Day 1	Day 13	Day 1	Day 13
Cmax (ug/ml)	10.4	23.1	41.9	50.9	81.6	89.6
Tmax (hours)	0.75	0.75	0.75	0.75	1.5	0.75
AUC 0-24h (ug*hr/ml)	39.5	48.1	126.6	115.8	462.3	496.3
TBC* (ml/min/kg)		8.0		6.5		3.0
T1/2 (h)	1.4		0.7		(1.7)	
Peak/Arcugn	200	>200	182	255	69	27

UCB 28556 was fairly absorbed with little drug accumulation. Elimination was rapid with T1/2 being 1.7 hr. A large fraction of the dose (44-59%) was secreted unchanged in the urine. There was no significant in vivo inversion of UCB 28556 based from chiral urinary analysis.

SUMMARY AND EVALUATION:

The two enantiomers did not demonstrate better antihistaminic efficacy than cetirizine based on two in vivo pharmacodynamic models in animals. Extent of general behavioral effects produced by two enantiomers was comparable to that by cetirizine following oral administration (see original NDA review of 4/11/89 by Dr. Jean). Similarly, in acute toxicity studies in mice, rats and dogs, both compounds did not exhibit different LD50s than that of cetirizine (see original NDA review of 4/11/89). In the 4 week histopathology study in rats, both enantiomers produced hepatotoxicity similar to that produced by cetirizine at 75 mg/kg (see original NDA 19835 review of 4/11/89). However, an additional renal toxicity was reported at 75 mg/kg and 225 mg/kg UCB 28556 groups and 225 mg/kg UCB 28557 group. In the 4 week histopathology study in dogs, thymic atrophy and tracheitis were observed in the UCB 28556 45 mg/kg and 135 (90) mg UCB 28556 groups and hepatocyte vacuolation was found in UCB 28556 135 (90) mg/kg group. In the 4 week oral toxicity study of cetirizine in dogs (see original NDA review of 4/11/89), no specific target organ of toxicity was identified at doses up to 135 mg/kg. Therefore, neither of both enantiomers show any distinct advantages over that of cetirizine in terms of their efficacy or toxicity.

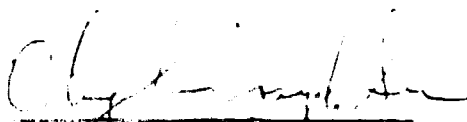
Pharmacokinetics data indicated that there was no significant in vivo inversions of UCB 28556 and UCB 28557 in rats and UCB 28556 in rabbits.

UCB 28556, like cetirizine, did not produce mutagenicity in Ames test, chromosomal aberrations assay, mouse lymphoma assay and in vivo micronucleus test in mouse.

Previous submission of May 22, 1989 also demonstrated that cetirizine and its two enantiomers appeared to have similar antihistaminic action and acute toxicity (see review of 2/9/90 by Churi).

In conclusion, based on the submitted data no clear advantage of either of two enantiomers over that of cetirizine was demonstrated to warrant further development for any of the enantiomers.

RECOMMENDATION: NAI.



C. Joseph Sun, Ph. D.

Oct 18, 1993

Orig. NDA
HFD-155/Division file
HFD-155/Dr. Sun

ASJ 10-18-93

PHARMACOLOGISTS REVIEW COVERSHEET

4/11/89

NDA 19-835
APPLICANT: Pfizer Pharmaceuticals, New York, NY 10017
DRUG: Cetirizine
CATEGORY: antihistamine/antiallergic agent
EVALUATION: Dou Huey Jean

The submission generally consistent with Agency's format guidelines:
Yes (X) No ()

Appropriate studies submitted:
Yes (X) NO ()

Primary adverse pharmacological effects:
None apparent; less sedating than hydroxyzine.

Target organ in toxicity studies:
(1) None in beagle dogs and cynomolgus monkeys.
(2) Liver: hypertrophy, vacuolation and fat deposition in mice and rats. Male rodents were more sensitive. The adverse liver effects may be due to greater extent of metabolism and the extension of this metabolic effects.

Reproductive or development toxicity:
Yes (X) No (). If yes, explain briefly:

- (1) Embryocidal effect in rats (225 mg/kg), but not in mice or rabbits.
- (2) Male and/or female mating performance affected at 64 mg/kg in mice.
- (3) Lactating/nursing performance affected at 96 mg/kg in mice.

Carcinogenicity studies: Rat (X) Mouse (X) Other ().

Results: + - or +
Site of tumors: -
(1) Liver: benign liver tumors in male mice at 16 mg/kg.
(2) Thyroid: follicular adenoma in male rats at 20 mg/kg.

Subchronic/chronic blood level studies:
Rat (X) Dog (X) Other ().

GLP problems:
Yes () No (X).

Other comments:
Adverse liver effects appeared to be species specific (in rodents only). The occurrence at low dosage levels, however, indicated that clinical data should be appraised for liver enzyme profile.

NDA 19-835
Pfizer Pharmaceuticals
New York, NY 10017

DEC 7 1992
Review # 1

Date of Submission: June 30, 1988

Date of Review: April 11, 1989

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Initial Submission of June 30, 1988
Original Summary

Drug:

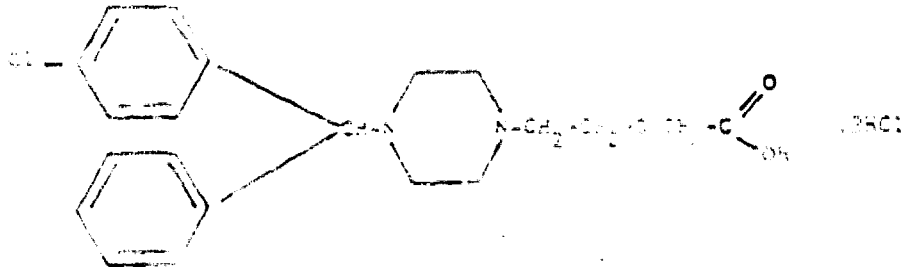
Trade name: Not established

Code name: UCBP071

Generic name: cetirizine HCl

Chemical name, empirical formula, molecular weight and structure:

2-[2-[4-[(4-chlorophenyl) phenylmethyl]-1-piperazinyl] ethoxy] acetic acid, dihydrochloride.



Molecular Formula: $C_{21}H_{29}N_2O_3Cl \cdot 2HCl$

Molecular Weight: 461.8

Dosage form: Tablets at 5, 10 and 20 mg strengths
Category: Antihistamine

Proposed indication:

Seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria.

Proposed dosage:

The recommended daily dose is 5 to 10 mg given as a single dose with or without food. If sufficient response is not obtained, the maximum daily dose is 20 mg.

Compositions:

Components	mg/tablet	
	5 mg	10 mg
Cetirizine Dihydrochloride Pharmaceutical Grade	5.00	10.00

(1) Solids contain hydroxypropyl methylcellulose 2910, USP, polyethylene glycol 3350, NF, and titanium dioxide, USP.

Related drugs/INDs/NDAs/MFs:

IND

NDA 10-392: hydroxyzine HCl

Pertinent memos/correspondence:

End of phase II meeting: IND of June 16, 1986

Preliminary studies and testing laboratories:

(1) UCB Pharmaceutical, Brussels, Belgium

NDA 19835

9 OF 11

From page 4-15, summary tables are copied from NDA submission.
The tables included brief summaries of studies and principal findings.

- I. PHARMACOLOGY STUDIES (p. 4-6)
- II. TOXICOLOGY STUDIES (p. 7-9)
 - (A) ACUTE TOXICITY STUDIES (P. 7)
 - (B) SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY STUDIES (p. 7-9)
 - (C) CARCINOGENICITY STUDIES (p. 10)
 - (D) REPRODUCTION STUDIES (p. 10-11)
 - (E) GENETIC TOXICOLOGY STUDIES (p. 11)
- III. ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION STUDIES (p. 12-15)

From page 16 to 88, the summaries of I-III were prepared by this reviewer from individual study reports.

- I. PHARMACOLOGY STUDIES (p. 16-22)
- II. TOXICOLOGY STUDIES (p. 23-88)
 - (A) ACUTE TOXICITY STUDIES (P.24)
 - (B) SUPACUTE/SUBCHRONIC/CHRONIC TOXICITY STUDIES (p.25-60)
 - (C) CARCINOGENICITY STUDIES (p.61-67)
 - (D) REPRODUCTION STUDIES (p.68-87)
 - (E) GENETIC TOXICOLOGY STUDIES (p.88)
- III. ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION (p.89-100) copied from NDA submission.

I. PHARMACOLOGY STUDIES:

**Ceftazidime IMB
Phase 2a and Phase 2b
Pre-clinical
Toxicology Data**

Table 1. Antimicrobial Activity in Mice

Study No.	Animal Species/Strain	Study Design	Number of Animals	Treatment Dose (mg/kg)	Route of Administration	Time of Testing After Last Dose	Results
1. General Antimicrobial Activity							
MP-2	Sprague-Dawley Rat Male	Assessment of MIC50-induced lethality	50 per group	Ceftazidime: 0.01, 0.10, 1.0 mg/kg Hydrocortisone: 0.01, 0.1, 1.0 mg/kg Placebo	p.o. i.v. i.p.	2 hrs	Ceftazidime induced MIC50-induced lethality at rates ED 50 = 0.010-0.10 mg/kg and was more potent than hydrocortisone ED 50 (rate than 0 mg/kg)
MP-7	Murphy Guinea Pig/ Male/6 weeks	Assessment of bacteremia-induced lethality	8 MP per group	Ceftazidime: 0.01-0.12 mg/kg Placebo	p.o./i.v.	1-16 hrs	Ceftazidime protected guinea pigs from bacteremia-induced lethality at bacteremia ED 50 = 0.1 mg/kg. Ceftazidime 0.1 mg/kg p.o. protected all animals for 12 hours and 50% for a 24 hour period.
MP-3	Guinea Pig/ Male	Assessment of bacteremia-induced lethality	10A	Ceftazidime: 0.1 mg/kg Hydrocortisone: 0.1 mg/kg	i.v./i.p./i.o.	1 hr	Guinea pigs treated with ceftazidime 0.1 mg/kg either i.v. or p.o. were protected from 100 and 100 times the lethal dose of bacteremia, respectively.
2. Protection Against Amphotericin B Infection							
MP-4	Sprague-Dawley Rat Male	Protection against amphotericin B-induced bronchopneumonia	120	Ceftazidime: 0.01-100 mg/kg Hydrocortisone: 0.1-100 mg/kg Chlorthalidone: 0.1-100 mg/kg Methoxypropyl-beta-D-glucopyranoside (MOP-β-D-Glc) Placebo	i.v./i.p.	Immediate	Ceftazidime demonstrated some efficacy in blocking antigen-induced bronchopneumonia primarily a corticosteroid-induced effect but the ED 50 (0.1-100 mg/kg) could not be determined.
MP-5	Murphy Guinea Pig/ Male	Protection against antigen-induced bronchopneumonia	120	Ceftazidime: 0.01-1.00 mg/kg Hydrocortisone: 0.01-0.20 mg/kg Chlorthalidone: 0.01-0.10 mg/kg Terfenadine: 0.15-0.75 mg/kg Hydroxyzine: 0.200-2.00 mg/kg Placebo	p.o./i.v.	1 Hour	Ceftazidime (ED 50 = 0.1 mg/kg) significantly inhibited antigen-induced bronchopneumonia in the guinea pig. Activity was similar to hydrocortisone (ED 50 = 0.1 mg/kg), superior to chlorthalidone and terfenadine (ED 50 = 0.5 mg/kg for both) and less potent than hydroxyzine (ED 50 = 0.02 mg/kg).

a All doses are expressed as normally unless otherwise specified.
b All studies were sponsored by GCB with the exception of MP-2 which was a Pfizer sponsored study.
c Study - Single dose
10A - Substitution not available in report.

NDA Report No.	Animal Species	Study Design	Number of Animals	Treatment (Dose [mg/kg])	Route of Administration/Division of Treatment	Time of Testing After Last Dose	Results
NP-6	Harley Guinea Pig Males, Female	Protection against antigen-induced bronchospasm	5 per group	Cetirizine (0.24-100) Mepyramine (0-100) Chloramine (0-100) Placebo	p.o./i.v.	1 Hour	Cetirizine significantly protected guinea pigs from antigen (guinea by aerosol induced bronchospasm and was more potent than chloramine and mepyramine.
NP-7	Harley Guinea Pig Males, Female	Protection against histamine, acetylcholine, serotonin induced by group	5 per group	Cetirizine (0.01-100) Chloramine (0.01, 0.2) Mepyramine (0.01-100) Terfenadine (0.01-100) Placebo	i.v./i.v.	2 Hours	Cetirizine significantly inhibited histamine-induced bronchospasm (ED 50 = 0.2 mg/kg) in guinea pigs. Cetirizine had some effect (ED 50 = 7.1 mg/kg) on serotonin-induced bronchospasm and no effect (ED 50 greater than 100 mg/kg) on acetylcholine-induced bronchospasm.
3. Effect on Histamine/Allergen Induced Cutaneous Reactions							
NP-8	M888 Mice/ female	Protection against histamine induced cutaneous reactions	7-12 per group	Cetirizine (0.010-1) Hydroxyzine (0.1-10) Placebo	p.o./i.v.	2 Hours	Cetirizine significantly inhibited histamine-induced cutaneous reactions in mice (ED 50 = 0.066 mg/kg; 0.19 mg/kg) and was 30 times more potent than hydroxyzine.
NP-9	Sprague-Dawley Rat/ Female	Protection against histamine and serotonin induced cutaneous reactions	5 per group	Cetirizine (N/A) Mepyramine Chloramine Placebo	p.o./i.v. and i.v.	Immediate (i.v.) 15 min (p.o.)	Cetirizine significantly blocked histamine induced cutaneous reaction in rats following p.o. (ED 50 = 0.2 mg/kg) and i.v. (ED 50 = 1.1 mg/kg) administration and was 2.5 and 30 times less potent against serotonin induced cutaneous reactions following oral and i.v. administration, respectively.
NP-10	Harley Guinea Pig/ Males, Female	Protection against histamine induced cutaneous reactions	5 per group	Cetirizine (N/A) Mepyramine Chloramine Hydroxyzine Terfenadine Placebo	i.v./i.v. and p.o.	1 Hour	Cetirizine effectively inhibited histamine-induced cutaneous reactions in guinea pigs after p.o. (ED 50 = 0.6 mg/kg) and i.v. (ED 50 = 0.18 mg/kg) administration.
NP-11	Beagle Dog/ Female	Histamine and Acetate induced cutaneous reactions	N/A	Cetirizine (0.01, 0.1, 0.2 mg/kg) Atracurium (0.25) Chloramine (0.25) Hydroxyzine (0.25) Terfenadine (0.25)	p.o./i.v.	0.5-20 Hrs	In dogs, cetirizine demonstrated significant suppression of histamine and Acetate induced skin reactions. The duration of activity following 0.1 and 1.0 mg/kg was 0.5 and 20 hours, respectively.

*L50 - Intradermally.
N/A - Information not available in report.

Table 1. Activity (continued)

NDA Report No.	Animal Species/No.	Study Design	Number of Animals	Treatment/Dose (mg/kg)	Route of Administration	Time of Testing After Last Dose	Results
NP-11	Dog/	Metaraminol, Aorta, DPT, Heart Dose 1-hour continuous reactions	7	Cetizine 0.12 Cetizine 0.127 mg/kg	i.v./acute	6-70 hrs	Cetizine (0.127 mg/kg) significantly inhibited histamine, Aorta and heart dose induced continuous reactions in dogs at 6 hours post dose.
NP-13	Sham Monkey/70, 17	Metaraminol, M/BB, Substance P, VIP induced continuous reactions	8	Cetizine 10 mg/kg Clemastine 100 mg/kg Cetizine 10 mg/kg + Clemastine 100 mg/kg	i.v./acute	2 hrs	Cetizine significantly inhibited continuous reactions induced by histamine, M/BB, substance P, and VIP in dogs, whereas clemastine was weakly effective. Cetizine plus clemastine was less active than cetizine alone.
NP-16	Monkey Dog/64, 18	Effects on Metaraminol and Serotonin induced changes in Blood Pressure	5	Cetizine 1.12-1.17 mg/kg Hydroxyzine 0.32-1.1 mg/kg Dipyrone 0.1-1.8 mg/kg	i.v./acute, cumulative doses	5, 10 Mins	Cetizine had a significant effect on metaraminol induced hypertension but had no effect on serotonin induced hypertension.

2. Effects on Metaraminol - Induced Blood Pressure Changes

**II. TOXICOLOGY STUDIES:
ACUTE/SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY STUDIES:**

ITEM 2: APPLICATION SUMMARY
V. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY SUMMARY
B. NONCLINICAL TOXICOLOGY

Table 1. Principal Findings

NIH Report No.	Type of Study	Species	Duration	Single Dose	Route of Administration	Dose Levels mg/kg/day	Principal Findings
T-1	Acute	Mouse Rat, Dog			PO, IV		Oral LD ₅₀ values about 700 mg/kg in mice, and 800 mg/kg in rats. Max. non-lethal oral dose in dogs was 320 mg/kg. I.V. LD ₅₀ values about 300 mg/kg in mice, and 70 mg/kg in rats. Max. non-lethal I.V. dose in dogs was 70 mg/kg. Clinical signs were CNS-related.
T-2	Subchronic	Mouse	13 Day		Oral (Diet/Gavage)	0, 5, 10, 20, 40, 80, 160	Increased liver weights and hepatic hypertrophy induced by both routes of administration. Hepatic steatosis at 160 mg/kg by gavage dosing; NOEL = 89 mg/kg (gavage); greater than 24 (male) and 37 (female) mg/kg (diet).
T-3	Subchronic	Mouse	9 Week		Oral (Diet)	0, 1, 3, 9, 27, 81	Hepatic changes in males only: Pharmacologic (increased liver weights; hypertrophy, and microsomal enzyme induction) Toxicologic (steatosis and serum enzyme modifications) - NOEL = 9 mg/kg Elevated serum triglyceride levels (81 mg/kg and microsomal enzyme induction (9 mg/kg and higher) in female mice.
T-4 T-5	Subchronic Electron Microscopy - Addendum to NDA Report T-4	Mouse	Week		Oral (Diet)	0, 40, 160	Additional hepatic changes included elevated hepatic cholesterol, triglyceride and total lipid, and SER proliferation. Reversibility of all retinitis-induced hepatic changes at both dose levels after 13 weeks of recovery.

ITEM 2: APPLICATION SUMMARY

V. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY SUMMARY
B. NONCLINICAL TOXICOLOGY

Table 1. Principal Findings (Cont'd)

NDA Report No.	Type of Study	Species	Duration	Route of Administration	Dose Levels mg/kg/day	Principal Findings
T-6	Subchronic	Rat	28 Day	Oral (Diet/Gavage)	0, 5, 10, 20, 40, 80, 160	Hepatic changes (increased liver weights; hypertrophy, and steatosis) induced by both routes of administration. NOEL for hepatic steatosis was 80 mg/kg in male and 20 mg/kg in female rats by gavage dosing and 25 mg/kg in male and 11 mg/kg in female rats by diet dosing.
T-7 T-8	Subchronic Liver Histopathology Review - Addendum to NDA Report T-7	Rat	1 Month	Oral (Gavage)	0, 25, 75, 225	Hepatic changes (increased liver weights; hypertrophy, and steatosis) at 75 and 225 mg/kg were more pronounced in male rats. NOEL for hepatic steatosis was 25 mg/kg for male and 75 mg/kg for female rats.
T-9	Subchronic	Rat	4 Week	Oral (Diet)	0, 2, 6, 18, 54, 160	Hepatic changes (increased liver weights; hypertrophy; steatosis, and microsomal enzyme induction) were more pronounced in male rats. NOEL=18 mg/kg.
T-10 T-11	Subchronic Electron Microscopy - Addendum to NDA Report T-10	Rat	4 Week	Oral (Diet)	0, 40, 160	Additional hepatic changes included elevated hepatic cholesterol, triglyceride and total lipids, and SER proliferation. Reversibility of all cetirizine-induced hepatic changes at both dose levels after 4 and 13 weeks of recovery.
T-12 T-13	Subchronic Electron Microscopy - Addendum to NDA Report T-12	Rat	6 Month	Oral (Gavage)	0, 5, 25, 75	Dose-related incidence of hepatic changes (increased liver weights; hypertrophy, and steatosis). SER proliferation at 75 mg/kg (only level examined). NOEL for hepatotoxicity was 8 mg/kg.

ITEM 2: APPLICATION SUMMARY

V. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY SUMMARY

B. NONCLINICAL TOXICOLOGY

Table 1. Principal Findings (Cont'd)

NDA Report No.	Type of Study	Species	Duration	Route of Administration	Dose Levels mg/kg/day	Principal Findings
T-10	Subchronic	Dog	1 Month	Oral (Capsule)	0, 15, 45, 135	At 135 mg/kg: toxic clinical signs; body weight losses and reduced food intake in two females not associated with any other changes. NOEL=45 mg/kg.
T-13	Subchronic	Dog	6 Month	Oral (Capsule)	0, 8, 25, 75	No target organ toxicity. At 25 and 75 mg/kg: increased incidence of vomiting; decreased body weight gains in females; one male dog died and a second male dog sacrificed. NOEL=8 mg/kg.
T-16	Subchronic-Pilot	Monkey	14 Day	Oral (Gavage)	50, 100, 200	At 50 and 100 mg/kg: vomiting/salivation and body weight losses. At 200 mg/kg: toxic clinical signs and marked body weight losses. NOEL less than 50 mg/kg.
T-17	Subchronic	Monkey	4 Week	Oral (Gavage)	0, 17, 50, 150	At 50 and 150 mg/kg: toxic clinical signs and marked body weight losses not associated with any other changes. One debilitated female at 150 mg/kg was sacrificed moribund due to marked reduction in food intake and body weight loss. NOEL=17 mg/kg.
T-18	Chronic	Dog	1 Year	Oral (Capsule)	0, 4, 15, 60	No target organ toxicity. Cetirizine induced a dose-related incidence of vomiting. NOEL=60 mg/kg.
T-19	Chronic	Monkey	1 Year	Oral (Gavage)	0, 5, 15, 45	No target organ toxicity. Cetirizine induced a dose-related incidence of salivation. NOEL=45 mg/kg.

CARCINOGENICITY, REPRODUCTION AND GENETIC TOXICOLOGY STUDIES:

ITEM 2: APPLICATION SUMMARY

V. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY SUMMARY
B. NONCLINICAL TOXICOLOGY

Table 1. Principal Findings (Cont'd)

<u>NDA Report No.</u>	<u>Type of Study</u>	<u>Species</u>	<u>Duration</u>	<u>Route of Administration</u>	<u>Dose Levels mg/kg/day</u>	<u>Principal Findings</u>
T-20	Carcinogenicity	Mouse	2 Year	Oral (Diet)	0, 0, 1, 4, 16	Not carcinogenic. Increased incidence of spontaneously occurring benign liver cell tumors only in males at 16 mg/kg.
T-21	Carcinogenicity	Rat	2 Year	Oral (Diet)	0, 0, 3, 8, 20	Not carcinogenic.
T-22	Segment I	Mouse	Males: 8 weeks prior to mating, through mating, gestation and lactation. Females: 2 weeks prior to mating, through mating to termination either on day 17.5 of gestation or day 21 post partum.	Oral	0, 4, 16, 64	At 64 mg/kg: decreased maternal body weight gain; slightly lower pregnancy rate; lower fetal and litter weights; lower total litter size at birth, and delayed skeletal development and associated commonly occurring malformations. NOEL=16 mg/kg.
T-23	Segment II	Mouse	Days 6 to 15 of gestation	Oral	0, 6, 24, 96	Cetirizine was not teratogenic. Maternal and embryo-feto toxicity at 96 mg/kg. NOEL: 24 mg/kg.
T-24	Segment II	Rat	Days 6 to 15 of gestation	Oral	0, 8, 25, 75, 225	Cetirizine was not teratogenic. Maternal toxicity at 75 mg/kg and higher; embryo-feto toxicity at 25 mg/kg and higher. NOEL=8 mg/kg.

ITEM 2: APPLICATION SUMMARY

V. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY SUMMARY

B. NONCLINICAL TOXICOLOGY

Table 1. Principal Findings (Cont'd)

NDA Report No.	Type of Study	Species	Duration	Route of Administration	Dose Levels mg/kg/day	Principal Findings
T-25	Segment II	Rabbit	Days 6 to 18 of gestation	Oral	0, 15, 45, 135	Cetirizine was not teratogenic. Maternal and embryo-feto toxicity at 45 mg/kg and higher. NOEL=15 mg/kg.
T-26	Segment III	Mouse	Day 15 of gestation throughout lactation	Oral	0, 6, 24, 96	At 96 mg/kg: reduced maternal body weight gains and lower pup weights throughout lactation. NOEL=24 mg/kg.
T-27	Historical Data	Rat	-	-	-	-
T-28	Historical Data	Rat	-	-	-	-
T-29	Genetic	AMES Test			8-5000 mcg/plate	No mutagenic activity.
T-30	Genetic	Chromosomal Aberrations Assay - Human Peripheral Lymphocytes			20, 100, 500 mcg/ml	No mutagenic activity.
T-31	Genetic	Mouse Lymphoma TK Locus Assay			100-660 mcg/ml	No mutagenic activity.
T-32	Genetic	Micronucleus Test-Mouse			14, 70, 350 mg/kg/day	No mutagenic activity.

¹ NOEL-No Effect Level

III. ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION STUDIES:

NDA 19-835
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CETIRIZINE NDA

ATTACHMENT A. ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION (ADME) STUDY SUMMARY

NDA Report No.	Type of Study	Species	Duration	Route of Administration	Dose Levels	Principal Findings
NPK-1	PK	Mouse	Single Dose	IV, Oral	10 mg/kg	Rapid and extensive absorption, urinary excretion of cetirizine = 34% of dose.
NPK-2	Disposition	Mouse	Single Dose	IV, Oral	10 mg/kg	Males metabolized more cetirizine than females. One metabolite is PO26.
NPK-3	PK	Mouse Rat	14 Days 14 Days	Oral (Diet) Oral (Diet)	3, 9, 27 mg/kg/day 6, 18, 54 mg/kg/day	Oral cetirizine well absorbed in mice and rats; saturation of metabolism in rats.
NPK-4	Monitoring	Mouse	4 Week	Oral (Diet)	1, 3, 9, 27, 81 mg/kg/day	Non-linear urinary excretion of drug.
NPK-5	PK	Rat	Single Dose	IV, Oral	10 mg/kg	Rapid absorption, extensive metabolism, greater in male rat than female.
NPK-6	Disposition	Rat	Single Dose	IV, Oral	1, 3, 25, 75 mg/kg	Non-linear pharmacokinetics, male rats metabolize drug more extensively than females.
NPK-7	Antipyrine Elimination	Rat	7 Days	Oral	75 mg/kg/day	Antipyrine metabolism increased with cetirizine treatment.
NPK-8	PK	Rat	Single Dose	Oral	1, 10, 100 mg/kg	Extensive oral absorption, excretion mainly in bile, metabolism is a saturable process.

CETIRIZINE NDA

ATTACHMENT A. ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION (ADME) STUDY SUMMARY

NDA Report No.	Type of Study	Species	Duration	Route of Administration	Dose Levels	Principal Findings
NPK-9	Monitoring	Rat	1 Month	Oral	25, 75, 225 mg/kg	Male metabolize drug to a greater extent than females. Non-linear pharmacokinetics.
NPK-10	Excretion	Rat	28 Days	Oral (Net)	2, 6, 18, 54, 160 mg/kg/day	Females excreted more unchanged drug than males.
NPK-11	Monitoring	Rat	6 Months	Oral	8, 25, 75 mg/kg/day	Non-linear kinetics, males metabolize drug more extensively than females.
NPK-12	PK	Rabbit	Single Dose	IV, Oral	1, 15, 45, 135 mg/kg	Linear dose response. Extensive and rapid distribution into tissues.
NPK-13	PK	Dog	Single Dose	IV, Oral	1, 10 mg/kg	No sex-related differences in kinetics, rapid and extensive absorption, half-life 8-10 hours.
NPK-14	Disposition	Dog	Single Dose 9 Days	Oral (Net)	0.64 mg/kg/day	Rapid and extensive absorption and tissue distribution. No sex-related difference in kinetics; steady-state reached in 4 days.
NPK-15	Metabolism	Dog	Single Dose	Oral	10 mg/kg	Rapid and extensive absorption, low first-pass metabolism. About 30% of drug metabolized.
NPK-16	Excretion	Dog	Single Dose	IV	10 mg/kg	3.2% of dose excreted into milk.
NPK-17	Monitoring	Dog	1 Month	Oral	15, 45, 135 mg/kg/day	Linear dose response (trough values) at entire dose range. Up to 32% of drug excreted unchanged in urine. Small amounts of P ₀ Z ₆ found, mainly in bile.

CETIRIZINE NDA

ATTACHMENT A. ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION (ADME) STUDY SUMMARY

NDA Report No.	Type of Study	Species	Duration	Route of Administration	Dose Levels	Principal Findings
NPK-18	Monitoring	Dog	6 Month	Oral	8, 25, 75 mg/kg/day	Linear dose response, steady-state reached by day 9. Up to 45% of daily dose excreted in urine as unchanged drug. PO26 minor component in plasma and urine.
NPK-19	Monitoring	Dog	52 Week	Oral	4, 15, 60 mg/kg/day	No sex-related differences in kinetics, dose-proportionality.
NPK-20	PK	Baboon	Single Dose	IV, Oral	1, 10 mg/kg	Rapid absorption, C _{max} and AUC linearly proportional to dose. No sex-related differences in kinetics.
NPK-21	PK	Monkey	Single Dose	IV, Oral	1, 10 mg/kg	Rapid absorption, C _{max} and AUC linearly proportional to dose. No sex-related differences in kinetics.
NPK-22	Monitoring	Monkey	34 Day	Oral	50, 100, 200 mg/kg/day	No consistent pattern to data.
NPK-23	Monitoring	Monkey	28 Day	Oral	17, 50, 150 mg/kg/day	Concentrations linearly proportional to dose. Excretion mainly via bile.
NPK-24	Monitoring	Monkey	52 Week	Oral	5, 15, 45 mg/kg/day	Concentrations linearly proportional to dose. No sex related differences in kinetics.
NPK-25 2	Assay Development	-	-	-	-	GLC assay in plasma, detection range 4-12 mcg/ml.

CETIRIZINE NDA

ATTACHMENT A. ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION (ADME) STUDY SUMMARY

NDA Report No.	Type of Study	Species	Duration	Route of Administration	Dose Levels	Principal Findings
NPK-26	Assay Development	-	-	-	-	GLC assay in urine, detection range 10 to 300 mcg/ml.
NPK-27	Assay Development	-	-	-	-	HPLC assay in urine, detection range 5 to 75 mcg/ml.
NPK-28	Stability	Human	Greater than or equal to 1 year	-	10, 20, 400, 800 mg/ml	Plasma and urine samples spiked with cetirizine stable for at least 1 year.

1. PHARMACOLOGY:

Primary activity: as an antihistamine or H1 receptor antagonist.

(A) In vivo studies: (Note: the ED₅₀ values on pages 2 38-2 39 are different from those listed under individual studies, e.g. NP-2, NP-4, NP-8, NP-10 on pages 5 31-5 139. The following summary is based on the results from individual studies. The applicant is to be requested to clarify the discrepancies)

Test/animal model	ED ₅₀ mg/kg	Dose mg/kg	Duration/remarks
(1) Lethality by (a) histamine guinea pig	0.35 (po)	0.1 (po)	protection: 100%-12 hrs 80%-24 hrs
		2.5 (iv)	800X LD ₅₀ hist
		2.5 (po-1hr)	400X LD ₅₀
		hydroxyzine:2.5 (iv)	800X LD ₅₀
(b) Compound 48/80: rat		1.4 (po)	80% protection
		hydroxyzine:44 (po)	40% "
(2) Bronchoconstriction by (a) Passive-immun. guinea pig	0.3(po)		
	0.3(po):hydroxyzine		
	0.8(po):terfenadine & clemastine		
	0.02(po):mepyramine		
rat	4.6(iv)		
	9.2(iv):mepyramine		
	1.4(iv):hydroxyzine		
	NE:clemastine		
guinea pig			some protection at cetirizine:4.6 mg/kg(po) mepyramine:46 mg/kg (po) clemastine:46 mg/kg (po)
(b) guinea pig histamine	0.09 mg/kg(iv)		iv: clemastine & mepyr- amine better than cetir.
	0.46 mg/kg(po)		po: 3 drugs comparable

(continued)

(continued)

Test/model	ED ₅₀	Dose	Remarks
serotonin Ach	3.4 mg/kg(iv) greater than 46 mg/kg (iv)		
(3) Cutaneous Rnx by (a) histamine mice	0.546 (po) 0.76 (po): hydroxyzine		
rat	1.9 (po) 0.49(iv)		po & iv: cetir-z. duration 6 hrs & better than clemastine & mepyramine.
guinea pig	0.8 (iv) 1.8 (po)		better than terfenadine, mepyramine, hydroxyzine; less than clemastine. cetirz best of the five.
dog		1 (po)	75% inh. 4-24 hrs, better than terfenadine, astemizole, clemastine. = hydroxyzine.
monkey(Rhesus)		10 (po)	76% inh. @ 2 hrs.
(b) Ascaris dog		1 (po) 0.15 (iv)	same as antihistamine 50% inh. 4-24 hrs.
(c) 48/80, VIP Substance P monkey		10 (po)	60-80% inh. @ 2 hrs
(4) Hypotension by histamine dog		0.12-1.19(iv)	reversed
serotonin dog		0.12-1.19(iv)	NE

(B) In vitro studies: (Vol 2.4)

Species	Tissue	Results (EC ₅₀ umol/l)
(1) Guinea pig	ileum	
(2) Guinea pig	Trachea	<u>histamine:</u> cetirz: 2 (or 9 ug/ml) hydroxz: 3 clemast: 10 mepyram: 0.05 <u>carbachol:</u> cetirz: 320-1000
(3) Human	bronchl	0.9 (or 0.4 ug/ml)
(4) Guinea pig	atrium	NE (100 ug/ml) (H ₂ receptor act.)
(5) Human	basophils	470 (or 217 ug/ml) (inhibition of histm-release)

Neuropharmacology:

Behavior studies:

Species	Test	Results
Mouse	Irwin (general behaviors)	46 mg/kg (ip): NE 92 mg/kg (ip): sedation 138 mg/kg (ip): lethal 462 mg/kg (po): stimulation 1384 mg/kg (po): lethal
Rat	Irwin	46 mg/kg (ip): NE 92 mg/kg (ip): dec act. & mus tone lethal 138 mg/kg (po): NE 462 mg/kg (po): LD50 hydroxyzine: 90 mg/kg (ip): convulsion
Rat	exploratory act in new environment	4.6 mg/kg (ip): NE 15 mg/kg (ip): hypoactivity 15-46 mg/kg (po): NE
Rat	retention of learning in passive avoidance test	15 mg/kg (po): NE
Dog	conditioning response	45 mg/kg: NE on selective atten. percept-motor coordination

Other neuropharmacological effects:

Activity	Species	Drug-ind	Effects	Dose(mg/kg)	Effects
(1) Anticonvulsant (NP-33)	mice	pentylentetrazol	seizure	15-46(ip)	NE
(NP-34)	mice	audiogenic	seizure	46 (ip)	NE 45-46 (ip):hydroxy- zine & clemastine protected.
(2) Neuroleptic (NP-35)	mice	apomorphine	climbing	15-46(ip)	inhibit
(NP-37)	rats	amphetamine	stereotype	46 (ip)	NE
(3) Interactions pentob (NP-32)	mice	pentobarbital	right-reflex	46(po,ip)	potent.
alcohol(NP-38)	rats	alcohol	open field	15 (po)	NE
(4) Ataxia (NP-36)	rats		Rotat-rod	45(ip)	NE
(5) EEG (NP-39)	rabbits		duration-arousal recording	1.5-46(iv)	dec.
			duration-sleep recording	1.5-46(iv)	inc.
			arousal rnx to sound	1.5-46(iv)	NE

Cardiovascular effects
in vivo studies:

Species		Dose (mg/kg)	HR	BP	Others
Rat	anesthetized	14.8 (iv) 26 (iv) 46 (iv)	NE NE lethal	NE -25%	
Dog	anesthetized (chloralose)	4.6 (iv) 14.8 (id) 46.1 (id) 67.7 (iv)cumul: 675 (id)cumul:	inc inc inc lethal lethal	inc. slig. dec	ECG/resp dep
Dog	conscious	1.2 (iv) 3.8 (iv) 11.9 (iv)	minor inc slig	minor +10% (dias) +10% (dias)	
Dog	anesthetized	11.9 (iv) 11.9 (iv)	NE on Ach- or Vagus-stim hypotension. NE on norepinephrine-hyperten. inh on carotid occlu-hypertens. NE on isoproterenol-hypotens & tachycardia.		
Dog	anesthetized	3.2 (iv)	NE on permanent-coronary-ligation induced arrhythmia.		

In vitro studies

Species	tissue/model	Drug-induced	Effects
Rat	aorta-contraction	norepinephrine KCl	150 mg/l : NE phentolamine: inh. 46 mg/l: NE
Guinea pig	right atrium left atrium	spontaneous electric-stim.	46 mg/l: NE on freq. 46 mg/l: NE on contractil.
Rat	working heart	none	46 mg/l: cardiotoxic on all parameters. 0.46 mg/ml: NE

Other effects:

Activity	Species	Drug-induced Effects	Dose(mg/kg)	Effects
(1) Anticholinergic (NP-30)	mice	light-pupillary diameter	138(po) 46(ip)	NE NE
(NP-31)	mice	oxotremorine-salivation -tremor	46(ip) 46(ip)	NE NE
(2) Anesthetic (NP-42)	guinea pig	corneal reflex	14.6 g/l	NE
(3) Analgesic (NP-40)	mice	acetic acid-writhing	ED ₅₀ =84(po)	
(NP-41)	rats	tail-flick latency	92(sc) 138(sc)	NE inhib.
		hydroxyzine	45(sc)	inhib.
(4) Antiinflam- matory(NP-55)	rats	carrageenan-edema	46(iv)	NE
		indomethacin	1.2(iv)	inhib.
(5) Delayed hyper- sensitivity(NP-54)	mice	sheep red cell-local inflamm.	3.2(sc)	NE
		dexamethasone	3.3(sc)	inhib.
(6) Immediate anaphylactic (NP-19)	human	basophil-anti IgE histamine rel.	EC ₅₀ 0.47mm/l	
		theophylline	EC ₅₀ 0.085mm/l	
(7) Ulcer (NP-56)	rats	stress(immob & immers.)	50(po)	NE

II. TOXICOLOGY

Acute Toxicity Studies (mouse, rat, dog):
Summary table: Page 24.

Subacute/Subchronic/Chronic Toxicity Studies:

Summary tables
Mouse: page 25.
Rat: page 26-27.
Dog: page 28.
Monkey: page 29.

Individual studies:

Mouse (1)-(3): pages 30 to 37
Rat (1)-(5): pages 38 to 50
Dog (1)-(3): pages 51 to 56
Monkey (1)-(3): pages 57 to 61

Carcinogenicity studies:

Mouse: page 62 to 63
Rat: page 64 to 68

II. Toxicology:

Acute Toxicity studies: performed by (1)

Rodents performed Feb-July, 1961; dogs in Feb. 1961 & March, 1963.
Observations for 14 days.

	Mice NHEI, Swt. breed 7 wks. 22-23g		Rats Wistar 7 wks. 112-122 gm		Dog Beagle 20-54 months 8.1-14.2 kg	
Dose	p.o.	i.v.	p.o.	i.v.	p.o.	i.v.
No./dose	20 (10 M + 10 F)		20 (10 M + 10 F)		2 (1 m)	2 (1M-1F)
Dose ranges (mg/kg)	100, 237, 562 & 1333	240, 270, 320 & 370	237-1162	42-100	40, 80, 160 & 320	70 & 125 1 F in 2 div doses because of vomiting. Dis not prev vom.
Observations	See below					
No death at (mg/kg)	237 (M) 100 (F)	240 (M) 240 (F)	237 (M) 237 (F)	none (M) 42 (F)	320 (M-F)	70
Death from (mg/kg)	562 (M) 237 (F)	320 (M) 270 (F)	962 (M) 962 (F)	42 (M) 56 (F)	none	125
LD ₅₀ (mg/kg) (95% conf.)	M: 600 (375-1391) F: 752 (432-2234)	M: 336 (301-475) F: 301 (264-366)	M: 703 (304-1175), 66 (58-96) F: 965 (553-1352), 70 (61-82)	ED		

Signs: Calm, cyanosis-all mice in 1 hr. Dyspnea & death. Survivors recovered in 24 hrs

imm. motor act. unsteady gait-all mice immediately. Convulsions death. Female mice lost 25% wt. at 240 mg/kg.

some on i.v. death following cardiac arrest.

No effect at 40 mg/kg po. Inc. heart rate-80 mg/kg p.o. nervousness-160. Food and weight-all normal.

I.V.:
nervousness, calm unsteady gait, salivation or tremor at 70 mg/kg. No ECG changes. Recovered in 24hrs

Autopsy: unremarkable in all animals.

Death at 125 mg/kg nervousness, muscu. hypertonicity, lost crine, fall on side head backwards, strong extension of its legs and died.

15-Day (T-2)

4-Week (T-3)

4-Week (T-4)

Species	Mouse		
Strain	OF1 SPF	CR CD-1	
Age/wt.			
by:			
M + F 12 ^{hr}	(a) 12 (6M + 6F) (b) 12 (6M + 6F)	32 (16M + 16F) main 20 (10M + 10F): Urine	24 (12M + 12F): ma 24 (12M + 12F): 4-wk 24 (12M + 12F): 13-wk
Route	(a) gavage, daily - 15d (b) diet (feeding)	P.O. (diet) daily - 4 wk	P.O. (diet) daily
Drug in	(a) in water (b) in diet	diet	diet
Dosage levels (mg/kg/day)	0, 5, 10, 20, 40, 80, 160	0, 1, 3, 9, 27, 81	0, 40, 160 Dosing: 12/16/85 - 1/2/86 Recovery: 1/13/86 - 4/15/86
Death at	40 gavage (1M)	0 (1F), 9 (2M), 27 (1M)	0 (1M), 40 (1M + 1F)
Cause	not drug-related	total 4 from urine group, not drug-related.	total 3, not drug-related
Signs			
Necropsy			
Body wt.	Gavage: dec. wt & food	NE	NE except HD-M.
Food consumption	20-160 (M) + 160 (M) feed: food inc 80-160 (M + F)		during 13-wk recov.
Signs	None	Hair loss/scab/ulceration of skin: M	None
Blood analysis	ND	Hgb: inc F (9-81) SGPT/OCT: inc. M (27-81) Triglycerides: dec M (81); inc. F (27-81)	SGPT/OCT: 160 (M + F) Cholesterol: dec 40-160 (M + F) Total lipids: 160 (M + F) ^ 40 (M)
Urinalysis	ND (1F)	positive ketone: most samples.	Triglyceride: inc. 160 (M + F) 40 (M)
Organ wt.	Liver (abs/rel.): inc 40 (M: gavage) 80 (M: feeding) 160 (F: both routes)	Liver: inc M (81)	Liver (abs/rel): inc. 160 (M + F)
Relative "no-effect" dose	5 (gavage + diet)	1 (M) 9 (F)	Not est. (M) 40 (F)
Approx. "effect" dose	10 (gavage + diet)	3 (M): liver 27 (F): Hgb/trigly	40 (M): liver 160 (F): liver
Target organs	Liver cells: hypertrophy	Liver cell hypertrophy	
Pathology			
Gross-	G: unremarkable	G: enlarged liver M (81)	G: enlarged liver 160 (M + F) 40 (M)
* Micro-			
(1) Peri-acinar hepatocyte	10-160 (M + F) Hypertrophy: both routes	Merc: (1): M (3-81) (2): M (9-81)	Merc: (1) 160 & 40 (M + F) (2) tot: 160 + 40 (M).
(2) Portal blood vessel	some		

(B) Rat Studies:

SUMMARY OF SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY STUDIES: rats (Vol 2.10-2.16)

Duration 15-Day(T-6) 1-month(T-7) 4-week(T-9) 4-Week(T-10) 6-month(T-13)

Performed by UCB

UCB

2/10-2/25/83 5/18-6/18/81 11/8-12/8/83

2/22-9/2/82
3-mo interim sac.

T-10: 11/11-12/8/85
Recov. 12/7/85-3/11/86
Recov sac. @ Wk 4 & 13

	12(6M+ 6F)	20(10M + 10F)	20(10M + 10F)main 12(6M + 6F)satellite	t:40(20M + 20F) i:10(5M + 5F)
(M+F)/group			total: 32(16M + 16F)	50(25M + 25F)

t(terminal)
i(interim)@3-mo
Satellite:drug monitoring

T-10:
t: 20(10M + 10F)
Wk 4 : 20(10M + 10F)
Wk 13: 20(10M + 10F)
total: 60(30M + 30F)

	(a)gavage (b)diet	gavage	diet	diet	gavage
Daily for	15 days	1 month	4 weeks	4 weeks	6 months

Drug in water for gavage and in diet for feeding studies.

Doses mg/kg/day	0.5,10,20, 40,80,160	0.25,75,225.	0,2,6,18, 54,160	0,40,160.	0,8,25,75

Deaths	20(1F) intub.err.	total:6 225(2M+2F) 75 (IM) poor condition, distended GI	2(1F)	total:34(22M +12F) intubation error: C(3)+L(3)+M(10)+H(10) accident: M(1) unknown: L(2)+M(2)+H(3)

T-10: total 3
160(1F), 40(1M)
C(1F)

Wt./food	NE	Both reduced in M only. wt. Food	Wt.160(M) Food 160(F)	Wt.160(M)	NE
		-7% -9%			
		-13% -9%			
		-22% -22%			

Signs	None	Noisy resp.(225) Day 1 only.	None	None	Quiet/nervous (75)

Duration	15-Day(T-6)	1-month(T-7)	4-week(T-9)	4-Week(T-10)	6-month(T-13)
Blood	ND	T-7: dec Hgb/Hct/RBC:225 (M) inc SGPT/AP/GLO/BUN: 225 (M + F) inc chols: 225 (M)		T-10: inc total lipid/trigly:40-160(M) inc Cholesterol:225(M)	T-13: dec Hct/RBC:75(M+F) inc SGPT/SGOT/SDH:25-75 dec trigl: 25-75
Organ wt.	T-6	T-7	T-9	T-10	T-13
Inc. liver	40-160	75-225(M+F)	54-160(M)	160 (M+F)	3-mo:25-75(M+F) 6-mo:75(M+F)
			Inc spleen:54-160(M)		Inc kidney:25-75(M+F) Inc adren/thyro:75(M)
Pathology					
Gross					
Enlarged liver	20(F) 40(M)	no	160(M+F)	no	no
Enlarged spleen	no	no	6-160(M)	no	no
Cellularity/spleen (inc.)			18-160(M)		
Histopathology					
Liver: hepatocytic hypertrophy	PA:40(M+F)		CL:54-160(M+F)	CL:160(M+F)	PA:8-75(M) 75(F)
		T-7: CL/ML:75-225(M+F)			
vacuolation	20(M+F)	225(M)	54-160(M+F)	40(M)	25-75(M) 75(F)
fat deposition	20	75-225(M)	54-160(M+F)	40(M)	25-75(M) 75(F)
necrosis		225(M)			
"no-effect"dose (mg/kg/day)	5 (M+F)	25 (M+F)	18 (M+F)	not est.(M) 40(F)	not est.(M) 8(F)
"Affect dose" (mg/kg/day)	10(spots/liver) 20(steatosis)	75	54	40(M) 160(F)	8(M) 25(F)
Target organ*	liver	liver	liver/spleen	liver	liver

see Recovery studies: reversible.
CL: centrilobular. ML: midzonal. PA: periacinar.

Chronic

one-month (T-14) 6-month (T-15) 1-yr (T-15)

Species	Dog		
Strain	Beagle		
Weight	12-15 months	7-9 months	9.2-10.6 kg, 10-15
M + F/Gr	6 (3M + 3F)	10 (5M + 5F)	10 (5M + 5F)
Route	Oral (capsule)	Oral (capsule)	Oral (capsule)
Duration	daily - one month	daily - 6 months Interim fast at 3-months	daily for 52 weeks
Drug in	gelatin capsule	4 (2M + 2F) gelatin capsule	gelatin capsule
Dosage level (mg/kg/day)	0, 15, 45, 135	0, 8, 25, 75	0, 4, 15, 60
Death	None	2M (75) on Day 87 #182	None
Bose Cause		Respiratory difficulty + Tracheitis	
Signs	Vomiting: 15-135 Salivation/tremor/ataxia red. food: 135 Body wt./Food: 135	Vomiting: 8-75 Behavior: jitter at 75 Body wt: dec. F (25-75)	Vomiting: 15-60 Body wt: dec. 15-60 ECG/BP: 60
Blood analysis	AP: inc. at 135	Food: dec. F (25-75) Cholesterol/triglyceride: dec. at 75 RBC/AP: inc at 75	Inc. RBC, Hgb, APTT: 15-60
Relative "no-effect" dosage	45 (except vomit)	8	4
Approx. "effect" dosage	135 (signs/wt.)	25-75 (signs/wt. ^{depression})	15 (vomiting, wt. ^{loss} in ^{therapeutic} range)
Pathology/Target organs	Unremarkable Kidney & adrenal: wt. inc. at 135 ECG: Unremarkable	Unremarkable ECG: Unremarkable Urinalysis: dec sp. gr. at 75	Unremarkable Hepatic enzymes: no effects
	(UCB)*	(UCB)*	

D) Monkey studies

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chronic

SUMMARY OF SUBACUTE/SUBCHRONIC/TOXICITY STUDIES: ^{by} Monkeys

	14-Day (T-16)	4-week Monkey (T-17)	one-year (T-19)
Species		Monkey	
Strain	Cynomolgus		
Weight			2-3 kg, 2-4 yrs
M + F/g	2 (1M + 1F)	6 (3M - 3F)	10 (5M + 5F)
Route	P.O. (gavage)	P.O. (gavage)	P.O. (gavage)
Duration	daily - 14 days	daily - 4 weeks	daily - 50 weeks
Drug	~~50 mg/kg~~ in water (5%)	in water (5%)	in water no diet (5%)
Dosage level (mg/kg/day)	50, 100, 200	0, 17, 50, 150	0, 5, 15, 45
Death	None	one F (150) sacrifice Day 22.	None
Dose			
Cause			
Signs	Salivation/vomiting: 50-200 Quiet behavior/piloerection/ tremor/loss muscle tone - 200	Vomiting/huddled posture/ poor coat/tremor/hypothermia: 50-150	Salivation: at 45 Body wt./food: NE
Blood analysis	Body wt.: losses 50-200 Food: dec. at 200 Hem. RBC: 50-200	Body wt.: losses 50-150 Food: dec. by the sacrifice Inc. Triglycerides @ 150	Unremarkable
Relative "no-effect" dosage	not established	17	15 ~~45~~
Approx. "effect" dosage	50 (signs + wt.)	50 (wt./signs)	45 (salivation only)
Pathology/Target organs	Liver: fat deposition at 200 Lung: congestion at 200	unremarkable microsomal enzymes: no sig. effect.	None

(A) Mouse Studies: (1)-(3)

(1) Subacute toxicity study: Range finding oral toxicity in mice (15 days). (T-2)

Performed by UCB Pharmaceuticals, Belgium

Animals: OF1 SPF mice, 6 weeks old, 23-25 gm.

No. of animals/dosage: 12 (6M + 6F)/dosage:gavage
12 (6M + 6F)/dosage:feeding.

Route and duration of administration:

(1) Gavage: compound in dist. water, orally 7 days/week for 15 days

(2) Feeding: compound in dietary mixture, orally 7 days/week for 15 days

Dosage levels: mg/kg/day

(1) Control:	0
(2)	5
(3)	10
(4)	20
(5)	40
(6)	80
(7)	160

Results:

Mortality: one male of 40 mg/kg (gavage) died after 5 doses. Cause of death: aggression between mice, according to sponsor.

Clinical signs: no signs.

Body weight and food consumption:

Gavage: Slight decreases of weight gains in 20, 40 and 160 mg/kg males and 160 mg/kg females. Food consumption showed decreases in some treated groups.

Feeding: no effect on weight gains; food consumption showed increases in 80 and 160 mg/kg. Food consumption was higher in feeding group than gavage group resulting in higher dose levels in feeding group.

Organ weight:

Liver: increased absolute and relative weights in males (at 40, 80 and 160 mg/kg gavage), in females (at 160 mg/kg gavage and feeding) and in males (at 80 and 160 mg/kg feeding).

Pathology

Gross pathology: unremarkable

Histopathology:

Liver: periacinar hepatocytic hypertrophy from 10-20 mg/kg. The "no-effect" levels were 5 mg/kg (males and females gavage), 6.3 mg/kg* (males feeding) and 9.7 mg/kg* (females, feeding).
*determined by food consumption.

(2) Toxicity to Mice by Continuous Dietary Administration for 4 weeks (T-3)

Performed by:

Animals:

Charles River CD-1 mice of Swiss origin
Manston, Kent, U.K.

No. of animals/dosage: 32 (16M + 16F)
Main study: 20 (10M + 10F)
Satellite study: 12 (6M + 6F), for urinary excretion and liver drug-metabolizing enzymes studies.

Route and duration of administration;
Orally through dietary mixture daily for 4 weeks.

Dosage levels: mg/kg/day

- (1) Control: control diet
- (2) 1
- (3) 3
- (4) 9
- (5) 27
- (6) 81
- (7) Health check 10(5M + 5F): no pathological finding or signs at the beginning of study.

Results:

Mortality: Total 4, all from satellite study.

Two M of 9 mg/kg and 1 F of control groups died during week 1. These deaths: not considered drug-related. One M of 27 mg/kg found dead in week 2 showed ulceration and swelling of perigenital region, and dark staining of contents of small intestines.

Clinical signs: hair loss/cutaneous scab formation and ulceration occurred incidentally in male mice.

Body weight and food consumption:

Body weight gain: slightly lower at 81 mg/kg (3-4% lower than control)

Food consumption: no significant effect; only high-F showed 5% less food consumption than control group mostly during Week 4.

Blood analysis:

Hematology:

Hgb: inc. in F of 9, 27 and 81 mg/kg groups. F of 27 mg/kg also had increases of Hct, RBC and WBC.

Chemistry:

(1) SGOT, SGPT* and OCT* (ornithine carbamoyltransferase) inc. in M mice of 81 mg/kg; inc. SGPT* in M mice of 27 mg/kg.

(2) Triglycerides: inc. in F mice of 27 and 81 mg/kg groups; dec. in M mice of 81 mg/kg group.

(3) BUN* and glucose: inc. in M mice of 81 mg/kg group.

*statistically significant.

Urinalysis:

Many mice failed to produce urine (or enough urine) during collection period. No adverse effects apparent, though positive ketones were found in most samples.

Ophthalmology: examined at Week 4. No adverse effect noted.

Organ weight: absolute wt.

Liver: significant inc. in M mice of 81 mg/kg; other dosed M groups showed some inc. over control without dose-related effect.

Pathology:

Gross pathology:

Liver: enlargement in 4/16M of 81 mg/kg

Histopathology:

Liver: (1) Minimal to moderate centrilobular hepatocyte enlargement in M mice of 3, 9, 27 and 81 mg/kg groups (dose-related effect). Some dosed male mice showed minimal centrilobular vacuolation, but no dose-related effect was observed.

(2) Minimal to moderate lipid deposition: M mice of 9, 27 and 81 mg/kg groups showed dose-related effect; F mice of all groups including control showed randomized incidence (graded as minimal) without apparent dose-related effects.

Assay of drug-metabolizing enzymes: See T-22 study.

- (1) Increased cytochrome P₄₅₀ and aniline hydroxylase: both M and F of 81 mg/kg.
- (2) Increased ethylmorphine N-demethylase: in M mice of 27 and 81 mg/kg, and in F mice of 9, 27 and 81 mg/kg groups.
- (3) Increased p-nitroanisole O-demethylase: in M mice of 27 and 81 mg/kg (not statistically significant though).

Urinary Excretion of UCB P071: on Day 2, 9 and 28 during 7-hr period.

- (1) Urinary excretion of unchanged drug: not detected in M mice of 27 mg/kg or F mice of 9 mg/kg.
- (2) Urinary excretion increased with times only in F mice of 27 mg/kg group; at 81 mg/kg levels, urinary excretions were similar in M and F mice and did not increase with time.
- (3) The urinary excretion generally accounted for less than 5% of doses at all time points in both M and F mice.

Subacute/Subchronic Toxicity Studies:

(3) A study to determine the reversibility of hepatic changes in mice (T-4)

Performed by:

Treatment: 12/16/85-1/12/86
Withdrawal: 1/13/86-4/15/86 for 4 and 13 weeks

Animals:

Charles River CD-1 mice. 5-6 weeks old

No./of animals/dosage: 72 (36M + 36F)/dosage

24 (12M + 12F): Main study
24 (12M + 12F): 4-week recovery period.
24 (12M + 12F): 13-week recovery period.

Route and mode of administration:

orally through dietary mix for 4 weeks.

Duration of treatment:

four weeks, followed by recovery periods of 4 weeks and 13 weeks.

Dosage groups: (mg/kg/day)

(1) Control: 0
(2) Low dosage group: 40
(3) High dosage group: 160

Results:

Signs: None attributable to treatment

Mortality: total 3 deaths (1 control M, 1 low M and 1 low F), not drug-related.

Body weight: no effect during the dosing period; slight reduction in wt. gain during recovery periods in high-dose males only.

Food consumption: no effect during the dosing period; slight reduction during recovery periods in low-dose males and high-dose females.

Achieved intake of test material: within target ranges.

Liver studies:

Parameters	Low		High	
	<u>Treatment</u>	<u>Withdrawal</u> 4-wk 13-wk	<u>Treatment</u>	<u>Withdrawal</u> 4-wk 13-wk
<u>Chemistry:</u>				
Inc. SGPT & OCT			M & F	recovered (4 wk)
Inc. SGOT			F	recovered (4 wk)
Inc. trig & cholest.	M	recovered (4 wk)	M	recovered (4 wk)
<u>Lipid analysis:</u>				
Inc total lipid & triglycerides	M		M & F	
Inc. Cholest.			M	recovered (4 wk)
<u>Enzyme assay:</u>				
microm protein	M		M & F	recovered (4 wk)
Cyto P-450	M		M & F	recovered (4 wk)
anf. hydro	M & F		M & F	recovered (4 wk)
<u>Organ wt</u>				
Inc. slig. in all mice, recovered at 13-wk excp high M				
<u>Gross pathology:</u>				
Enlarged	M		M & F	recv. (13-wk)
<u>Histopathology</u>				
Enlarged centri lob. hepatocytes	M & F		M & F	recv. (13-wk)
+ fat deposition	M		M	recv. (13-wk)

Note: T-4 Study

(1) Enzyme induction was observed in both 4-week studies. The induction was reversible following 4-week recovery period.

(2) Increased SGPT/SGOT/OCT* and inc. cholesterol, total lipids and triglycerides were reversible following 4-week recovery period.

(3) Gross and histopathological changes (hypertrophy and fat deposition) of liver were reversible only after 13-week recovery period.

*ornithine carbamoyltransferase

A study to determine the reversibility of hepatic changes in mice electron microscopy of liver (T-5)

Extension of Study T-4 , only mice from control and high groups sacrificed at end of 4-week treatment and 4-week of withdrawal were examined.

Summary of results was copied as follows:

After 4 weeks of treatment period

Increased amount of smooth endoplasmic reticulum was seen in hepatocytes in mice from groups receiving 180 or 40 mg/kg/day;

occasional concentric membranous bodies were seen in hepatocytes from 1 male and 1 female mouse from the group treated with 180 mg/kg/day;

a higher incidence of mice with minimally increased microbodies in hepatocytes were seen in males treated with 180 mg/kg/day;

increased lipid in hepatocytes in mice treated with 180 or 40 mg/kg/day.

After 4 weeks of treatment followed by 4 weeks withdrawal period

Marginally higher incidence of mice with minimal increase in amount of smooth endoplasmic reticulum in hepatocytes confined to females from high dose group;

other changes seen at termination revealed recovery.

(B) Rat Studies: (1)-(5)

(1) Subacute toxicity study: Range finding oral toxicity in rats (15 days). (T-6).

Performed by: UCB; males: Feb. 19, 1983; females: Feb. 10, 1983
Animals: Sprague-Dawley SPF rats, 5-6 weeks old, 138-147 gm
No. of animals/dosage: 12 (6M + 6F)/dosage: gavage or feeding each.
Route and duration of administration: *Orally 7 days/week for 15 days

* (1) gavage: compound in dist. water
(2) feeding: compound in dietary mixture

Dosage levels: mg/kg/day

(1) Control:	0
(2)	5
(3)	10
(4)	20
(5)	40
(6)	80
(7)	160

Results:

Mortality: one female (20 mg/kg) died on day 12. Autopsy revealed bloody liquid in the trachea and in thoracic cavity. The cause of death was probably tracheal intubation.

Clinical signs: No signs observed.

Body weight and food consumption:
Body weight: no effects.
Food consumption: no effects.

Organ weight:

Liver: dose-related increases of absolute and relative weights from 40-160 mg/kg. Male rats of both gavage and feeding were affected more than female rats.

Pathology:

Gross pathology:

Swollen liver: 1 female (gavage: 20 mg/kg) and in males (gavage: 80 mg/kg; feeding: 40mg/kg). White or yellow spots or nodules on the livers were observed in some of the dosed females (gavage and feeding; 10 mg/kg) and in males (only gavage: 40 mg/kg).

Histopathology:

Treatment related lesions occurred in liver. Periacinar hepatocytic hypertrophy: more frequent and severe in male rats. Gavage and feeding: from 40 mg/kg. Periacinar hepatocytic large vacuolation (steatosis): more frequent in female rats. Gavage: control, low to high female. feeding: from 20 mg/kg.

(2) Subacute toxicology studies: One month oral (gavage) toxicity study in rats. (T-7)

Performed by UCB, May 18, 1981-June 18, 1981. (GLP: not totally in compliance).

Animals: Sprague-Dawley SPF rats, 127-131 gm, 7 weeks old.

No. of animals/dosage: 20 (10 M and 10 F)/dosage.

Route and duration of administration: orally by gavage, 7 days/week for 1 month.

Dosage: drug in dist. water

- (1) Control: vehicle
- (2) Low dosage: 25 mg/kg/day
- (3) Mid dosage: 75 mg/kg/day
- (4) High dosage: 225 mg/kg/day

Mortality: total 6: 1 M (mid dose); due to intubation accident on Day 29.

3 M and 2 F (high dose): on day 11-16. All lost weight. Some had blood on the muzzle, respiratory difficulty and flatulence before death. Autopsy revealed flatulence in 2 M and distended stomach/intestines with yellowish liquid in 1 F.

Clinical signs: Noisy respiration was noted in high-dose group on Day 1. After 2 weeks no differences among 4 groups.

Body weight and food consumption:

No significant effects were observed in F. For male rats, the changes were as follows:

	BW	FC
L:	-7%	-9%
M:	-13%	-9%
H:	-22%	-22%

Blood analysis:

Hematology: F: no significant changes. In high-M rats, slight decreases of RBC, Hct, Hgb and MCV (5-10%) increases of MCHC (6%) and platelets (17%).

Chemistry: inc. ALAT (SGPT): 47-52%
(in the high AP: 20-30%
dose group) globulins (alpha and beta): 16-32%
albumin/globulin ratio: 10-14%
BUN: 15%

Urinalysis: in high-M, increased epithelial cells and decreased phosphates in the centrifuged deposit.

Ophthalmology: not performed.

Drug monitoring: urinary unchanged drug higher in F than M (mostly in free form). After 1 month no accumulation of unchanged drug or induction of metabolism was apparent.

Organ weight:

Liver: dose related increases of absolute and relative weights in the M and H groups.

Pathology:

Gross pathology: no significant findings.

Histopathology: in the mid (3M) and the high dose (10M) male rats, increased fat desposition and hepatocyte necrosis in the centrilobular and mediolobular areas (degenerative and necrotic lesions of the liver parenchyma in the midzonal and central areas of the lobules).

(3) Toxicity to Rats by Continuous Dietary Administration for 4 weeks (T-~~9~~⁹).

Performed by:

Main Study: 11/8/83 - 12/6-8/83; Satellite study: 11/8/83-12/6-21/83.

Animals: Charles River CD rats of Sprague-Dawley strain (Portage, MI, U.S.A.)

No. of animals/dosage: 30 (15 M+ 15 F): 20(10M+ 10F) for main study and 10(5M+5F) for satellite study. (Urine and drug metabolizing enzymes)

Route and duration of administration: orally through dietary mixture for 4 weeks.

Dosage levels:

- (1) Control diet
- (2) 2 mg/kg/day
- (3) 6 mg/kg/day
- (4) 18 mg/kg/day
- (5) 54 mg/kg/day
- (6) 160 mg/kg/day

Results:

Mortality:

One F from satellite group of 2 mg/kg died during week 3 of acute cystitis with necrosis of urinary bladder and epithelial hyperplasia of urethra.

Clinical signs:

No signs of ill health, behavioral changes or reaction to treatment was noted.

Body weight and food consumption:

Body weight gains: lower for 160-M and F only
Food: lower for 160-M and F only

Blood analysis:

Hematology:

160-M: increased erythrocytic parameters (Hct, Hgb, RBC and MCHC); Inc. WBC, neutrophils and lymphocytes.

160-F: Inc. Wbc; dec. monocytes.

Chemistry: Statistical changes were still within normal ranges.

Na+: slight dec. in dosed M and F.
Glucose: slight inc. at 54- and 160-F.

Urinalysis: Not performed.

Organ weight: (Absolute weight) statistically significant changes were observed in ~~only~~ liver and spleen (54 and 160), thyroid (160), gonad (18, 54 and 160). Dec. adrenal (160).

Pathology:

Gross pathology:

- (1) Liver: enlargement in 4/16M and 1/16F of 160 mg/kg group.
- (2) Spleen: enlargement in 2/16 M of 6 mg/kg, 2/16 M of 18 mg/kg and 1/16 M of 160 mg/kg.
- (3) Stomach: Nodules in antrum randomly (1-5 rats) in each group, no dose- or drug-related frequencies noted.

Histopathology:

- (1) Liver: Centrilobular hepatocyte enlargement and mid-zonal/centrilobular fat deposition at 54 and 160 mg/kg levels.
- (2) Spleen: Minimally increased cellularity of red pulp in 1 1/16 M of 160 mg/kg, 4/16 M of 54 mg/kg and 1/16 M, of 18 mg/kg groups.

Assay of Drug Metabolizing Enzymes

The levels of hepatic cytochrome P₄₅₀ and drug metabolizing enzymes (aniline hydroxylase, ethyl morphine-N-demethylase and p-nitroanisole-o-demethylase) were assayed in the microsomal fraction of hepatocytes following 4 weeks of treatment.

- (1) The relative "no-effect" dose was 18 mg/kg level.
- (2) Male rats showed increases of all enzymes from 54 mg/kg.
- (3) Female rats showed increases of O-demethylase and protein synthesis from 54 mg/kg.

Urinary Excretion of UCB P071:

Urinary excretion was measured during a 12-hour period on Days 1, 8, and 28.

- (1) Urinary excretions were below detection limit at 18 mg/kg on all days.
- (2) The urinary excretions, ^(UD) were greater in females than in males on all days and increased with the times in both M and F.
- (3) The urinary excretions, ^(UD) generally less than 5% of the doses for M and F on all 3 days.

(4) A study to determine the reversibility of hepatic changes in rats (T-10)

Performed by:

Treatment: Nov. 11, 1985-Dec. 8, 1985

Withdrawal: Dec. 9, 1985-Mar. 11, 1986

Animals:

Sprague-Dawley rats, 5-6 weeks old, Charles River, Portage, Michigan

No. of animals/dosage: 60 (30 M + 30 F): 20 (10 M + 10 F) each
sacrificed at end of 4-week treatment, 4- and
13-week withdrawal

Route and duration of administration:

Orally through dietary mix daily for 4 weeks

Dosage levels:

- (1) Control: control diet
- (2) Low dosage: 40 mg/kg/day
- (3) High dosage: 160 mg/kg/day

Results:

Mortality: 3 (control: 1 F, Low: 1 M, High: 1F).

Clinical signs: unremarkable

Body weight and food consumption:

Lower weight gains in high-M only. Food/efficiency; unremarkable.

LIVER STUDIES:

Parameters	40		160 mg/kg/day	
	<u>Dosing</u>	<u>Withdrawal</u>	<u>Dosing</u>	<u>Withdrawal</u>
<u>Chemistry</u>	unremarkable in both groups			
<u>Lipid analysis</u>				
Inc. cholest.			M	recovered (4 wk)
Inc. tot. lipid	M	recov. (4 wk)	H	recovered (4 wk)
Inc. triglycer.	M	recov. (4 wk)		
<u>Enzymes</u>				
Micro. protein				
p-450	M + F	recov. (4 wk)	M + F	recovered (4 wk)
P-NOD*			M + F	recovered (4 wk)
<u>Organ wt</u>				
abos. (inc)	M	recov. (4 wk)	M	recovered (4 wk)
<u>Gross pathology</u>				
unremarkable				
<u>Histopathology</u>				
Enlargement				
centrilobular				
hepatocytes	M	recov (4 wk)	M + F	recovered (4 wk)
+ fat depos.				
in midzone			M + F	recovered (4 wk)

*P-NOD: p-nitroanisole-O-demethylase

A study to determine the reversibility of hepatic changes in rats.
Electron microscopy of liver (T-11).

An extension of Study T-10, only rats from control and high dose groups sacrificed at the end of 4-week treatment and 4-week of withdrawal were examined.

In this electron microscopical examination of liver from rats treated with compound ucb P071 for 4 weeks followed by 4 and 13 weeks withdrawal, the results may be summarized as follows:

minimally increased amounts of smooth endoplasmic reticulum in occasional hepatocytes from 10/10 male and 8/10 female rats treated with 160 mg/kg/day and 3/10 male rats treated with 40 mg/kg/day at termination;

occasional concentric membranous bodies in hepatocytes from 7/10 male rats treated with 160 mg/kg/day and 2/10 male rats treated with 40 mg/kg/day at termination;

increased lipid in hepatocytes from rats treated with 160 mg/kg/day at termination.

These changes were not seen in rats from the 160 mg/kg/day treatment group allowed a 4-week recovery period.

NOTE:

Study T-9: The satellite study was for drug monitoring of urine (days 1, 8 and 28).

- (1) Urinary excretion increased with dosing days.
- (2) Urinary excretion of unchanged drug accounting for 5% dose was higher in F than M.
- (3) Metabolites were not indentified.

Study T-10: only liver effects (enzymes, fat contents, light and electron microscopies) were studied.

- (1) All liver effects (increased total lipids, triglycerides and cholesterol, histopathological changes of hypertrophy, fat deposition, vacuolation and EM findings of increased smooth endoplasmic reticulum, lipid droplets, concentric membrane bodies) were reversible after 4-13 weeks recovery period (most parameters recovered in 4 weeks).
- (2) Enzyme induction occurred at 40-160 mg/kg (M + F) more in M. The induction was reversible after 4-13 weeks recovery period.

(5) Chronic Toxicology studies: Oral toxicity study in rats (repeated dosage for 6 months). (T-12)

Performed by : (1), February 22, 1982-August 23/September 2, 1982.

Animals: Sprague-Dawley rats, 7 weeks old. M: 131 gm and F: 97 gm

No. of animals/dosage: 50 (25 M and 25 F)/dosage. Interim sacrifice at 3-month: 10 (5M + 5F)/dosage.

Route and duration of administration: orally by gavage, 7 days/week for 6 months. Interim sacrifice at 3 months.

Dosage: in dist. water

- (1) Control: vehicle
- (2) Low dosage: 8 mg/kg/day
- (3) Mid dosage: 25
- (4) High dosage: 75

Results:

Mortality: total 34 (22 M and 12 F). 26 deaths (C:3, L:3, M: 10 and H: 10): intubation in the trachea; 1 death (M): accidental; 7 deaths (L:2, M:2 and H:3): undetermined cause.

Clinical signs: High dose group: quieter, but hyperactive when handled in this group and mid dose group.

Body weight and food consumption: no significant finding.

Blood analysis:

Hematology: slight decreases of RBC and PCV in high group.

Chemistry: marked inc. of SDH; slight inc. of ASAT (SGOT) and ALAT (SGPT) and slight dec. of triglycerides in mid and high groups (started at 6 weeks)

Urinalysis: no significant finding.

Drug monitoring: Urinary excretion of unchanged drug was higher in F than M, esp. in low group.

Absorption and urinary excretion of UCB P071 in M and F did not appear to be affected following chronic dosings.

Organ weight:

Liver: both absolute and relative weights were increased in mid and high groups (at 3-month) and in high group (at 6-month).

Kidneys: slight increase (abs and rel) in high (M & F) and mid (M) group at 6 months.

Adrenals and thyroids: slight increase in high-M.

Pathology:

Gross pathology: no significant finding.

Histopathology:

A dose related increase in the frequency and severity of periacinar hepatocytic hypertrophy (male rats from low dose and female rats at high dose only) and slight to moderate periacinar hepatocytic large droplet fatty infiltration (male rats from mid dose and female rats at high dose only) were observed. More male rats were affected. EM study of livers of control and high dose, (3 M + 3 F) each group, revealed increased smooth endoplasmic reticulum and lipid droplets in all 3 male and 1 female rats of high dose group.

Interim sacrifice at 3-month:

Liver effects progressed from 3 months to 6 months while treatment continued.

Six-month toxicity study in rats with test substance UCB P071.
Electron microscopy of selected hepatic tissues of control and group 4 treated rats(T-13)

An extension of Study T-12, the results were based on the observations from three rats of each sex from control and 75 mg/kg/day groups. The results are copied as follows:

In the limited numbers of animals observed, ultrastructural changes in the hepatic tissue of the rat were almost totally confined to the males with an evident increase in smooth endoplasmic reticulum in the periactinar region and a slight increase in the centriactinar region. There were elevated numbers of lipid droplets observed in both centriactinar and periactinar regions with some clumping of lipid droplets in the periactinar region which on occasion formed very large lipid droplets. Many lipid droplets of varying size had a 'vacuolar' appearance, a not uncommon effect caused by storage of tissues in formaldehyde.

The female treated rats had numbers of lipid droplets similar to the female controls, and with the exception of the periactinar region of 4F Oil which had a slight increase in smooth endoplasmic reticulum, no observable increases in smooth endoplasmic reticulum were found in the centriactinar or the periactinar region.

In both male and female treated rats all other hepatic ultrastructural features were regarded as similar to those observed in controls.

(C) Dog studies: (1) - (3)

(1) Subchronic toxicity study: Toxicity to dogs in repeated oral administration for one month (T-14)

NDA 19-835

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Performed by: (1), April 14, 1981 - May 14, 1981.

Animals: Beagle dogs, 12-15 months old.

No. of animals/dosage: 6 (3M + 3F)/dosage.

Route and duration of administration: orally 7 days/week for 1 month.

Dosage levels: in gelatin capsules.

(1) Control:	0
(2) Low:	15 mg/kg/day
(3) Mid:	45
(4) High:	135

Results:

Mortality: none

Clinical signs:

- (1) Vomiting: drug-and dose-related increased incidences in all dose groups.
- (2) Impaired condition (body tremor, salivation, ataxia, reduced food consumption): in 2 high-dose females at end of treatment.

Body weight and food consumption:

Both showed decreases in high dose females (mostly due to 2 females).

Blood analysis:

Hematology: unremarkable

Chemistry: Increased AP in high dose M and F and increased α_2 globulins in high dose F.

Urinalysis: Significant decreases of specific gravity in high-dose M (-22%) and F (-34%); volume increased.

Ophthalmology: not performed.

Heart rate and EKG: no significant findings.

Organ weight: Relative weights of

kidneys: increased in high dose male and female dogs.

adrenals: increased in high dose male and female dogs

Pathology:

Gross pathology: unremarkable.

Microscopic pathology: unremarkable.

(2) Chronic toxicity study: Oral toxicity study in beagle dogs,
Repeated dosage for 6 months (F-15).

UCB Pharmaceuticals,

Performed by: GD January 13, 1982 - July 13, 1982

Histopathology:

Animals: Beagle dogs, 7-9 months old.

No. of animals/dosage: 10 (5M + 5F)/dosage.

Route and duration of administration: orally 7 days/week for 6 months.

Interim sacrifice at 3 months, (2 M + 2 F) from each group.

Dosage levels: in gelatin capsules.

- (1) Control: empty gelatin
- (2) Low: 8 mg/kg/day
- (3) Mid: 25
- (4) High: 75

Results:

Mortality: 2 males of high group. One died on Day 87 after displaying respiratory difficulties. Another male dog was sacrificed on Day 182. Autopsy revealed dense foam in trachea and an atrophy of mandibular salivary glands. Histopathological examination showed slight, diffuse acute tracheitis.

Clinical signs:

- (1) Vomiting: drug and dose-related increases of incidences.
- (2) Behavior changes: high dose dogs were quieter, but became nervous when touched.

Body weight and food consumption:

Body weight: reduced weight gains were observed in mid and high-dose F only. (Starting from week 2, dose and duration related decreases were observed).

Food consumption: in mid and high F only, correlating to reduced weight gains.

Blood analysis:

Hematology:

MCV: 10% decreases in high H and F.

RBC: 10% increases in high H and F.

Chemistry:

Cholesterol and triglycerides: tendency to decrease in high M.

Alk. phosphatase: slight increases in high M and F.

Urinalysis: tendency to slight decreases of specific gravity in high-dose group.

Ophthalmology: unremarkable.

Heart rate and EKG: no significant finding.

Organ weight: No significant changes were observed at 3-month, or at 6-month for male dogs. At 6 months, mid and high F showed increased relative weights of most organs (due to the suppressed weight gains at these levels).

Pathology:

Gross pathology: no significant findings at 3- or 6-months.

Histopathology: no significant findings at 3- and 6-months.

(3) One-year Oral Toxicity Study of Cetirizine (UCP PU71) in Beagle Dogs
(IND Report T-29, HRC Report UCB 208/851114/PFZ) (F-18)

Performed by:

June 28, 1984 - June 28, 1985

Animals:

Beagle Dogs, from
9.2 kg (F), age: 24-28 weeks

Farm, Wt. 10.6 kg (M)

No. of Animals/dosage:

10 (5M + 5F)

Route of Administration:

Orally through gelatin capsules daily for 52 weeks.

Duration of Treatment:

Daily for 52 weeks.

Dosage groups: (mg/kg/day)

(1) Control:	empty gelatin capsule
(2) Low dosage group:	4
(3) Mid dosage group:	15
(4) High dosage group:	60

Results:

Signs:

Vomiting: dose-related within 1-hour of dosing in M and F, only
occasional in low-dose group.

Mortality: None

Body weight: M (mid & high): decreased weight gains during 52 weeks.

Food consumption: No significant finding.

Physical examinations: on pre-dose, weeks 12, 24, 38, and 50.

ECG: sig. increase QTC in HD-M only at week 50.

BP: some increase in dosed F during pre-dose and week 50

Ophthalmic examination: pre-dose, weeks 12, 24, 38, and 50.

Unremarkable.

Hematology/bone marrow/coagulation:

Changes (mostly inc) in RBC, Hgb, McHc and APTT in MD and HD female during weeks 12 and 24.

Bone marrow smears: normal in cellularity, morphology and cell distribution at sacrifice.

Blood chemistry: No significant finding.

Urinalysis: Unremarkable.

Organ weights: Unremarkable.

Gross pathology: Unremarkable.

Histopathology: Unremarkable.

ADME data: Week 52 data

* F > M

(1) Dose (mg/kg/day)	Tmax(hr)	Cmax(ug/ml)	AUC(ug.hr/ml)	Bile/plasma
4	1.5	5.8	65.0	17.8
15	1.3	29.7	325.7	26.1
60	2.4	101.5*	1456.1	30.1

(2) Steady state reached in 1 week

(3) No accumulation was apparent.

(4) Except at HD where F > M in peak plasma levels, no sex difference in pharmacokinetics were observed.

Hepatic drug metabolizing enzymes: at sacrifice.

Parameters: microsomal protein, cytochrome P-450, aniline hydroxylase, ethylmorphine-N-demethylase, p-nitroanisole-o-demethylase: no significant effect.

D) Monkey studies: (1) -- (3)

(1) Preliminary Oral Toxicity Study in Cynomolgus Monkeys ~~(T-16)~~ (T-16)

Performed by:

Animals:

Wild-caught cynomolgus monkeys (*Macaca fascicularis*)

No. of animals/dosage: 2 (1 M+ 1 F), each pair was studied at a time.

Route and duration of administration:

Orally by gavage as a solution in distilled water, daily for 14 days.

Dosage levels: (4 ml/kg of 5% solution, except*)

(1) Control: distilled water

(2) Low dosage: 50 mg/kg/day

(3) Mid dosage: 100 mg/kg/day

(4) High dosage: 200 mg/kg/day *(vol. of 4 ml/kg - 1 day; 2.5% - 8 ml/kg - 13 days).

Results:

Mortality: none.

Clinical signs:

Salivation and vomiting from 50 mg/kg.

Quiet behavior/pilo-erection/tremor/loose, mucus feces: 200 mg/kg.

Body weight and food consumption:

Body weight: losses from 50 mg/kg (F), 100 mg/kg (*M and F) and 200 mg/kg (*M and F). *more losses.

Food: decreased in both M and F of 200 mg/kg group.

Blood analysis:

Hematology:

RBC: dec. from 50 mg/kg on Day 11.

Pathology: liver findings of fat deposition in both monkeys of 200 mg/kg group; F monkey had pallid and mottled liver. Both monkeys had congested lungs.

(2) 4-week Oral Toxicity Study in Cynomolgus Monkeys (T-26)¹⁷. -

Performed by:

Animals:

Wild-caught monkeys (*Macaca fasciculatrix*).

No. of animals/dosage: 6 (3M+ 3F)

Route and duration of administration:

Orally by gavage of solution in distilled water daily for 4 weeks.

Dosage levels:

- (1) Control: vehicle
- (2) Low dosage: 17 mg/kg/day
- (3) Mid dosage: 50 mg/kg/day
- (4) High dosage: 150 mg/kg/day

Results:

Mortality:

One F from 150 mg/kg group sacrificed on Day 22.

Clinical signs:

Vomiting (shortly after dosing), huddled posture, poor condition of the coat, limb tremors, abdominal scratching motion and drop in body temperature: at 150 mg/kg level.

Body weight and food consumption:

Body weight: marked losses in high dose group and moderate losses in 2 F of 50 mg/kg group.

Food: only the sacrificed F showed dec. food consumption.

Blood analysis:

Hematology:

No significant trends.

Chemistry:

- (1) Dec. ornithine carboxyltransferase: at 50 and 150 mg/kg.
- (2) Dec. sorbitol dehydrogenase: at 17, 50 and 150 mg/kg.
- (3) Inc. triglycerides: at 150 mg/kg.

Urinalysis: marginally dec. specific gravity in 150 mg/kg group.

Ophthalmology: unremarkable.

Heart rate and ECG:

ECG: only the sacrificed F showed low HR with sinus arrhythmia.

Organ weight:

Kidneys and lungs: increases of absolute and relative wts. only in 150 mg/kg group.

Pathology:

Gross pathology: No significant finding.

Histopathology: No significant finding.

Assay of Drug Metabolizing enzymes: at end of 4 weeks.

- (1) Liver weight: both absolute and relative weights were lower in F of 150 mg/kg group.
- (2) Total microsomal protein: lower in the F of 150 mg/kg.
- (3) Three hepatic microsomal enzymes (ethylmorphine-N-demethylase, aniline hydroxylase and p-nitroanisole O-demethylase) showed increased activities in F monkeys of 50 and 150 mg/kg groups and in M monkeys of 17 and 150 mg/kg groups, but no statistical significance was established.

(3) One-Year Oral Toxicity Study of Cetirizine (UCB P071) in Cynomolgus Monkeys (IND Report T-30, HRC Report UCB 220-g/86186) (T-19).

Performed by:

October 4, 1984 - October 4, 1985

Animals:

Wild-Caught Cynomolgus Monkeys (*Macaca fascicularis*), from :
wt. 2-3 kg, age: 2-4 yrs

No. of animals/dosage: 10 (5M + 5F)

Route and duration of administration:

Oral by gavage, as a solution in water daily for 52 weeks.

Dosage levels: (mg/kg/day)

- (1) Control: vehicle
- (2) Low dosage: .5
- (3) Mid dosage: 15
- (4) High dosage: 45

Results:

Mortality: None.

Clinical signs: Salivation: mainly at HD

Body weight and food consumption: No significant effect.

Blood analysis:

Hematology: No consistent/significant findings.
Bone Marrow smear: no effect.

Chemistry: No consistent changes.

Urinalysis: Inc. volume and dec. sp. gr. at HD

Ophthalmology: Unremarkable.

Heart rate and ECG: Unremarkable.

Organ weight: Testes: inc. abso & rel. wt. at HD

Pathology:

Gross pathology: Unremarkable.

Histopathology: Unremarkable.

ADME data:

* F M

Week 52 data

(1) Dose (mg/kg/day)	Tmax(hr)	Cmax(ug/ml)	AUC(ug.hr/ml)	Bile/plasma
5	0.9	3.3	9.9	
15	1.2	10.0	32.4	
45	1.5	31.9	134.4	

(2) Steady states reached in 1 week.

(3) No accumulation was apparent.

(4) No sex difference in pharmacokinetics were observed.

Hepatic drug metabolizing enzymes: at sacrifice.

Parameters: Microsomal protein, cytochrome P-450, aniline hydroxylase, p-nitroanisole-o-demethylase and ethylmorphine-N-demethylase: no significant effect.

Carcinogenicity Studies: 1-2.

1. Two-Year Dietary Mouse Carcinogenicity Study (T-20).

GLP statement: yes.

Performed by:

Animals: Charles River CD-1 mice, approximately 5-6 weeks old at the start of treatment, obtained from
M: 27 gm and F: 19 gm.

No of animals/dosage: 104 (52M + 52F).

Route, mode and duration of administration:

Orally through dietary mixture daily for 104 weeks or 2 years.

Dosage selection: based on 4-week dietary study that showed drug-related toxicological effects in livers. Lipid deposition and elevated liver enzymes at 27-81 mg/kg in male mice. Female mice showed elevated triglyceride at 27-81 mg/kg. Centrilobular hepatocyte hypertrophy (enlargement) in 3-81 mg/kg M mice was considered of no toxicological significance because it was related to enzyme adaptive changes.

Dosage levels (mg/kg/group): weekly analyses (body weight, food consumption and inclusion levels of test compound) revealed all within target ranges.

(1) Control: 0
(2) Control: 0
(3) Low dose group: 1
(4) Mid dose group: 4
(5) High dose group: 16

Health check group: 20 (10M + 10F)- no lesions or infectious diseases found on 6/13/84 (sacrificed and macroscopic and histopathological examination).

Results:

Signs: no significant signs attributable to treatment.

Body weight:

Weight gains comparable among groups during study period.

Food consumption: comparable among groups during study period.

Blood Smears:

Taken from all surviving mice during weeks 52, 53, 57 and at termination showed no significant effect.

Mortality: no significant finding. Cause of death attributed to injuries from fighting among males during the first 13 weeks. Mortalities ranged 50-58% (M) and 29-54% (F). One of the contributing factors to female deaths was lymphosarcoma accounting for 4, 8, 3, 9 and 9 deaths in Groups 1-5, respectively in female mice. Distribution of deaths are as follows:

	Group and dosage (mg/kg/day)									
	1 st Control	2 nd Control	3 rd 1	4 th 4	5 th 16	1 st Control	2 nd Control	3 rd 1	4 th 4	5 th 16
Initial group size	52	52	52	51	52	52	52	52	52	52
No. sporadic deaths occurring weeks:										
1 - 26	0	1	3	2	1	0	1	0	0	0
27 - 52	2	2	5	2	5	1	3 ^A	1	3 ^B	0
53 - 78	6	14	9	5	4	5	7	4	6	6
79 - 104	18	13	13	19	18	18	17	10	12	15
105 - 106	0	0	0	0	0	0	0	0	0	1
Terminal sacrifice	26	22	22	24	24	28	24	37	31	30
% survival of mice at termination	50	42	42	46	46	54	46	71	60	58

^A Includes 2 mice, Nos. 339 and 340 (044? and 444) sacrificed in week 44 after receiving inappropriate diets

Pathology:

Gross pathology: no significant finding, except high-dose males with higher incidences of liver mass than control. In addition, high-dose males that were dead or sacrificed during study period also having higher incidence of liver mass.

Number of	Sex	Group	1		2		3		4		5	
			10	11	12	13	14	15	16	17	18	19

D: found dead or sacrificed; T: terminal sacrifice

Liver	10	11	12	13	14	15	16	17	18	19
Mass of Spleen	0	0	0	0	0	0	0	0	0	0
nodules	0	0	0	0	0	0	0	0	0	0
pale area of area	0	0	0	0	0	0	0	0	0	0
dark area of area	0	0	0	0	0	0	0	0	0	0
Cyst of cysts	0	0	0	0	0	0	0	0	0	0
fibrosis	0	0	0	0	0	0	0	0	0	0
irregular surface depressions	0	0	0	0	0	0	0	0	0	0
pale	0	0	0	0	0	0	0	0	0	0
lobular structure abnormal	0	0	0	0	0	0	0	0	0	0
enlarged	0	0	0	0	0	0	0	0	0	0

Histopathology:

Neoplastic changes:

(1) Benign liver cell tumor: increased incidence of benign liver cell tumors was observed in high-dose male mice only. In addition, a greater number of them also was found bearing multiple benign liver cell tumors (see tables). Statistical analysis on liver cell tumors (benign and malignant combined) and on malignant liver cell tumors alone for male mice was

performed. The high-dose male mice had significantly more liver cell tumors than control ($p=0.02$). The test for trend over all groups was significant ($p=0.01$). The test for trend for the first 4 groups excluding the high-dose group, however, was not significant. No significance was found in the incidence of malignant liver tumor.

(i) Incidence of male mice with liver cell tumors

	Group				
	1	2	3	4	5
Benign	13	14	15	15	25
Malignant	7	5	7	5	8
Benign and/or malignant	18	19	22	20	33
Number of animals examined	52	52	52	52	52

(ii) Incidence of male animals with benign liver cell tumors

	Group				
	1	2	3	4	5
Benign liver cell tumour (one)	12	10 ^a	9	8	12 ^a
Benign liver cell tumour (two)	0	2	4	6	9 ^a
Benign liver cell tumour (three)	1	2	1	2	3
Benign liver cell tumour (four)	0	0	1	1	1
Animals with any benign liver cell tumour	13	14	15	15	25
Percentage	25.0	26.9	28.8	28.8	48.1
Animals examined	52	52	52	52	52

NOTE: In comparison with the main tables:

- ^a includes the animal with the infarcted li cell tumour, but excludes the animal with the benign tumour in the ORG section
- ^b includes the animal with the benign liver cell tumour in the ORG section
- ^c includes the animal with the necrotic benign liver cell tumour

Historical control data from 9 studies from the performing lab. showed an incidence of 3.8%-26.9%. The concurrent control groups showed incidences of 25.0% and 26.9%, within historical control ranges.

Incidence of liver cell tumours in unselected control male mice

	Study								
	01E	02A	02B	02C	02D	02E	02F	03A	03B
Benign liver cell tumours	3	13	15	6	16	11	12	14	9
Percentage	5.8	12.5	14.6	11.5	18.2	21.2	23.1	26.9	17.3
No. of mice	52	104	104	52	88	52	52	52	52

(2) lymphosarcoma in multiple organs: increased in 16 mg/kg female mice (35, 51, 30, 27 and 56 total incidences in groups 1-5, respectively).

Non-neoplastic changes:

Some macroscopic findings mostly at high dose: liver masses/cysts (M), fluid in abdomen/thoracic cavity, subcutis edema/hemorrhage, stomach (depression in corpus mucosa, dark/blood contents) and ovarian cysts (F). Histopathology did not reveal significant finding in treated mice.

2. Two-Year Dietary Rat Carcinogenicity Study (T-21).

GLP statement: yes.

Performed by

Animals: CD-rats, Sprague-Dawley strain, 5-6 weeks old at the start of treatment, obtained from

No. of animals/dosage: 100 (50M + 50F).

Route, mode and duration of administration: orally through dietary mixture, daily for 104 weeks or 2 years.

Dosage election: based on 4-week dietary study that showed drug-related toxicological effects in livers. Hepatotoxicity (enlargement of the centrilobular hepatocytes and vacuolation of midzonal hepatocytes with associated fat deposition) were observed at 54-160 mg/kg in both males and females. The relative "no-effect" level was 18 mg/kg.

Dosage levels (mg/kg/day): weekly analyses (body weight, food consumption and inclusion levels of test compound) revealed all within target ranges.

- (1) Control: 0
- (2) Control: 0
- (3) Low dose group: 3
- (4) Mid dose group: 8
- (5) High dose group: 20

Health check (Feb. 16, 1984) on 10 M and 10F revealed no lesions associated with infection except ro nodule of antrum mucosa in the sotmach of 2 M (Ectopic focus of non-glandular epithelium in the glandular region).

Signs: none related to treatment was reported. Sialodacryoadenitis was found in most rats of all groups during week 83 and 84 resulting in swelling of ventral cervical region, dryness of eyes, reduced food intake and body weight gains. The symptoms regressed and all animals recovered.

Mortality: no treatment related mortality (M:50-72%; F:52-64%) was evident. The distribution of deaths was follows:

	Group and dosage (mg/kg/day)									
	1/ Control	2/ Control	3/ 3	4/ 8	5/ 20	17 Control	21 Control	29 3	33 8	39 20
Initial group size	50	50	50	50	50	50	50	50	50	50
No. animals deaths during week:										
1- 26	2	0	1	1	0	2	0	0	0	0
27- 52	1	1	2	1	2	2	0	2	1	1
53- 78	0		0	0	10	5	0	12	10	10
79-104	18	1	26	18	22	19	30	18	21	15
105-106	1	1	2	1	1	2	1	0	0	0
Total deaths	20	19	26	22	13	22	20	18	18	24
% survival of rats at termination	60	58	58	58	58	66	66	58	58	58

Body weight: no significant finding.

Food consumption: no significant finding.

Efficiency of food utilization: no significant finding except for mid F and high F with higher efficiency during month 4-6.

Blood smears: no significant finding at Week 52, 78 and 104.

Pathology: gross and histopathology were performed.

Neoplastic changes: thyroid follicular adenoma, pituitary tumors (carcinoma and adenoma) and Tiver malignant tumor were increased in some dosed groups.

(1) Thyroid follicular adenoma:

Number of thyroid follicular tumours in male rats

Groups	1	2	3	4	5
Adenoma	1	3	1	2	5
Adenocarcinoma	2	1	0	2	1
Total	3	4	1	4	6
Number of rats examined	50	50	50	50	50

- This number includes a thyroid follicular cystadenoma

Incidence of thyroid follicular tumours in untreated male Sprague-Dawley rats (Historical control values)

Study identity	A	B	C	D	E	F	G	I	J	K	L	M	N	O	P
Number of rats with:															
Adenoma	1	2	2	6	3	1	4	0	4	2	1	2	3	6	2
Adenocarcinoma	0	1	0	1	1	0	0	0	1	0	1	2	0	1	1
No. of rats examined:	99	50	100	50	98	49	100	100	99	50	49	99	50	100	50

Increased incidence was observed at 20 mg/kg male rats. The historical data showed thyroid follicular adenoma in male Sprague-Dawley rats ranged 0-12%. The statistical analysis by sponsor concluded as follows:

Male rats receiving 20 mg/kg/day ucb P071 showed significantly more benign follicular tumors than the pooled controls, $P = 0.047$ and the test for trend over Groups 1 to 5 was significant $P = 0.003$, but did not persist when the high dose group was excluded.

For combined benign and malignant follicular tumors the test for trend over Groups 1 to 5 was significant $P = 0.03$, although the pairwise comparison between the high dose group and the pooled controls was not significant.

The incidence of benign follicular tumors in male rats receiving 20 mg/kg/day ucb P071 of 0/50 is within the range of historical control values in this laboratory. In addition, there was no evidence of a treatment-related effect on non-neoplastic lesions in the thyroid gland. Bearing these facts in mind, the increased incidence of thyroid follicular tumors was considered of no biological significance.

(2) Pituitary tumors:

Pituitary carcinoma increased in 8 mg/kg female rats. Pituitary adenoma increased in 8 and 20 mg/kg female rats. When the carcinoma and adenoma are combined, the incidences were increased in 8 and 20 mg/kg female rats

Number of pituitary tumors in female rats

Groups	1	2	3	4	5
Adenoma	26	31	27	20	32
Carcinoma	2	1	1	7	3
Total	28	32	28	27	35
Number of rats examined	50	50	50	50	50

Incidence of pituitary tumors in
UNIFRAC 28818 SCRCHE-DAVLEY F123
(Historical control values)

Study identity	A	B	C	D	E	F	G	I	J	K	L	M	N	O	P
Number of rats with:															
Adenoma	63	20	85	28	72	34	52	32	56	36	27	54	31	53	31
Carcinoma	8	1	8	2	11	1	4	7	2	3	2	7	1	4	4
No. of rats examined	100	49	98	47	106	50	99	100	95	50	49	101	48	100	50

The historical control data in female S-0 rats revealed adenoma at 60-82% and carcinoma at 2-11%.

The statistical analysis by Sponsor concluded as follows:

For malignant pituitary tumors in females the 8 mg/kg/day group showed significantly more tumors than the controls, $P=0.01$. Since the 20 mg/kg/day group was not significantly different from the controls the test for a linear trend across Groups 1 to 5 was not significant, but the test for non-linearity was $P=0.04$.

Where benign or malignant pituitary tumors combined were analysed the 8 mg/kg/day group showed a higher incidence of tumors than controls, but again the test for trend was not significant.

The incidence of pituitary carcinoma in female rats receiving 8 mg/kg/day ucb P071 (7/50) is greater than the historical control data, however, in the absence of an increased incidence of this change at the high dose level this result, confined to the intermediate dose level, is considered unlikely to be of any toxicological importance.

Moreover the incidence of pituitary tumors in female rats receiving 8 mg/kg/day and 20 mg/kg/day ucb P071 of 37/50 and 35/50 is within the range of historical control values in this laboratory (see table) and as such this result is considered to be of no biological significance.

- (3) Liver malignant tumors:
Liver malignant tumors increased in 8 mg/kg male rats.

Group	Number of liver cell tumours in male rats				
	1	2	3	4	5
Benign	1	0	0	1	0
Malignant	0	1	0	1	2
Total tumours	1	1	0	2	2
No. of rats examined	50	50	50	50	50

The statistical analysis revealed no significant differences from controls.

- (4) Mammary gland:
Fibroadenoma with epithelial atypia (2, 2, 4, 4, and 5 for C, C, low, mid and high, respectively) appeared increase in the dosed groups.

Non-neoplastic changes:

(1) Stomach:

Ulceration in the non-glandular stomach was observed from 3 to 20 mg/kg in female rats (see Table). Minimal to marked hyperplasia and hyperkeratosis of the epithelium of the non-glandular region (18, 14, 18, 24 and 20 for males, and 13, 18, 21, 19 and 26 for females for C, C, low, mid and high groups, respectively) occurred in all groups, but showed treatment-related effects at 8 mg/kg (males) and at 20 mg/kg (females). Pale (5, 3, 7, 8 and 9, respectively) increased at 3-20 mg/kg (males). Depression (7, 7, 13, 14 and 12, respectively), or thickness (2, 4, 5, 7 and 7, respectively) of forestomach increased at 3-20 mg/kg (females). The "NOEL" was not established in both male and female rats.

Incidence of ulceration in the non-glandular stomach

Group	1	2	3	4	5
Ulceration non-glandular stomach	3	6	10	10	11
No. of rats examined	50	50	50	50	50

(2) Liver:

Masses (2, 0, 1, 4, 2 for males and 1, 0, 1, 0, 0 for females) showed increase only in 8 mg/kg male rats. For male rats, enlarged (10, 7, 6, 16 and 16) /swollen (12, 14, 11, 18 and 19) /darken (25, 29, 34, 37 and 26) liver and periportal fat deposition (17, 22, 20, 26 and 27) increased at 8-20 mg/kg. Centrilobular vacuolation (13, 7, 8, 15 and 21 for males, and 13, 10, 7, 10 and 17 for females) increased at 20 mg/kg. The "NOEL" appears to be at 3 mg/kg for both male and female rats.

(3)-Kidneys:

Enlarged with minimal to marked progressive glomerulonephrosis (34, 36, 37, 41 and 42 for males, 21, 25, 31, 27 and 22 for females for C, C, low, mid and high groups, respectively) occurred in all groups, but showed some treatment- and dose-related effects in male and female rats.

(4) Thyroids:

Epithelial whorls were 3, 4, 2, 1 and 6 (male rats) and 3, 4, 1, 7 and 7 (female rats) for C, C, low, mid and high groups, respectively.

(5) Pituitary: Enlarged (27, 33, 33, 43 and 35 for C, C, low, mid and high groups, respectively) with microscopic finding of dilated/congested sinusoids (15, 22, 22, 29 and 24 for C, C, low, mid and high groups, respectively) in female rats at 8-20 mg/kg.

(6) Pancreas: masses (6, 5, 2, 12 and 8 for C, C, low, mid and high groups, respectively) in 8-20 mg/kg female rats.

(Cetriizine: UCBP071)
SUMMARY OF REPRODUCTION STUDIES
(Oral by Gavage)

Segment	I	II	II	II	III
Species	mouse	rat	rabbit	mouse	mouse
Duration (1) M: 8wks prior to mating, continued on until sacr. (2)F: 2 wks prior to mating, continued on until (a) Day 17.5 pregnancy (b) Day 21 postpartum	Day 6-15	Day 6-15	Day 6-18	Day 6-15	Day 15 Day 21 postpartum
No. (1) M:20 (2) F:40: Day 21, from each group for F ₁ & F ₂	25-26F	16-18F	30F	32F	
Doses mg/gk/day	4 16 64*	8 25 75 225	15 45 135	6 24 *96	6 24 *96
*increased liver weight					
Adult data:					
Effect doses:	64	75-225	135	96	96
	(pregnancy/ mating perf)	(wt./sign/ death)	(wt./deaths)	(wt.)	(wt.)
					(96:nursing/ lactating performance)
No effect doses:	16	25	45	24	24

(continued)
(Cetirizine: UCBP071)
SUMMARY OF REPRODUCTION STUDIES
(Oral by Gavage)

Letter data:	I	II	II	II	III
	(mouse)	(rat)	(rabbit)	(mouse)	(mouse)
Effect doses:	64 (embryocidal) 64(malformations (cleft palate) 16-64(skeletal variants/anomalies)	225(embryocidal) 25-225 (skeletal anomalies/variants)	135 (skeletal anomalies/ variants)	NE	96 (lower pup wt/ day 4-21 lower M/F @birth & weaning.
No-effect doses:	4	8	45	96	24
Significance:					
Embryocidal:	NE	225	NE	NE	NE
Teratogenicity:	64(?)		NE	NE	
Skeletal(anomaly variants)	16-64	25-225	135		
Pregnancy/mating	64				
Nursing/lactating:					96
F1 & F2 generations (no treatments)	No effects: development and reproductive functions Liver and kidney weight			(F1 only) No effect: development and liver and kidney wt.	

Reproduction Studies: 1-5

i. Segment I Reproduction Study:

Fertility and General Reproductive Performance of the Mouse (T-26).

Performed by:

March 24, 1984 - July 20, 1984

Animals:

Mice (CD-1 strain) from Charles River UK Ltd. Margate, Kent.
M (weeks old), F (9 weeks old).

Route and duration of administration: orally by gastric intubation

- (1) Dosed M: 8 weeks prior to mating and continued until sacrificing.
- (2) Dosed F: 2 weeks prior to mating and continued on until either sacrificed on Day 17.5 of pregnancy or after rearing young to Day 21 postpartum.

Dosage levels: (0.1 ml/10gm)

- (1) Control: distilled water
- (2) Low: 4 mg/kg
- (3) Mid: 16 mg/kg
- (4) High: 64 mg/kg

Results:

Maternal data:

Mortality: Total 3-(1 F of 16 mg/kg, 21 of 64 mg/kg)

Body weight and signs:

Body weight and food consumption were slightly lower at 64 mg/kg level, only food consumption attained statistical significance.

Signs: reported as unremarkable.

Pregnancy: pregnancy rate slightly lower only at 64 mg/kg level.

Mating performance: median precoital time was 3 days for all groups, but more mice of mid and high groups mated on or after 6 days. In addition, more mice of mid and high groups showed no positive mating.

Labor: not commented upon.

Necropsy: no significant finding. Liver: centrilobular hypertrophy at 64 mg/kg level.

Liver: relative weight was significantly increased only at 64 mg/kg level
F sacrificed on Day 17.5: relative liver wt. increased at 16 mg/kg level.

Length of gestation: *slightly* prolonged only in high group.

Litter data: On Day 21, 16 M and 16 F pups per group were retained for further study.

Litter Size: from dams allowed to litter.

Control, low and mid groups: had litter size of 10.1 - 10.3
High group: 9.1 (statistically significant).

Survival:

Pup survivals at birth and through day 4-21 were not adversely affected by drug.

Sex ratio: 50% at birth and day 21.

Body weight: Pups weight: comparable at birth, not adversely affected from day 4-21.

Malformations:

Cleft palate: higher incidences (both in terms of litters and fetuses) at 64 mg/kg (control and low: 0, mid: 1 fetus, high: 4 fetuses).

Skeletal anomalies and variants:

unossified 5th metacarpals, total variant sternabrae (unossified, reduced, asymmetric/bipartite) affected cervical vertebrae, reduced metatarsals and occipitals were higher (in terms of litters and fetuses) at 16 and 64 mg/kg.

Visceral anomalies (dilatation of renal pelvis, abdominal hemorrhage ect.): lower among dosed groups.

Necropsy:

Macroscopic findings on weaned litters showed no significant effects.

Liver and kidneys weight: from 1 M and 1 F of weaned litters showed comparable relative weights.

F₁ Generation (No Treatment)

Pre weaning development: group mean age (days post coitum).
Surface righting: 23 days for all groups
Air righting: 28 days for all groups
Startle response: 30.5 days for all groups

Post-weaning development:

(a) Signs and mortality:

No signs in F₁ generation; one F from 64 mg/kg parents was sacrificed on Day 55 (age) - failed to show vaginal opening.

(b) Body weight: no significant effects noted.

(c) Vaginal opening: comparable opening age in all groups.

(d) Pupil reflex test: comparable among groups (tested at week 4).

(e) Behavioral tests: tested at 5 weeks of age.

(i) Actimat (testing activity):

(ii) Rotarod test (testing motor coordination and balance)

(iii) Passive avoidance (tested at 7 weeks of age for learning): no effects seen.

(f) Mating performance and pregnancy rate:

(i) Mating performance (median pre-coital times and positive indication of mating): similar among groups.

(ii) Pregnancy rate: 100% in all groups.

(g) Gestation period: 18.6 days (18-19 days) in all groups.

(h) Terminal autopsy: no significant finding.

Liver and kidneys weights: relative weights were comparable among groups.

Litter data:

(a) Total litter loss: two dams showed total litter loss. One from 64 mg/kg parents and the other from 4 mg/kg parents.

(b) Litter size and pup mortality: comparable among groups.

(c) Litter and mean pup weight: comparable.

(d) Terminal autopsy: no significant finding. Liver and kidneys weight: relative weights of both organs taken from 1M and 1F from each litter were comparable among groups.

Segment = : trials 2

TABLE 3

Mating performance and pregnancy rate - F0 generation

Group	Dosage level P0 ^a (mg/kg/day)	Number of females paired	Number of successful mating pairs on Days:								Total No.	Pregnancy rate (%)	Median pre-ovital times days	Observation at mating	
			1	2	3	4	5	6	>6	Vaginal plug				No indication of mating ^b	
1	0	40	11	6 ^a	11 ^a	8	0	1	3	40	100	3.0	39	1	
2	4	40	6	11 ^a	13 ^a	5	1	0	4	40	100	3.0	39	1	
3	16	39	7	9 ^a	15 ^a	6	0	1	1	39	100	3.0	36	3	
4	64	40	9	2 ^a	12 ^a	3	0	3	7 ^a	36	90	3.0	32	4	

^a Includes one (a, two, three) female(s) with no indication of mating on day of conception - day derived retrospectively assuming a 19 day gestation

^b Time by which half of the paired females had conceived

Segment I: mouse

TABLE 10

Group mean incidence of malformations and anomalies

Group	Dosage mg/kg/day	Number of litters	Number of foetuses									
			Malformations				Anomalies /					
			Examined	Affected		Mean	Examined	Skeletal		Visceral (Wilson technique)		
				litters	foetuses			Total No.	Mean	Examined	Total No.	Mean
1	0	20	201	2	4	2.3	98	4	5.2	99	7	10.0
2	4	120	225	1	1	0.4	111	8	6.8	112	7	6.7
3	16	19	211	3	3	1.8	135	12	16.7	103	1	1.1
4	64	17	173	5	9	5.5	82	12	15.3	82	1	1.2

1 Foetuses with malformations excluded

2 Skeletal anomalies: statistical analysis non-significant at Kruskal-Wallis test ($P > 0.05$)

Background data

Data from control and inactive test groups from three mouse teratology studies using CD-1 mice performed at Saint Joseph Research Centre 1983 - 84.

Number of litters examined 310
 Number of foetuses examined 3885
 Number of foetuses with malformations 34

Type of malformations observed *

Cleft palate 17
 Neural tube defects
 (e.g. craniorhachischia) 8
 Digital and limb defects 5
 Open eye 4
 Others 11

* Includes foetuses with multiple malformations

2. Reproduction Study: teratogenicity study in mouse (T-27)

Performed by:

August 23, 1984-September 5, 1984

Animals:

Mice (CrL: COBS CD-1 (ICR) BR strain) from Charles River
20-27 gm

Route and duration of administration:

Orally by gastric intubation from Day 6-15 of pregnancy; sacrificed
on Day 17.5 of pregnancy.

No. of animals/group

30F/group:

Dosage levels: (0.1 ml/10 gm)

- (1) Control: distilled water
- (2) Low: 6 mg/kg/day
- (3) Mid: 24 mg/kg/day
- (4) High: 96 mg/kg/day

Results:

Mortality: None

Signs: Incidental signs of eye discharge, fur loss, noisy respiration.

Body weight and food:

Mean weight gains slightly higher at mid and high doses during the
later part of pregnancy.

Food consumption slightly lower in all dosed groups from Day 8-13.

Pregnancy Rate: comparable among groups.

Necropsy:

Liver: absolute and relative weights significantly increased at 96 mg/kg level.

Kidneys: weights decreased at 96 and 6 mg/kg

Resorption: no apparent drug-effect.

Implantations: Pre-and post-implantation losses showed no drug-related effect.

Litter data:

Litter Size: comparable among groups

Sex ratio: no significant difference

Body weight: comparable

Visceral anomaly: No effect

External anomaly: no effect

Skeletal anomaly: no effect.

TABLE 7

Group mean incidence of malformations and anomalies

Group	Dosage ucb P071 (mg/kg/day)	Number of litters	Number of fetuses								
			Malformations			Anomalies ¹					
						Skeletal			Visceral (Wilson technique)		
			Examined	Total No.	Mean %	Examined	Total No.	Mean %	Examined	Total No.	Mean %
1	0	23	199	0	0.0	100	10	8.1	99	3	3.4
2	6	20	181	1	0.4	91	5	4.7	89	6	7.7
3	24	21	212	2	0.8	104	8	8.1	106	1	1.0
4	96	24	250	1	0.4	124	6	5.6	125	6	4.6

¹ Fetuses with malformations excluded

3. On oral teratological study in rats.

Performed by UCB Pharmaceuticals, Belgium, November 4-December 9, 1981.

Animals: Sprague-Dawley rats (OFA, CD-IOPs caw), 10 weeks old, weight 229 gm.

No. of animal/dosage: 25-26

Route and duration of administration: orally by gavage the compound (in dist. water) from Day 6-Day 15 of gestation.

Dosage level:

- (1) Control: water
- (2) Low: 8 mg/kg/day
- (3) Mid: 25
- (4) High: 75
- (5) Highest: 225

Results:

(A) Maternal data:

- (a) Mortality: 8 deaths (1 F from 75 mg/kg and 2 F from 225 mg/kg were considered accidental deaths due to tracheal intubation; 5 F from 225 mg/kg died of toxic effects of drug. Blood on the muzzle and respiratory difficulties, reduced body weight gains were observed before deaths). Autopsy revealed flatulence in most deaths.
- (b) Clinical signs:
 - Hair losses: in 8 and 75 mg/kg/day rats
 - Respiratory difficulties: in 75 and 225 mg/kg/day rats.
 - Arched back, nervousness and difficult to handle: 225 mg/kg/day rats.
- (c) Body weight and food consumption: weight gains and food consumption were suppressed only in 225 mg/kg/day rat.
- (d) Pregnancy rate: comparable among groups.
- (e) No macroscopic abnormalities were observed.

(B) Litter Data:

(a) Pre- and post-implantation losses:
Although not statistically significant, both pre- and post-implantation losses (%) were considerably higher at 225 mg/kg level, mainly due to 4 litters.

(b) Fetal weight:

Mean fetal weights were significantly lower in 8, 75 and 225 mg/kg groups, but may not be biologically significant because of the nominal values. More runts at 225 mg/kg:

(c) Malformations: Unremarkable

One fetus from 8 mg/kg group had major anomalies (absence of lower jaw with eyes and ears displaced). This fetus also had major visceral anomaly (left microphthalmia) and lower body weight. Another pup from 225 mg/kg had left microphthalmia and lower body weight.

(d) Visceral anomalies: Unremarkable.

Visceral minor anomalies (increased renal pelvic cavitation, uni- or bilateral with papilla present) were found in control and dose groups. Hypertrophy of one or both kidneys with or without hemorrhage/slightly external or medial displacement of kidney were observed in 3 fetuses of 8 mg/kg, 1 fetus of 25 mg/kg, 2 fetuses of 225 mg/kg.

(e) Skeletal anomalies/variants:

Skeletal minor anomalies (retarded ossification of isolated bones of the skull-parietal, interparietal or multiple-bone-, sternbrae-bipartite or irregular, thoracic or caudal vertebrae-reduced or unossified) were higher in 25, 75 and 225 mg/kg groups with no dose-related effect. Pronounced retardation of ossification were observed in 2 pups of 2 litters from 75 mg/kg groups and 7 pups of 1 litter from 225 mg/kg group.

Segment II: rat

TABLE VI

Litter data : means per litter

Compound dose (mg/kg/ day)	N of pregn. females	% grafted	Mean N of litters considered	Corpora lutea	Implan- tations	Live foetus	Dead foetus	Early resorpt.	Late resorpt.	Mean total loss	Pre- implant loss	Post- implant loss	Foetal weight (g)		Placental weight (g)	
													Mean litter foetal wt	Mean foetal wt	Mean litter foetal wt	Mean foetal wt
Control	26/26	100	26	10.4	14.4	13.4	0	0.92	0.08	1.00	19.55	8.94	51.33	3.82	7.29	0.54
P071 B	23/25	52	23	19.0 MS	10.5 MS	13.7 MS	0	0.65 MS	0.09 MS	0.74 MS	21.31 MS	4.96 MS	51.20 MS	3.73 MS	7.28 MS	0.53
P071 ZS	23/25	92	23	17.0 MS	12.5 MS	11.6 MS	0	0.65 MS	0.22 MS	0.87 MS	24.43 MS	11.19 MS	49.78 MS	3.06 MS	6.55 MS	0.54
P071 ZS	22/26	84.62	21	16.7 MS	13.0 MS	12.1 MS	0	0.68 MS	0.18 MS	0.86 MS	21.13 MS	7.15 MS	53.20 MS	3.09 MS	7.33 MS	0.54
P071 ZS	25/26	96.15	17	19.6 MS	13.6 MS	12.0 MS	0	1.12 MS	0.53 MS	1.65 MS	29.79 MS	12.55 MS	44.59 MS	1.72 MS	6.63 MS	0.55

Comparison of means : each group versus control by two-sample : Wilcoxon test (1)
Student t test (2)

Segment II: rat

Table VII

Group mean incidence of major and minor anomalies - Summary.

Doses	Nr of foetus and litters													
	Total nr of foetuses examined		Major malformations						Minor anomalies (x)					
			Wilson sl.			Skeletal ex.			Wilson sl.			skeletal variants		
	W. (i)	S. (ii)	Total malif. (1)	Nr litter (2)	Mean % (3)	Total malif. (1)	Nr litter (2)	Mean % (3)	Total anom. (1)	Nr litter (2) (b)	Mean % (3) (a)	Total anom. (1)	Nr litter (2) (b)	Mean % (3) (a)
Control	176	173	0	0/26	0	0	0/26	0	18	12/26	10,1	12	10/26	6,4
PO71 8 mg/kg	158	158	1	1/23	0,9	0	0/23	0	31	16/23 NS	19,6 NS	16	10/23 NS	9,6 NS
PO71 25 mg/kg	136	131	0	0/22	0	0	0/22	0	17	12/22 NS	11,5 NS	17	11/22 NS	17,9 NS
PO71 75 mg/kg	141	146	0	0/21	0	0	0/21	0	30	15/21 NS	20,7 NS	22	13/21 NS	14,5 NS
PO71 225 mg/kg	102	102	1	1/17	0,8	0	0/17	0	15	7/17 NS	14,4 NS	18	9/17 NS	17,2 NS

(1) Wilson' technique = W

(ii) Skeletal examination = S

(1) Number of foetuses presenting malformations or anomalies.

(2) Number of litters affected versus number of litters examined.

(3) Mean of percentages of foetuses affected per litter per group.

(a) Comparison of means : each group versus control group by two-sample : Wilcoxon test.

(b) Comparison between treated group and control is made with a Chi² test.

(x) Foetuses showing major malformations excluded.

4. Oral teratological study in rabbits: (T-25)

Performed by UCB Pharmaceuticals, Belgium, March 9, 1982-April 20, 1982

Animals: New Zealand White rabbits, 6 months old, 3.5 kg.

No. of animals/group: 14-18 females

Route and duration of administration:

orally by gavage the compound (in dist. water) from Day 6-Day 18 of pregnancy.

Dosage levels: mg/kg/day

(1) Control:	water	(17 rabbits)
(2) Low	15 mg/kg	(16 rabbits)
(3) Mid	45	(16 rabbits)
(4) High	135	(18 rabbits)
(5) Positive control:	150 mg/kg/day thalidomide (as 0.5% of methylcellulose suspension).	(14 rabbits).

Results:

(A) Maternal data:

(a) Mortality: 3 (1 control and 2 high dose rabbits).

One control and one high dose females were sacrificed on Day 15-17 of pregnancy. Autopsy revealed tracheal intubation as cause of death. Another high dose rabbit was found dead on Day 9. Tracheal intubation was also the cause of death. These 3 rabbits were not included in calculations.

(b) clinical signs: none reported.

(c) Body weight and food consumption:

During the treatment, only high dose group showed suppressed weight gains (-23%) than control group. After the treatment period, all 3 dosed groups showed lower weight gains. Thalidomide showed an 80% lower weight gains during this period. Food consumption (by visual inspection only) showed decreases in some control and treated rabbits.

(d) Pregnancy rate: comparable among groups.

(e) No macroscopic abnormalities were observed in dams.

(B) Litter data:

(a) Pre- and post-implantation losses:

No significant findings were observed up to 135 mg/kg level, whereas significant post-implantation losses were seen in thalidomide group which had fewer live fetuses.

(b) Fetal weight: both fetal and placental weights were lower in thalidomide group only.

(c) Malformations: unremarkable (none in control group, 2 fetuses from 15 mg/kg, 2 fetuses from 45 mg/kg and 1 fetus from 135 mg/kg groups).

These anomalies included internal hydrocephaly, meningocele, microcephaly, failure of development of the frontal and parietal bones, kidneys smaller or missing descending tubules in medulla or hydronephrosis. In the thalidomide group, in addition to the aforementioned anomalies, missing digits, fibula reduced to a trace, absences of talus, malrotation of limbs, reduced caudal vertebrae and agenesis of kidneys were observed in 50% of litters.

(d) Visceral anomalies: Unremarkable.

(e) Skeletal anomalies/variants:

These included 4th and 5th sternbrae fused, reduced ossification in control, 15 and 45 mg/kg groups. At 135 mg/kg, in addition to the aforementioned skeletal anomalies, fontantella very enlarged, sternbrae irregular were also observed. Higher incidences of skeletal minor anomalies were observed at 135 mg/kg level and thalidomide group.

TABLE V

Litter data : mean per litter

Compound & doses mg/kg/day	Nr of pregn. females	% of pregnancy	Nr of litters	Mean	Corpora lutea	Implantations	Live foetus	Dead foetus	Early resorpt	Late resorpt	Mean total loss	Pre-implant loss	Post implant loss	Foetal weight			Placental weight		
														Mean by group of litter weight	Mean by group of individual foetal weight	Mean by group of the mean by litter of foetal weight	Mean by group of placental litter weight	Mean by group of the individual placental weight	Mean by group of the mean by litter of placental weight
Control	17/17	100	16	A-B	12.3	9.0	0.1	0	0.94	0.30	1.31	19.97	14.02	152.08	43.33	43.86	50.55	6.22	6.25
PO71 15	16/16	100	16	A-B	15.7	8.6	7.0 NS	0.06	0.44 NS	0.38 NS	0.81 NS	23.74	10.02 NS	142.08 NS	44.14 NS	45.30 NS	48.29 NS	6.23 NS	5.41 NS
PO71 45	15/16	93.8	15	A-B	11.7	8.3	8.0 NS	0	0.27 NS	0.07 NS	0.33 NS	20.39	3.81 NS	130.94 NS	41.37 NS	42.70 NS	45.95 NS	5.74 NS	5.86 NS
PO71 135	16/16	88.9	14	A-B	11.9	9.1	8.1 NS	0	0.57 NS	0.36 NS	0.93 NS	21.62	9.26 NS	143.61 NS	42.20 NS	43.46 NS	48.50 NS	5.56 NS	6.17 NS
Thalid. 150	13/14	92.9	13	A-B	11.1	9.7	5.5 NS	0.08	2.54 NS	1.62 NS	4.15 NS	12.46	41.87 NS	219.07 NS	40.11 NS	40.27 NS	30.63 NS	5.61 NS	5.39 NS

Regression analysis : analysis of variance for regression

Control versus treated linearly	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Around linearity	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

Comparison of means : each group versus control by two-sample Wilcoxon test (1)
Student t test(2)

TABLE VI

Group mean incidence of major malformations and minor anomalies - Summary

Compound and doses (mg/kg/day)	Number of foetuses and number of litters									
	Total number of foetuses examined	Major malformations			Minor anomalies (a)					
		Nr of foetuses with (2)	Mean % per litter (1)	Nr of litters with (2)	Gross autopsy			Skeletal examination		
					Nr of foetuses with (2)	Mean % per litter (1)	Nr of litter with (2)	Nr of foetuses with (2)	Mean % per litter (1)	Nr of litter with (2)
Control	130	0	0	0/16	0	0	0/16	5	3.6	3/16
ucb P071 15	124	(b) 2 NS	2.1 NS	1/16	0	0	0/16 NS	4	3.8 NS	0/15 NS
ucb P071 45	120	2 NS	1.7 NS	2/15 NS	1 NS	0.8 NS	1/15 NS	4 NS	2.9 NS	3/15 NS
ucb P071 135	114	1 NS	0.7 NS	1/14 NS	0	0	0/14 NS	14 NS	10.9 NS	7/14
Thalidomide 150	71	(b) 34 ***	50.5 **	11/13 **	3 **	4.10 NS	2/13 NS	20 ***	26.8 **	10/13 **

(a) foetus showing major malformations excluded

(b) 1 dead foetus excluded (see table IV)

Comparison of means : each group versus control : - Wilcoxon test (1)

- (CHI)² test (2)

(5) Segment III Reproduction Study: Peri- and post-natal reproduction study in mouse. (T-28)

Performed by:

September 15 - October 12, 1984

Animals: Mice (CrL.: COBS CD-1 (ICR) BR strain), from Charles River

Route and duration of administration:

Orally by gastric intubation from Day 15 of pregnancy to Day 21 postpartum.

No. of animals/group: 32 F/group

Dosage levels: (0.1 ml/10gm)

- (1) Control: distilled water
- (2) Low: 6 mg/kg/day
- (3) Mid: 24 mg/kg/day
- (4) High: 96 mg/kg/day

Results:

Maternal data:

Mortality: None

Body weight and signs:

Reduced body weight and food consumption were observed at 96 mg/kg level during postpartum.

No unusual signs observed.

Necropsy:

Significant increase of liver weight (absolute and relative) at 96 mg/kg level.

Pregnancy: comparable among groups (91%-97%)

Labor: Not commented on.

Nursing performance:

Judging from lower pup weight gain from Day 4 postpartum to weaning, nursing performance was probably affected at 96 mg/kg.

Length of gestation: No significant effect.

Necropsy: Unremarkable

Liver: weight increase at 96 mg/kg.

Kidneys: no effect.

Litter data:

Litter size: Comparable among 4 groups

Survival: No significant difference among 4 groups.

Pre-weaning development: surface and air righting reflex were comparable among 4 groups. Startle response: Statistically delayed from 24 mg/kg level, but not of biological significance because of marginal differences.

Sex ratio:

Lower M/F ratio observed at 96 mg/kg level at birth and weaning.

Body weight:

From Day 4 postpartum to weaning on Day 21:
Significantly lower pup weight at 96 mg/kg level only.

Anomaly: None reported; cold pups were noted in 2 litters (24 mg/kg) and 3 litters (96 mg/kg) and none in control and low groups.

Liver and kidney weight (1 M and 1 F pups per litter for these organ weight data): no significant findings.

V. GENETIC TOXICOLOGY STUDIES

Summary of mutagenicity testings

Life Science Research : (1), (2) and (4)
 Huntingdon Research: (3)

Tests	(1) Ames	(2) Clastogenic Activity Assay	(3) Forward Mutation Assay	(4) Micronucleus test
Study No.	T-29	T-30	T-31	T-32
Date	March, 1982	March-May, 1982	1986	July-Sept. 1982
Strains/Cells:	Salmonella typhimurium TA 1535, 1537, 1538 TA 98 and 100	Human peripheral lymphocytes	mouse lymphoma L5178Y cells	mice 10(5M +5F)
Positive control	yes	cyclophosphamide	yes	Chlorambucil 30 mg/kg/day
Solvent	water	water	water	water
Conc. or dosages	5, 50, 500 and 5,000 ug/plate (+ S-9 mix)	20,100 500 ug/ml (+ S-9)	260-420 (-S-9) 150-300 (+S-9) (ug/ml)	14,70 and 350 mg/kg day P.O. for 2 days
Cytotox. positive@	5000 ug/pl	500 ug/ml	420 (-S-9) 300 (+S-9)	
Results	No increase of revertants (+9-S)	no damage to chromosomal structure	no increase of mutant frequency	N/A no increase of micronuclei (+ S-9)
Remarks	Negative	Negative	Negative	Negative

V. ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION:Table 1. Pharmacokinetics of Cetirizine in Animals (10 mg/kg) and in Man (10 mg)¹

Parameter	Mouse		Rat		Rabbit		Dog	Monkey	Man
	M	F	M	F	M	F	(M&F)	(M&F)	(M)
C _{max} (mcg/ml)	11.6	11.3	1.6	4.2	13.6 ²	13.4 ²	18.6	8.3	0.
T _{max} (hr)	0.7	0.7	0.5	0.5	0.7	0.7	3.0	1.3	1.
AUC (hr.mcg/ml)	65.4	52.3	-	-	29.0 ²	35.0 ²	334.0	23.8	3.
Half-Life (hr)	3.5	3.0	0.5 ⁴	0.7 ⁴	1.9	2.8	10.0	1.4 ⁴	8.
Urinary Excretion of unchanged cetirizine (% dose) ³	24.1	29.8	1.5	9.6	60.7	65.8	34.2 ⁶	35.0	60.
NDA Report No.	NPK-1		NPK-5		NPK-12		NPK-13	NPK-21	CPK-1

¹ Mean data of 2-10 animals, or 35 human subjects in 2 single dose bioequivalence studies, expressed as the dihydrochloride salt.

² Adjusted to 10 mg/kg.

³ Calculated for 10 mg/kg (based on 50 kg man) C_{max} = 20 and AUC = 170.

⁴ Determined after IV administration.

⁵ 72 hours;

⁶ 96 hours.

⁷ Mean daily excretion of unchanged cetirizine from multiple dose study; no excretion data was collected in the bioequivalence studies.

TABLE I. PHARMACOKINETIC STUDY DATA SUMMARY IN ANIMAL SPECIES

SPECIES/ STRAIN	NDA REPORT NO.	DOSE (mg/kg)	ROUTE OF ADMINISTRATION	NUMBER OF ANIMALS	Cmax (ng/ml)		Tmax (hr)		PARAMETERS IN (hr)		AUC (ng·hr/ml)		Bioavailability (%)	
					M	F	M	F	M	F	M	F	M	F
New Zealand White	NPK-1	10	IV	10					2.8	3.1	61.3	37.3		
		10	PO	16	11.6	11.3	0.67	0.67	3.3	3.0	63.8	34.3	106	91
New Zealand White	NPK-2	10	IV	12					0.3	0.7				
		10	PO	16	17.0	26.9	0.3	0.3					36	60
New Zealand White	NPK-12	1	PO	6	1.9	1.3	0.67	0.67	1.9	2.8	2.9	3.3	73	71
		1	IV	6					1.0	1.3				
		13	PO	6	16.0	10.3	1.0	1.0	2.0	2.7				
		13	PO	6	16.2	63.7	1.3	1.0	1.3	1.6				
		133	PO	6	163.6	107.8	3.0	1.3	3.3	3.0				
Dog/ Beagle	NPK-13	1	IV	8					8.6		61.8			
		10	IV	8	2.7				2.2		63.3		103	
		10	IV	4					9.3		36.1			
		10	PO	4	18.4		3		10		33.7		97	
Dog/ Beagle	NPK-14	0.6	PO	6	1.67	1.93	1.56	2.38	8.2	7.9				
		0.6 x 5 days	PO	5	1.80	1.98	1.08	1.70	11.3	10.3				
Dog/ Beagle	NPK-15	10	PO	3	29.6		4.3		9.9		223			
		10	PO	2	0.3	0.3	2	0.3	6.2		2.1	1.6	61	
New Zealand White	NPK-20	10	IV	2					1.2	1.3	21.8	21.1		
		10	PO	2	3.8	6.1	0.3	0.3	1.3	1.3	48.3	35.7		
		10	IV	2					1.6	1.6	2.9	2.8	26.6	
		10	PO	2	6.8	9.7	2	0.3	1.3	1.3	3.3	2.8	63.0	

* Determined from urinary excretion of radiolabel.
 ** Numbers in center of column indicate combined MAF results.
 *** Results of individual animal.
 **** AUC (16 hr)
 ***** AUC (8 hr)
 ***** AUC (20 hr)
 ***** AUC (12 hr)

TABLE 2. EXCRETION OF CETIRIZINE IN DIFFERENT ANIMAL SPECIES

Species/ Strain	NDA Report No.	Dose (mg/kg)	Route of Administration	Sampling Time (hr)	Total Amount Excreted (% dose Cetirizine)			
					Urine		Feces	
					Male	Female	Male	Female
Mouse/NMRI	NPK-1	10	IV	0-72	31.8	36.2		
		10	PO	0-72	24.1	29.8		
Mouse/OF1 SPF	NPK-2	10	IV	0-96	41.5*	53.8*	66.3*	43.2*
		10	PO	0-96	36.5*	57.6*	59.8*	46.4*
Rat/Wistar	NPK-5	10	IV	0-72	4.1	26.8		
		10	PO	0-72	1.5	9.6		
Rat/ Sprague Dawley	NPK-6	1	IV	0-96	11.8*	21.6*	79.1*	76.6*
		5	PO	0-96	16.4*	25.8*	82.6*	71.0*
		25	PO	0-96	15.4*	41.1*	73.2*	53.6*
		75	PO	0-96	20.0*	52.8*	64.6*	43.2*
Rat/ Sprague Dawley	NPK-8	1	PO	0-8	4.4*		5.9*	
		10	PO	0-24	5.3*		64.8*	
		100	PO	0-48	23.8*		64.6*	
Rat/ Sprague Dawley	NPK-9	25	PO	0-24	1.5	17.9		
		75	PO	0-24	11.5	22.5		
		225	PO	0-24	17.4	23.5		
		25 x 1 month	PO	0-24	5.8	20.6		
		75 x 1 month	PO	0-24	20.8	22.0		
		225 x 1 month	PO	0-24	16.3	32.7		

TABLE 2. (Cont.) EXCRETION OF CETIRIZINE IN DIFFERENT ANIMAL SPECIES

Species/ Strain	NDA Report No.	Dose (mg/kg)	Route of Administration	Sampling Time (hr)	Total Amount Excreted (% dose Cetirizine)			
					Urine		Feces	
					Male	Female	Male	Female
Rat/ Sprague Dawley	NPK-11	8	PO	Day 1				
				0-24	0.6	5.6		
				0-24	6.9	10.5		
		25	PO	0-24	15.3	21.6		
				Day 9				
				0-24	0.6	11.8		
		75	PO	0-24	2.9	14.2		
				Day 43				
				0-24	14.2	14.1		
		8	PO	0-24	0.4	8.9		
				Day 180				
				0-24	6.8	15.0		
		25	PO	0-24	19.3	22.2		
				Day 180				
				0-24	1.4	12.7		
75	PO	0-24	9.8	19.5				
		Day 180						
		0-24	19.4	19.8				
Rabbit/ New Zealand	NPK-12	1	PO	0-72	60.7	65.8		
			IV	0-72	46.7	64.7		
		15	PO	0-72	49.1	69.3		
			PO	0-72	62.4	76.4		
		45	PO	0-72	62.4	76.4		
			PO	0-72	51.2	71.0		
135	PO	0-72	51.2	71.0				

TABLE 2. (Cont.) EXCRETION OF CETIRIZINE IN DIFFERENT ANIMAL SPECIES

Species/ Strain	NDA Report No.	Dose (mg/kg)	Route of Administration	Sampling Time (hr)	Total Amount Excreted (% dose Cetirizine)			
					Urine		Feces	
					Male	Female	Male	Female
Dog/Beagle	NPK-13	1	IV	0-96	25.7			
		1	PO	0-96	27.3			
		10	IV	0-96	31.9			
		10	PO	0-96	34.2			
Dog/Beagle	NPK-14	0.6 x 9 days	PO	Day 1	25.6*		6.6*	
				2	37.5*		30.4*	
				3	35.3*		45.2*	
				4	38.1*		31.3*	
				5	42.5*		53.0*	
				6	41.0*		55.8*	
				7	40.9*		41.7*	
				8	38.7*		68.0*	
Dog/Beagle	NPK-15	10	PO	0-120	40.1*		55.7*	
Dog/Beagle	NPK-17	15	PO	0-24	23.5			
		45	PO	0-24	31.0			
		135	PO	0-24	32.3			

TABLE 2. (Cont.) EXCRETION OF CETIRIZINE IN DIFFERENT ANIMAL SPECIES

Species/ Strain	NDA Report No.	Dose (mg/kg)	Route of Administration	Sampling Time (hr)	Total Amount Excreted (% dose Cetirizine)			
					Urine		Feces	
					Male	Female	Male	Female
Dog/Beagle	NPK-18	8	PO	Day 1				
				0-24	16.2			
				25	19.8			
		25	PO	0-24	17.1			
				8	32.3			
				25	27.4			
		75	PO	0-24	34.5			
				8	33.9			
				25	34.8			
		75	PO	0-24	43.8			
				8	45.2			
				25	37.0			
		75	PO	0-24	41.2			
				1	34.5			
				1	26.9			
Baboon/Papio Spp.	NPK-20	10	PO	0-72	29.0			
			IV	0-72	35.5			
		10	PO	0-72	37.3			
			IV	0-72	39.3			
Monkey/Cynomolgus	NPK-21	1	PO	0-72	35.0			
			IV	0-72	19.7			
		10	PO	0-72	37.3			
			IV	0-72	39.3			

TABLE 2. (Cont.) EXCRETION OF CETIRIZINE IN DIFFERENT ANIMAL SPECIES

Species/ Strain	NDA Report No.	Dose (mg/kg)	Route of Administration	Sampling Time (hr)	Total Amount Excreted (% dose Cetirizine)							
					Urine		Feces					
					Male	Female	Male	Female				
Monkey/Cynomolgus	NPK-23	17	PO	Day 1 0-24	28.9							
					50	PO	0-24	29.6				
								150	PO	0-24	31.5	
		17	PO	Day 9 0-24							38.2	
					50	PO	0-24				25.0	
								150	PO	0-24	32.4	
		17	PO	Day 28 0-24							29.5	
					50	PO	0-24				25.8	
								150	PO	0-24	37.6	
	Monkey/Cynomolgus	NPK-24	5	PO							0-24	32.5
					15	PO	0-24					26.1
								45	PO	0-24		28.6

• = Percentage of Dose of Radioactivity Excreted

TABLE 1. METABOLIC PROFILE OF CETIMIZINE IN DIFFERENT ANIMALS

Species/ Strain	NDA Report No.	Dose (mg/kg)	Route of Administration	Biological Fluid	Sampling Time (hr)	Cetizimine (%)		Metabolites (% of Dose)		Other		
						Male	Female	Male	Female			
Moose/MUR1	NPK-1	10	IV	Urine	0-72	31.8	36.2	1.3	1.7			
		10	PO	Urine	0-72	29.1	29.8	3.3	2.3			
Moose/DF1 378	NPK-2	10	IV	Plasma	0-0.5	23.3	27.6	N.D.	N.D.			
					0-0.5	16.7	17.9	N.D.	N.D.			
					0-1.0	13.9	17.2	8.8	11.1			
					0-1.5	18.8	15.3	8.1	11.1			
					1	9.6	9.8	0.30	0.31			
					2	3.3	6.3	0.37	0.33			
					4	8.2	2.7	0.59	0.43			
					6	3.7	1.2	0.89	0.29			
					8	7.5	1.7	0.88	0.20			
					16	0.70	N.D.	N.D.	N.D.			
					0-24	23.6	20.1	1.8	1.0			
0-36	19.6	16.5	1.3	1.1								
Rat/ Sprague-Dawley	NPK-3	1	PO	Plasma*	1	37	3	3	18			
					4	83	6	6	7			
					12	PO	Plasma*	1	26	3	3	15
								2	37	1	1	8
					24	PO	Plasma*	1	71	13	13	12
								2	23	2	2	7
					100	PO	Plasma*	1	81	3	3	10
								2	20	2	2	3
					12	PO	Plasma*	1	73	2	2	13
								2	30	9	9	11
					1	PO	Urine	0-8	0.1	N.D.	N.D.	1.2
								0-32	0.4	0.4	0.4	2.7
10	PO	Urine	0-24	2.4	6.4	6.4	2.8					
			0-8	11.9	0.1	0.1	1.4					
120	PO	Urine	0-12	21.3	14.3	14.3	2.9					
			0-24	31.7	0.1	0.1	1.3					
1	PO	Feces	0-8	23.0	0.3	0.3	4.0					
			0-8	0.4	1.6	1.6	2.7					
10	PO	Feces	0-12	3.0	3.3	3.3	33.8					
			0-24	13.9	3.6	3.6	35.9					
100	PO	Feces	0-12	2.9	0.3	0.3	21.4					
			0-24	4.6	0.4	0.4	17.4					
0-48	13.7	3.8	3.8	31.2								

TABLE 1. (Cont.) METABOLIC PROFILE OF CETIRIZINE IN DIFFERENT ANIMALS

Species/ Strain	NDA Report No.	Dose (mg/kg)	Route of Administration	Biological Fluid	Sampling Time (hr)	Radioactivity (% of Dose)							
						Cetirizine		P326		Other			
						Male	Female	Male	Female	Male	Female		
Dog/Beagle	NPK-10	0.6	PO	Urine	Day 1	20.5		0.22					
					Day 2	32.8		0.45					
					Day 3	28.0		0.32					
					Day 4	23.1		0.41					
					Day 5	33.2		0.68					
					Day 6	30.6		0.60					
					Day 7	31.7		0.54					
					Day 8	30.0		0.52					
Dog/Beagle	NPK-11	10	PO	Urine	0-48	11.1		0		7.9			
				Feces	0-48	27.6		4.3		20.0			
Dog/Beagle	NPK-12	8	PO	Plasma	Day 1								
					1.5	22.9		0.15					
					4	26.5		0.21					
					8	12.1		0.30					
					24	6.9		0.24					
					25	PO	Plasma	1.5	64.5		0.06		
								4	69.2		0.24		
								8	37.9		0.64		
								24	18.4		0.62		
					75	PO	Plasma	1.5	103.5		0.52		
								4	127.1		0.79		
								8	83.9		1.54		
		24	52.1					2.18					
		8	PO	Plasma	Day 180								
					0	13.6		0.77					
					1.5	37.1		0.82					
					4	33.1		0.97					
					8	20.6		1.15					
					24	9.9		0.74					
					25	PO	Plasma	0	32.7		1.85		
								1.5	82.3		1.75		
								4	89.2		2.27		
								8	54.2		1.66		
					24	40.1		1.54					
75	PO				Plasma	0	93.4		3.76				
		1.5	185.2			8.92							
		4	217.9			8.37							
		8	144.6			7.10							
24	90.0		4.94										

* ND - none detected * Data expressed as % sample radioactivity

TABLE 3. TISSUE DISTRIBUTION OF RADIOACTIVITY AFTER ADMINISTRATION OF INC-CETIRIZINE

TREATED STAIN	NDA REPORT NO.	DOSE (mg/kg)	ROUTE OF ADMINISTRATION	SAMPLING TIME (hr)	PLASMA		LIVER		LUNG		KIDNEY		BRAIN									
					M	F	M	F	M	F	M	F	M	F	M	F						
					CONCENTRATION OF RADIOACTIVITY (mcg/g)																	
Mouse/ C57BL/6J	NPK-7	10	IV	0.033	29.7	28.7	86.3	17.5														
				0.066	22.3	20.6	97.3	11.8														
				0.167	16.7	18.2	28.3	34.5														
				0.5	12.9	18.1	38.8	30.7														
				1	11.1	18.6	23.2	23.1														
				2	6.6	7.8	21.6	19.1														
				4	3.8	3.7	22.3	10.3														
				6	3.0	2.9	18.6	8.8														
				8	2.6	2.8	11.7	3.8														
				16	0.3	0.2	1.6	0.6														
Rat/ Sprague Dawley	NPK-6	1	PO	1	0.033	0.222	0.274	1.882	0.081	0.167	0.237	0.493	0.003	0.012								
				2	0.066	0.031	0.263	0.703	0.071	0.212	0.232	0.006	0.011									
				4	0.036	0.030	0.167	0.173	0.091	0.274	0.089	0.009	0.011									
				6	0.066	0.032	0.230	0.181	0.179	0.089	0.082	0.001	0.006									
				24	0.028	0.019	0.383	0.060	0.009	0.250	0.034	0.001	0.003									
				1	0.140	0.074	1.93	1.93	0.102	0.493	0.009	0.009										
				2	0.140	0.074	1.49	2.73	0.020	0.193	0.474	0.393	0.008	0.011								
				4	0.161	0.077	0.99	0.99	0.092	0.049	3.471	0.324	0.007	0.008								
				8	0.178	0.066	0.67	0.316	0.033	0.075	0.213	0.164	0.006	0.006								
				20	0.073	0.028	0.26	0.082	0.034	0.031	0.193	0.092	0.006	0.006								
Rat/ Sprague Dawley	NPK-8	1	PO	1	0.03	0.03	0.430	0.020	0.020	0.160	0.006	0.006										
				6	0.27	0.27	28.00	0.430	0.430	0.240	0.006	0.006										
				8	0.06	0.06	0.50	0.610	0.610	0.090	0.006	0.006										
				1	1.05	1.05	21.00	0.150	0.150	1.170	0.006	0.006										
				6	0.21	0.21	1.70	0.210	0.210	0.410	0.006	0.006										
				8	1.30	1.30	9.10	0.230	0.230	0.380	0.006	0.006										
				12	0.26	0.26	2.60	0.010	0.010	0.050	0.006	0.006										
				24	0.16	0.16	2.60	0.030	0.030	0.170	0.006	0.006										
				1	68.9	68.9	16.70	0.240	0.240	2.030	0.006	0.006										
				6	20.0	20.0	8.50	0.220	0.220	0.990	0.006	0.006										
8	31.1	31.1	5.60	0.230	0.230	0.490	0.006	0.006														
12	2.9	2.9	1.70	0.080	0.080	0.130	0.006	0.006														
24	2.7	2.7	2.10	0.180	0.180	0.180	0.006	0.006														
80	0.8	0.8	0.70	0.020	0.020	0.030	0.006	0.006														

TABLE 9. (Cont.) TISSUE DISTRIBUTION OF RADIOACTIVITY
AFTER ADMINISTRATION OF 14C-CEFTIZIME

SPECIES/ STAIN	NDA REPORT NO.	NOSE dose/ freq	ROUTE OF ADMINISTRATION	SAMPLING TIME, (hr)	PLASMA		LIVER		LUNG		KIDNEY		SPINAL FLUID		
					M	F	M	F	M	F	M	F	M	F	
Rabbit/ New Zealand	NPK-12	1	PO	0.47		2.06	4.17	0.63	0.63			6.00			
				3		0.36	1.03	0.33	0.33			1.93		0.07	
						0.32	2.83	0.36	0.36			1.93		0.61	
Dog/ Beagle	NPK-14	0.6 (pregnant)	PO	0.47		0.33	1.91	0.19	0.19			1.48			0.01
				3		0.36	1.28	0.23	0.23			3.19			0.07
				6		0.32	0.47	0.23	0.23			1.36			0.07
				24		0.32	0.17	0.03	0.03			0.66			0.01
				2		2.37	2.71	1.06	1.06			1.21			0.27
				6		0.26	2.19	0.21	0.21			0.27			0.27
Dog/ Beagle	NPK-15	0.6 x 9 days	PO	2		1.96	0.53	0.27	0.27			0.26			0.16
				6		0.70	4.18	1.86	1.86			2.12			0.66
				24		0.70	2.17	1.11	1.11			0.82			0.38
				48		0.36	1.31	0.18	0.18			0.66			0.27
				6		16.4	23.6	9.0	9.0			11.8			
				12		9.7	12.4	6.3	6.3			3.7			
24		3.8	7.6	4.2	4.2			6.2							

* = Concentration in mcg/gm
 * = Percent of Dose

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TABLE 5. IN VITRO PROTEIN BINDING OF CETIRIZINE IN DIFFERENT SPECIES

<u>Species</u>	<u>NDA Report No.</u>	<u>Concentration Range (mcg/ml)</u>	<u>% Protein Bound</u>
Rat/ Sprague Dawley	NPK-6	0.05 - 10	88
Rabbit/ New Zealand	NPK-12	0.02 - 50	94
Dog/Beagle	NPK-14	0.05 - 20	90
Baboon	NPK-20	0.1 - 10.0	85
Monkey/ Cynomolgus	NPK-21	0.1 - 10.0	85



Summary and evaluation:

Cetirizine, code name UCBP071 and chemically known as 2-(2-(4(4-chlorophenyl)phenylmethyl)-1-piperazinyl)-ethoxy-acetic acid dihydrochloride, is to be marketed as an antihistamine (H₁-receptor antagonist). The tablet formulation is indicated for seasonal and perennial allergic rhinitis and chronic idiopathic urticaria. The proposed dosage is 5 to 10 mg a day given as a single dose. The daily dosage, however, may be increased to a maximum of 20 mg if sufficient response has not been obtained. Cetirizine is a member of piperazine class of compounds (diphenylmethane piperazine group) that include cyclizine, chlorcyclizine, meclizine and hydroxyzine. Cetirizine is a human metabolite of hydroxyzine which has been marketed as Atarax by Pfizer for more than 30 years. According to the Applicant, cetirizine possesses less sedating effect than hydroxyzine. Other members of piperazine compounds that are not marketed in this country include cinnarizine (antihistamine), flunarizine (vasodilator) and oxatomide (anti-allergic agent).

The preclinical studies were carried out by UCB (a Belgium corporation). Most of the studies were in compliance with the GLP; some had deviations that should not affect the data interpretation.

Efficacy:

Note: The ED₅₀ values on pages 2 38-2 39 are different from those listed under individual studies (e.g. NP-2, NP-4, NP-8, NP-10 on pages 5 31-5 193). The following review is based on the results from individual studies. The applicant will be asked to clarify the discrepancies.

The efficacy as an antihistamine (H₁ receptor antagonist) and anti-allergic agent was demonstrated in various standard tests. These tests included in vivo studies of lethality, bronchospasm and cutaneous reaction induced by histamine, bronchospasm induced by antigen and in vitro studies in guinea pig ileum, guinea pig trachea and human bronchi.

In histamine-induced lethality test, cetirizine was effective at 0.1 mg/kg (po) in the guinea pig-the most sensitive species. The onset was 1 hr and the duration was 12 hrs at this dose. The ED₅₀ value was 0.35 mg/kg (po). In histamine-induced bronchospasm in guinea pigs, cetirizine had ED₅₀ of 0.09 mg/kg (iv) and 0.46 mg/kg (id) and was less potent than clemastine and mepyramine. In histamine-induced cutaneous reaction test, the oral ED₅₀ values were 0.046 mg/kg (mice), 1.9 mg/kg (rat) and 1.8 mg/kg (guinea pig). In dogs the efficacy (50-75%) against histamine- or antigen-cutaneous reaction was observed in 1-2 hr at 0.1-1 mg/kg po and lasted 4-24 hrs. In this test cetirizine was more potent than terfenadine, clemastine, mepyramine and astemizole, but was equally potent as hydroxyzine. In Rhesus monkeys not only the histamine-induced, but also Compound 48/80, Substance P, Vasoactive Intestinal Peptide induced cutaneous reactions were inhibited at 10 mg/monkey (or 10 mg/kg, the exact dose unknown. see p 58 and p 5247, np-13) po at 2 hrs.

The anti-histamine and anti-allergic activities were further shown in antigen-induced bronchospasm tests. Cetirizine was effective in reducing the bronchospasms in passively immunized guinea pigs (ED₅₀ of 0.3 mg/kg po against iv antigen and effective at 4.6 mg/kg po against aerosol antigen). Against iv antigen challenge, cetirizine was equi-potent as hydroxyzine, was more potent than clemastine and terfenadine, but was less potent than mepyramine. Against aerosol antigen challenge, cetirizine was shown to be more potent than either mepyramine or clemastine.

In passively immunized rats (by anti-IgE serum), the bronchospasm was mainly due to the serotonin released from the mast cells on the respiratory smooth muscles of lungs and bronchi. Cetirizine and mepyramine had low efficacy, whereas hydroxyzine was effective. In compound 48/80-induced lethality in rats (both serotonin and histamine were released), cetirizine was highly effective (oral ED₅₀ of 0.14 mg/kg) and hydroxyzine (44 mg/kg po) was not effective.

The data suggested some anti-serotonin activity for cetirizine.

The anti-histamine activity was also demonstrated in *in vitro* studies such as guinea pig ileum, guinea pig trachea and human bronchi. In guinea pig ileum, cetirizine was less potent than hydroxyzine, terfenadine, mepyramine and clemastine. The specificity as an antihistamine, however, was demonstrated: cetirizine was without significant effect against Ach-, serotonin-, nicotine-induced contractions. The specificity as an antihistamine was also demonstrated in *in vivo* studies which included evaluating the efficacy against serotonin-, Ach- and histamine-induced bronchospasms in guinea pigs, against Compound 48/80-induced lethality, and serotonin- and histamine-induced cutaneous reactions in rats. It should be noted that some anti-serotonin activity (3.30X less potent than antihistamine activity) was demonstrated in these *in vivo* tests.

The antihistamine activity was further demonstrated in the histamine-induced hypotension in dogs. Significant reversal of BP were observed at 0.12-1.19 mg/kg (iv) which by themselves did not show cardiovascular effects in anesthetized dogs. But contrary to the findings in rats, no antiserotonin activity was demonstrated in dogs: the serotonin-induced hypertension was not affected.

The high potency as antihistamine was demonstrated in the isolated H₁ receptor preparations. Cetirizine bound to H₁ receptors from the brain and the lung of the guinea pig with as high affinity as terfenadine. But hydroxyzine, a sedating antihistamine, showed higher affinity (5-10X) than either cetirizine or terfenadine in this test. Although in isolated H₁ receptors, cetirizine showed equally high affinity for both brain and lung preparations, the penetration through the blood brain barrier following systemic administrations, nonetheless, was low.

In in vivo mouse study following 10 mg/kg ip, cetirizine penetrated through the blood brain barrier to less extent than those of chlorpheniramine and hydroxyzine (10% occupancy of brain H₁ receptor by cetirizine vs 85% occupancy by either chlorpheniramine or hydroxyzine): one of the bases for cetirizine as less sedating antihistamine. In another mouse study, the ratio of oral ED₅₀'s (3.9 mg/kg for inhibiting brain H₁ receptor binding vs 0.4 mg/kg for antihistamine skin reaction) showed better separation for cetirizine than for terfenadine or mepyramine. Pharmacokinetic studies also showed low concentrations in the brains of rats and dogs following either single or chronic administration.

In in vitro preparations isolated from guinea pig brain, no significant activity against serotonin, dopamine, alpha-1 adrenergic, muscarinic receptors and calcium channel was observed; some of these receptors may involve in the sedating effect of antihistamines.

No effect on anti-IgE-mediator release from human basophils was observed; higher doses caused mediators release due to cytotoxicity.

Thus the efficacy as an anti-histamine and anti-allergic agent acting through a mechanism of an H₁ receptor antagonist was demonstrated in the standard preclinical tests. Although the potency of cetirizine varied with the tests, cetirizine was shown to be more potent than hydroxyzine, terfenadine, clemastine and mepyramine in many of the tests where comparison drugs were included. Following oral administration the onset was generally observed in 1 hr and the duration is dose-dependent ranging from 4-24 hrs.

Neuropharmacology

The effects on CNS were evaluated in behavior, interaction and EEG studies.

The behavioral studies included general behavior studies in mice and rats, spontaneous exploratory activity and habituation to a new environment in rats, learning and retention of passive avoidance in rats, conditioned responses in dogs and retention and extinction of a conditioned food response in rats.

The general behavior studies showed no effects in mice at 45 mg/kg (ip & po) and in rats at 4.6 mg/kg (ip) or at 138 mg/kg (po). Sedation was observed at high doses of 92 mg/kg (ip) and at 138 mg/kg (po) in mice and at 46 mg/kg (ip) and 461 mg/kg (po) in rats. Deaths following stimulation and/or depression of CNS occurred at even higher doses: 138-462 mg/kg (ip) and 462-1364 mg/kg (po) in mice and 92 mg/kg (ip) and 462-923 mg/kg (po) in rats. In mice comparison was made following intraperitoneal administration of mepyramine and terfenadine. Mepyramine was without effect at 1 mg/kg and was stimulating/depressing at 3-46 mg/kg; terfenadine was without effect at 14 mg/kg and was stimulating/depressing at 47-141 mg/kg. In rats comparison was made with hydroxyzine only. Hydroxyzine was without effect at 13 mg/kg (ip) and at 48 mg/kg (po), but was sedating at higher doses of 48 mg/kg (ip) and at 134 mg/kg (po). The data suggest that cetirizine is less sedating than hydroxyzine, mepyramine or terfenadine.

No significant effects on learning, perceptive-motor, memory, motor coordination were observed in rats or dogs at 15 to 46 mg/kg (po or ip).

No neuroleptic, anticonvulsant, antiepileptic or interaction with pentobarbital in mice were observed up to 45 mg/kg (ip or po). No interaction with alcohol was observed in rats at 15 mg/kg po. In rabbits EEG study showed sedative effect (decreased durations of arousal at 1.5 mg/kg iv and increased duration of sleep at 46 mg/kg iv) though the arousal to the sound was not affected.

Thus the data showed that cetirizine was less sedating than hydroxyzine, mepyramine and terfenadine. Cetirizine was not shown to possess significant CNS effects, but at high dose cetirizine was also sedating.

Cardiovascular effects:

Both in vivo (rat and dog) and in vitro (rat aorta and perfused heart and guinea pig atrium) studies were carried out.

In anesthetized rats no significant cardiovascular effects were observed at 15 mg/kg (iv). At 26 mg/kg (iv) decreased blood pressure and at 46 mg/kg lethality were observed. In anesthetized dogs, slight increases of heart rate and blood pressure were observed at 15 mg/kg (iv), increased heart rate and decreased respiratory rate were observed at 15 mg/kg (id). ECG changes (conduction block) and decreased blood pressure were observed at sublethal cumulative doses of 87 mg/kg iv or 670 mg/kg id in dogs. In conscious dogs increased heart rate and blood pressure were observed at 12 mg/kg (iv), but no effect on ECG was observed. No modulation effects on the muscarinic, adrenergic (alpha and beta) receptors of the heart, no vagolytic, arrhythmic-inducing or inhibiting activities were observed.

The data therefore showed that cardiovascular effects were minimal. In dogs at 15 mg/kg (iv or id) some 10-20% increases of heart rate and blood pressure were observed. Sublethal doses caused conduction block and decreased blood pressure.

H₂ receptor activity:

No significant H₂ receptor activity was demonstrated. The conclusion was based on the results obtained from both in vivo (stress-induced ulcer in rats at 50 mg/kg po) and in vitro studies (rat aorta, atrium and heart preparations and isolated membrane preparation from guinea pig brain).

Anticholinergic activity:

In mice no mydriasis was observed at 138 mg/kg (po) or at 46 mg/kg (ip); no effects on oxotremorine-induced salivation and tremor was observed at 46 mg/kg (ip).

Thus no significant anticholinergic activity was demonstrated.

Analgesic and local anesthetic activity:

No significant analgesic activity was observed in acetic acid-writhing test in mice up to 92 mg/kg (po) or in tail-flick test in rats up to 138 mg/kg (sc). No local anesthetic activity was observed in corneal reflex test in guinea pigs up to a concentration of 14.6 mg/ml.

Anti-inflammatory activity and delayed hypersensitivity

No effects on the inflammatory response (carrageenan-induced paw edema in rats) or delayed hypersensitivity (sheep red cells-induced paw edema in mice) were observed at 46 mg/kg (iv) and 3 mg/kg (sc), respectively.

Pharmacology of PO26 (oxidative O-dealkylation product): the only identified metabolite in the urine and feces of all animal species and human studied. PO26 was a minor metabolite accounting for 5-10% dose in either urine or feces. PO26 was also detected in the plasma.

Efficacy:

In guinea pigs both the in vivo study of histamine-induced bronchospasm and the in vitro study of isolated ileum preparation, cetirizine is 30X more potent than PO26. In histamine-induced cutaneous reactions in mice and dogs, cetirizine was significantly more potent than PO26 which was also shown to be devoid of activity against antigen-induced bronchospasm in guinea pigs.

Behavioral effects:

General behavior study in mice following intraperitoneal administration showed "no-effect" doses at 46 mg/kg for cetirizine and at 11 mg/kg for PO26.

The only identified metabolite PO26 did not possess significant anti-histamine and anti-allergic activities. PO26 did not show significant CNS activity.

Toxicity:

The toxicity of Cetirizine was evaluated in acute (oral and intravenous studies in mice, rats and dogs), subacute (15-day and 1-month studies in mice and rats), and chronic (6-month studies in rats and dogs and 1-year studies in dogs and monkeys) studies.

Oral LD₅₀ values were 600 and 752 mg/kg in male and female mice and 703 and 865 mg/kg in male and female rats, respectively. The oral lethal dose was not determined in dogs due to vomiting at 160 mg/kg and above. The intravenous LD₅₀ values were 336 and 301 mg/kg in male and female mice, and 66 and 70 mg/kg in male and female rats, respectively. The intravenous lethal dose for dogs is 125 mg/kg. In the rat, the vast difference in the LD₅₀ values from oral and intravenous administrations indicated poor oral absorption and/or significant first pass effect in this species.

In rodents, the signs following oral and intravenous administrations were similar and were CNS-related. Sedation, unsteady gait, body tremors, jerking, hypertonicity of the hind legs, convulsions, dyspnea and cyanosis were observed. In dogs, increased heart rate at 80 mg/kg (po), nervousness and vomiting at 160 mg/kg (po); nervousness, unsteady gait, body tremors, muscular weakness at 70 mg/kg (iv) were observed. The surviving rodents and dogs appeared normal after 24 hrs. Necropsies were unremarkable, except for necrosis of tails following intravenous injection in the rodents.

Repeated dose toxicity studies showed species-specific effects/target organ toxicity in the livers of the rodents only, but not in the livers of either Beagle dogs or Cynomolgus monkeys.

-The adverse liver effects observed in rodents (mouse and rat) included increased liver weight with grossly enlarged liver, elevated liver enzymes such as SGPT/SGOT, increased/decreased (generally more increased) cholesterol and triglycerides/total lipids and microscopic findings of hypertrophy, vacuolation, fat deposition/steatosis of hepatocytes in periacinar, centrilobular or midzonal areas (necrosis only rarely). The applicant attributed the liver hypertrophy to enzyme induction and considered vacuolation and fat deposition as of toxicological significance.

The liver effects were observed at low-doses (10-20 mg/kg) in rodents following either gavage or diet administration for as short as 15 days. Some of the rodent studies were dose-range finding studies for carcinogenicity testings (mouse and rat), whereas other studies were designed to evaluate the reversibility of the liver effects with recovery periods of 4-weeks and 13-weeks following 1-month treatment (mouse and rat). In rats one chronic 6-month study (8, 25 and 75 mg/kg) was carried out with interim sacrifice at 3 months. Dose- and duration-related frequency and severity of liver effects were again shown. Three histopathological findings of hypertrophy, vacuolation and fat deposition of hepatocytes in the periacinar, centrilobular or mid-zonal areas were observed at 8-75 mg/kg in male rats and at 25-75 mg/kg in female rats. At 8 mg/kg (M) and 25 mg/kg (F) predominately the hypertrophy with some vacuolation were observed. At 75 mg/kg (the highest dose and the most affected group) extensive hypertrophy and vacuolation with some fat depositions were observed in many of the rats. The NOEL's was 8 mg/kg for female rats (20X maximum human dose of 20 mg/day), but was not established for male rats.

In both subacute and chronic studies, the liver effects were more prominent in male rodents, particularly the male rat and were attributed to greater extent of metabolism of the compound in these animals. Enzyme induction (increased microsomal enzymes and protein), proliferation of smooth endoplasmic reticulum (electron microscopic study) were observed in the rodents. The adverse liver effects (elevated liver enzymes, microsomal drug metabolizing enzymes, microsomal proteins and organ weights) were reversible following 4-week of recovery period. The histopathological changes, however, showed signs of reversibility only after 13-week of recovery.

The NOEL's in mice ranged 1-5 mg/kg (M) and 5-9 mg/kg (F) in different subacute studies of 15 days to 1 month. The liver effects were observed at 3-10 mg/kg (M) and at 10-40 mg/kg (F). In rats, the NOEL's ranged 18-25 mg/kg (M + F) in two 1-month studies. The affected levels were 54-75 mg/kg (M + F). In the 15-day study in rats, however, the affected levels (10-20 mg/kg) and the NOEL's (5 mg/kg) were lower than those of 1-month study. The reason was not given. The studies, however, were carried out by different laboratories (Sponsor and Huntingdon Research Centre). In rats other non-specific effects such as signs, body weight and food consumption were seen only at high doses of 75-160 mg/kg. Drug-related deaths were rare and occurred at high doses of 160-225 mg/kg (1-month) or 75 mg/kg (6-month).

In Beagle dogs and Cynomolgus monkeys, no specific target organ toxicities were established in both subacute and chronic studies. Deaths occurred only at high doses of 75 mg/kg (dogs) and 150 mg/kg (monkeys). Weight losses, decreased food consumption and signs were observed in dogs at 135 mg/kg (1-month), 25 mg/kg (6-month) and 15 mg/kg (1-year) and in monkeys at 50 mg/kg (14-day and 4-Week) and 45 mg/kg (1-year). The signs depending on the doses included vomiting, salivation, tremor, ataxia, quiet behavior, hypothermia, poor coat/piloerection and loose mucus feces in both dogs and monkeys. The relative "no-effect" levels were noted in dogs at 45 mg/kg (1-month), 8 mg/kg (6-month) and 4 mg/kg (1-year) and in monkeys at 17 mg/kg (4-Week), and 15 mg/kg (1-year). These "no-effect" doses were 10X maximum human dose of 20 mg/day in dogs and 40X maximum human dose in monkeys following chronic administration. Non-specific adverse effects on body weight, food consumption and signs occurred at 40X human dose in dogs and at 112X human dose in monkeys.

From the pharmacokinetic data, dogs and monkeys shared more similar ADME patterns with human than the rodents. Therefore, the animal toxicity studies particularly those from the dog and the monkey provided adequate margin of safety for the proposed human use. The liver effects in rodents appear to be species-specific. The available human data did not show significant drug-related liver effects. It should be noted that in the female rat, the NOEL's for liver (from 6-month study) was 8 mg/kg, but NOEL's for stomach was not established (drug-related ulceration of stomach occurred from the low dose of 3 mg/kg in the 2-year carcinogenicity study). In the male rat, the NOEL's for liver (from 6-month study) was not established, but was shown to be at 3 mg/kg from the 2-year carcinogenicity study. The stomach effect was considered another species specific effect, since it was not found in other species.

Thus the toxicological profiles from four species of laboratory animals support the relative safe use for the proposed 10-20 mg/day in human. The

species specific target organ toxicities (liver and stomach) in the rodents, however, should be included in the Package Insert under "Animal Toxicology" section.

Carcinogenicity studies in two species were carried out by Huntingdon Research Centre of England in 1984 according to the GLP rules and regulations.

In a mouse 2-year feeding study, 5 groups of CD-1 mice (52/sex/group) consisted of 2 control groups and 3 dosed groups at 1, 4 and 16 mg/kg, which approximated 5X, 20X and 80X human dose of 10 mg/day or 2.5X, 10X and 40X maximum human dose of 20 mg/day.

During and at the end of the study, no drug-related effects were observed in mortality, signs, body weight, food consumption and blood smears. The target organ toxicities of liver such as hypertrophy, vacuolation and fat deposition were not observed. Thus it can be questioned whether MTD was employed, especially in the female mice. The MTD's, however, were selected based on the profiles from 3 subacute toxicity (15 day-4 week) studies which showed liver effects at 3-10 mg/kg (M) and at 10-27 mg/kg (F). The selection of 16 mg/kg as high dose or MTD therefore was justified.

The neoplastic changes included increases of benign liver tumors in 16 mg/kg-male mice and lymphosarcoma in multiple organs in 16 mg/kg-female mice. The statistical analysis and evaluation by Division of Biometrics (HFD-715) concluded that benign liver tumor was significant (same conclusion by the Applicant). The dosage represents 80X human dose of 10 mg/day or 40X maximum human dose of 20 mg/day. Lymphosarcoma in multiple organs were not statistically significant. The non-neoplastic changes included liver masses in male mice at 16 mg/kg level.

In a rat 2-year feeding study, 5 groups of rats (50/sex/group) consisted of 2 control groups and 3 dosed groups at 3, 8 and 20 mg/kg, or approximately 15X, 40X and 100X human dose of 10 mg/day or 7.5X, 20X and 50X maximum human dose of 20 mg/day.

During and at the end of the study, no drug-related effects were observed on mortality, signs, body weight, food consumption and blood smears in these rats. Drug-related target organ toxicities of the livers (enlarged/swollen liver with periportal fat deposition, and vacuolation), however, were observed at 8-20 mg/kg (M) and at 8 mg/kg (F). The MTD was employed.

The neoplastic changes included thyroid follicular adenoma in 20 mg/kg male rats, pituitary carcinoma in 8 mg/kg female rats and malignant liver tumors in 8 mg/kg male rats. The malignant liver tumors and pituitary carcinoma were not considered biologically significant, because the high dose group was not affected. The thyroid follicular adenoma in 20-mg/kg male rats was statistically significant, the trend over groups 1-5 was also significant. In addition, for combined benign and malignant follicular tumors, the test for trend over groups 1 to 5 was also significant. The thyroid follicular adenoma was considered a common tumor in male rats based on the historical control data showing greater than 1% incidence. The statistical evaluation by HFD-715 concluded the finding not significant (for a common tumor type to be significant, the p-value should be less than 0.01). Mammary gland fibroadenoma with epithelial atypia appeared to increase in the dosed female groups, but was not found to be statistically significant.

The significant non-neoplastic changes were ulceration of stomach in 3, 8 and 20 mg/kg female rats and liver effects (enlarged liver with fat deposition, and vacuolation) in 8-20 mg/kg male rats and 8 mg/kg female rats. Enlarged kidneys with progressive glomerulonephrosis in dosed male and female groups were probably due to old age and exaggerated by the compound. The stomach and kidney effects were not observed in other rat studies of shorter durations (1-6 month). Subchronic and chronic studies in dogs and monkeys did not show stomach and kidneys effects either. The stomach effect in female rats probably represents another species specific effect.

From the results of the carcinogenicity studies, cetirizine induced benign liver tumors in male mice at 16 mg/kg or 40X maximum human dose of 20 mg/day. Since no significant finding of either benign or malignant liver tumors were observed in rats, the significant finding of this common liver tumor in male mice alone should not affect the approvability of the application. The thyroid follicular adenoma in the male rats at 20 mg/kg was not considered significant from statistical point of view. The findings of benign liver tumors in male mice and thyroid follicular adenoma in male rats should be included in the Package Insert.

Reproduction studies:

In comparison with the rat, the mouse exhibited a pharmacokinetic pattern relatively closer to man (both mouse and man metabolize cetirizine to less extent than rat). Therefore the mouse was chosen by Applicant as the species in the Segment I, II and III studies. In addition, Segment II reproduction studies were carried out in the rat and the rabbit.

The Segment I study was carried out in the dosed male and dosed female mice at 4, 16 and 64 mg/kg. The durations were in males 8 weeks prior to mating and through mating and in females 2 weeks prior to mating and continued on until either sacrificing on day 17.5 of pregnancy or after rearing young to day 21 postpartum. The study also extended to the development and reproductive functions of F₁ and F₂ generations. The results showed that the pregnancy rate was decreased slightly at 64 mg/kg (90% vs 100% control). This was probably due to the effects on the mating performance: delayed and reduced mating performance (more mid and high dosed mice mated on or after 6 days and showed no positive mating). In addition, increased gestation period, lower litter size and some malformations (cleft palate, partial or bilateral open eyes) at 64 mg/kg, total skeletal variants/anomalies (sternbrae: unossified, reduced, bipartite; cervical ribs, reduced metatarsals and occipital) at 16-64 mg/kg, but mostly at 64 mg/kg, were observed. The relative "no-effect" dose was 4 mg/kg. F₁ and F₂ generations did not show adverse effect on their development or reproductive function. In this study, high dosed dams but not the offsprings showed increased liver weight with histopathology of hepatocyte hypertrophy at 64 mg/kg.

Segment II studies were carried out in mice (6, 24, 96 mg/kg), rats (8, 25, 75, 225 mg/kg) and rabbits (15, 45 and 135 mg/kg). No significant embryocidal or teratogenic effects were observed in mice and rabbits up to the highest doses tested or 240X and 338X maximum human doses, respectively. In rats embryocidal effects (percent of pre- and post-implantation losses) at 225 mg/kg (562X maximum human dose), but no teratogenic effects were observed. Skeletal variants or anomalies (refer to the preceding paragraph) were observed at 135 mg/kg (rabbits) or from 25 mg/kg (rats).

Although the results of Segment II reproduction studies in mice, rats and rabbits showed that cetirizine was not teratogenic, it should be noted that other structurally related antihistamines such as cyclizine, meclizine, chlorcyclizine and hydroxyzine are known teratogens in the laboratory animals. Cleft palates were observed in 1 fetus of 16 mg/kg and 4 fetuses of 64 mg/kg in Segment I mouse study. In light of negative findings from all three Segment II studies in 3 species (i.e. mouse, rat and rabbit), the finding of cleft palate from Segment I study are not considered significant. Other anomalies in the kidneys (pelvic cavitation/hypertrophy/hemorrhage/displacement/hydronephrosis in rats and in rabbits) and in brain (meningocele, hydrocephaly, microcephaly with incomplete development of frontal and parietal bones in rabbits) were sporadically observed in the dosed groups without apparent dose-related effects. The cyclizine compounds, however, have not been shown to be teratogens in human.

Segment III reproduction study in mice (6, 24 and 96 mg/kg) suggested that nursing and/or lactating performance was affected at 96 mg/kg because of lower pup weight gains from Day 4 to weaning (Day 21). No significant adverse effects on the development of the pups were evident based on several parameters monitored. Late fetal development or labor did not appear to be affected. Increased liver weights were again observed in the dams of 96 mg/kg. Thus the relative "no-effect" dose in this segment was at 6 mg/kg. Nursing/lactating performance (decreased pup weight gains on Day 4-weaning) was probably affected at 96 mg/kg (240X maximum human dose).

Based on the results from all reproduction studies, the relative "no-effect" doses were 4-6 mg/kg in mice, 8 mg/kg in rats and 15 mg/kg in rabbits. These doses represent at least 20X human dose of 10 mg/day or 10X maximum human dose of 20 mg/day. Adverse reproductive effects in mice included male and/or female mating performance (delayed mating days and no positive mating resulting in slightly lower pregnancy rate) at 64 mg/kg or 160X maximum human dose and lactating/nursing performance (decreased pup weight gains on Day 4 to weaning) at 96 mg/kg or 240X maximum human dose. Skeletal variants/anomalies were generally affected at high doses of 64 mg/kg in mice, 225 mg/kg in rats and at 135 mg/kg in rabbits.

Embryocidal effects in rats were observed at 225 mg/kg or 562X maximum human dose. It should be noted that the mouse, though metabolizing cetirizine to less extent than the rat, still metabolizes cetirizine to greater extent than human. The animal reproduction studies, nonetheless, revealed a profile that provides adequate margin of safety for the drug to be used in women of childbearing potential. The adverse effects at high doses should be included in the package insert.

In the package insert cetirizine is placed under Pregnancy Category C. The wording, however, should be as follows: Cetirizine has not been shown to be teratogenic in mice, rats or rabbits. Cetirizine has been shown to have an embryocidal effect only in rats (at 225 mg/kg or 562X maximum human dose of 20 mg/day), but not in mice (at 96 mg/kg or 240X maximum human dose) or in rabbits (at 135 mg/kg or 338X maximum human dose). Mating performance of male and/or female mice (delayed and reduced matings) appeared to be affected at 96 mg/kg (240X maximum human dose). Skeletal variants/anomalies together with maternal toxicity were predominately observed at the high doses of 64 mg/kg (or 160X maximum human dose) in mice, 225 mg/kg (or 562X maximum human dose) in rats and 135 mg/kg (or 338X maximum human dose) in rabbits. Nursing/lactating performance (retarded pup weight gains on Days 4-21 postpartum) were affected at 96 mg/kg (or 240X maximum human dose) in mice. There are no adequate and well-controlled studies in pregnant women. Cetirizine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Mutagenesis Studies:

Four studies were carried out. Ames Test (8-5000 mcg/plate), Chromosomal Aberrations Assay in Human Peripheral Lymphocytes (20-500 mcg/ml), Mouse Lymphoma TK Locus Assay (100-460 mcg/ml), and Micronucleus Test in Mouse (14-350 mg/kg/day) showed negative results suggesting no mutagenic potential for the compound.

Absorption, distribution, metabolism and excretion:

Twenty four studies were conducted in six animal species (mouse, rat, rabbit, dog, baboon and cynomolgus monkey). Both C^{14} -cetirizine and cold drug (GLC and HPLC) were used in animal and human studies. The results showed qualitative similarity among animals and man; though dogs and monkeys exhibited patterns closer to those of man.

Absorption:

Cetirizine is well and rapidly absorbed following oral doses (10 mg/kg) in all animal species and man. The peak plasma concentrations of 8-19 mcg/ml were reached in 1 hr (mouse, rabbit, monkey) and 3 hrs (dog) and of 300 mcg/ml was reached in 1 hr (man). The rat is the species that showed extensive metabolism resulting in lower peak plasma levels of unchanged drug of 2 mcg/ml (M) and 4 mcg/ml (F), reached in half hour. In addition, the rat is the species that showed sex-related difference: the male metabolized cetirizine to even greater extent than the female. The oral bioavailability is 71-100% in mouse, rabbit and dog, 51-87% in baboon and monkey and only 36-46% in rat. The pharmacokinetics are linear up to 10 mg/kg in all species and man except the rat. The elimination half-life is less than 1 hr (rat), 1-3 hrs (mouse, rabbit and monkey) and 7-9 hrs (dog and man). The apparent volume of distribution was 0.45 l/kg in man. In animals and man no significant accumulation was observed.

Distribution:

In rats and dogs, liver and kidneys had the highest levels, followed by lungs, plasma, adrenal, spleen, heart and pituitary gland. The cerebrum and cerebellum had the lowest level. Placental transfer was observed in the rat (radioautography) but not in the rabbit (measurement of tissue radioactivity level). The drug was secreted in the milk of dogs. The drug showed high plasma protein binding in all species and man (90% and more).

Metabolism:

Cetirizine was not extensively metabolized except in the rat and mouse. Male rodents metabolized the compound to the greatest extent (80-90% dose). Oxidative O-dealkylation to PO26 is the only metabolite identified in both urine and feces of all animal species tested and the man. PO26, however, appeared to be a minor metabolite, accounting no more than 5-10% dose in either urine or feces from either rats or dogs. In these species, there are additional 4-7 unidentified metabolites. The biotransformation pathways therefore are not fully known. In man about 20% of the dose was metabolized; less than 4% as PO26.

Excretion:

Both urine and feces contributed to the excretion which was generally completed in 96 hrs. In the rat excretion of unchanged drug were low (1-20% in male urine and 9-33% in female urine following chronic dosings at 8-225 mg/kg/day). Urinary excretion accounted for 12-53% dose and fecal excretion accounted for 65-83% dose in rats. In mice, urinary excretion accounted for 37-58% dose and fecal excretion accounted for 44-66% dose. In man, 60% of the administered dose was excreted unchanged in urine. Nonrenal clearance accounted for 20% of total body clearance.

In both rodents, females had higher urinary excretion than fecal excretion and males had higher fecal excretion than urinary excretion. In dogs following oral 0.6 mg/kg/day for 9 days, urinary excretion accounted for 40% dose and fecal excretion accounted for 46% dose over 96 hrs. In urine unchanged drug represented 32-40% dose. The accumulation rate was 14% in 9 days. In primates (baboon and monkey), 30% dose was collected in 72 hr-urine as unchanged drug.

Enterohepatic circulation occurred in rats, dogs and monkeys, especially the male rodents

In summary, dogs, baboons and monkeys eliminated a constant proportion of unchanged drug in urine over wide ranges of doses whereas rats showed dose-dependent rates of elimination. There were sex-related differences in rats and mice but not in dogs and primates. The rodents, especially the male rat, metabolized the compound extensively. From the data, dogs, monkeys and man share more similar patterns of ADME.

Conclusions

- (1) Cetirizine has been shown to possess antihistamine activity. Its potency varied with the models and tests, ranging from 1X-10X that of hydroxyzine. In many studies where comparison drugs were included cetirizine was shown to be more potent than terfenadine, clemastine and mepyramine. Following oral administration, the effect was generally observed in 1 hr, and the duration varied with doses ranging from 4 to 24 hrs in different studies.
- (2) Cetirizine crossed the blood brain barrier to less extent than hydroxyzine. EEG study in rabbits showed sedative effects at intravenous dose of 1.3 mg/kg. Additional behavioral studies did not show significant CNS effects at oral dose below 14 mg/kg. Higher doses caused excitation and/or depression.
- (3) No significant cardiovascular effects were observed except at high doses of 14-461 mg/kg which progressively cause decreased BP/tachycardia/ECG changes/respiratory depression/death. No significant H₂-receptor, anticholinergic, analgesic, local anesthetic or anti-inflammatory activities were demonstrated in animal studies. No effects on mediator release were shown. No active metabolite was demonstrated.
- (2) Acute toxicity was low in rodents and dogs. Repeated-dose treatment showed species-specific target organ toxicity in rodents only. In mice and rats, liver appeared to be the target organ with hypertrophy, vacuolation/steatosis (fat deposition). The liver effects, mostly reversible, were attributed to extensive metabolism and enzyme induction (hypertrophy/enlargement) and toxic effect (vacuolation and fat deposition). Male rat with the highest extent of metabolism was the most sensitive species. The liver effects were observed at 8 mg/kg (male rats) and 25 mg/kg (female rats) in the 6-month study. The "no-effect" level was not established in male rats and was established at 8 mg/kg in female rats.

In both beagle dogs and cynomolgus monkeys, no specific target organ toxicity was demonstrated in the 1-year studies. Non-specific effects such as body weight and/or signs of salivation and vomiting were observed at 15 mg/kg (dogs) and at 45 mg/kg (monkeys); the relative "no-effect" doses were 4 mg/kg (dogs) and 15 mg/kg (monkeys).

Cetirizine was not carcinogenic or tumorigenic in female rats or in female mice. In male rodents, benign tumors were increased. In male mice, significant increases of benign liver tumors (common benign tumors in male mice) and liver masses were observed at 16 mg/kg (40X maximum human dose). The finding, represents species-specific, should be included in the labeling. Thyroid follicular adenoma observed at 20 mg/kg (or 50X maximum human dose) in the male rat should be included in the labeling.

Cetirizine was not shown to be mutagenic in four in vitro and in vivo mutagenesis studies.

- (3) Pharmacokinetic studies showed qualitative similarity among animals and man. The compound was absorbed following oral administration and distributed to liver, kidneys and lungs. Cetirizine crossed placental blood barrier in the rat but not in the rabbit. Cetirizine was secreted in the milk of the dog. Both urine and feces contributed to the excretion which generally was completed in 96 hrs. The most significant finding was the extent of metabolism between rodents and other animal species (i.e. dog, monkey). Cetirizine was extensively metabolized in rats (especially male rats-90% metabolized), followed by mice (60%), dogs (30-40%) and man (20%). Therefore unchanged drug accounted for 30-40% (dogs) and 10-20% (rats) each in the urine and the feces. An oxidative O-dealkylation product, PO26, and additional 4-7 unidentified metabolites were present in both urine and feces. No active metabolite was identified. Comparatively, dog and monkey exhibited patterns closer to those of human.
- (4) Cetirizine has not been shown to be teratogenic in the mouse, the rat and the rabbit. Embryocidal effect was observed in rats at 225 mg/kg (562X maximum human dose), but not in mice (96 mg/kg or 240X maximum human dose) or in rabbits (135 mg/kg or 338X maximum human dose). Skeletal variants/anomalies were observed at 64 mg/kg (160X maximum human dose) in mice, at 75 mg/kg (188X maximum human dose) in rats and at 135 mg/kg (338X maximum human dose) in rabbits. Maternal toxicity was observed at high doses of 225 mg/kg in rats and at 135 mg/kg in rabbits. Mating performance (delayed and reduced matings) were affected at high doses of 64 mg/kg (160X maximum human dose) in mice. Lactating and/or nursing performance (decreased pup weight gains on Day 4-21 postpartum) were affected at 96 mg/kg (or 240X maximum human dose) in mice.
- (5) The Deficiencies in the Package Insert should be amended before the application can be approved.
- An "Animal Toxicology" section should be included. Species-specific target organ toxicities in the livers (male and female mice and rats) and stomach (female rats only) should be described.
 - Under Carcinogenesis, mutagenesis, impairment of fertility, the actual dosage (16 mg/kg) at which benign liver tumors in male mice was observed should be included in addition to the human multiples which are described. The finding of thyroid follicular adenoma in male rats at 20 mg/kg or 50X maximum human dose of 20 mg/day should be included.
 - Under "Overdosage" section, oral (LD₅₀ values or) minimal lethal doses in the rodents should be included in addition to the human multiples.

(d) Under "Pregnancy Category C", the following wording is recommended:

Cetirizine has not been shown to be teratogenic in mice, rats or rabbits. Cetirizine has been shown to have an embryocidal effect in rats (at 225 mg/kg or 562X maximum human dose of 20 mg/day), but not in mice (at 96 mg/kg or 240X maximum human dose of 20 mg/day) or in rabbits (at 135 mg/kg or 338X maximum human dose). Adverse reproductive effects generally associated with maternal toxicity were observed at high doses or high multiples of the maximal human dose. Mating performance of male and/or female mice (delayed and reduced matings) appeared affected at 96 mg/kg (240X maximal human dose). Skeletal variants/anomalies mostly due to reduced- and/or un-ossification were observed at 64 mg/kg (160X maximum human dose) in mice, at 225 mg/kg (562X maximum human dose) in rats and at 135 mg/kg (338X maximum human dose) in rabbits. Nursing/lactating performance (retarded pup weight gains on Day 4-21 postpartum) was affected at 96 mg/kg (240X maximum human dose) in mice. There are no adequate and well-controlled studies in pregnant women. Cetirizine should be used during pregnancy only if potential benefit justifies the potential risk to the fetus.

Recommendations:

From the conclusions (1)-(4) above, cetirizine has been studied extensively in the laboratory animals to document its pharmacological and toxicological profiles. Cetirizine can be labeled to support its relatively safe and efficacious use in human. The application is therefore approvable based on pharmacology. However, before the application can be approved, the deficiencies in the Package Insert should be amended.

To Medical Officer:

Although adverse liver effects in the rodents appear to be species-specific, the clinical studies should be appraised for liver enzymes profile (toxicity).

Pharmacology Portion of Letter to Applicant:

From pharmacology standpoint, in order to provide assurance of relatively safe and efficacious use of cetirizine in human, the Package Insert should be amended before the application can be approved.

The deficiencies in the Package Insert are as follows:

- (a) An "Animal Toxicology" section should be included. Species-specific target organ toxicities in the livers (male and female mice and rats) and stomach (female rats only) should be described.
- (b) Under Carcinogenesis, mutagenesis, impairment of fertility, the actual dosage (16 mg/kg) at which benign liver tumors in male mice was observed should be included in addition to the human multiples which are used solely. The finding of thyroid follicular adenoma in male rats at 20 mg/kg or 50X maximum human dose of 20 mg/day should be included.

- (c) Under "Overdosage" section, oral (LD₅₀ values or) minimal lethal doses in the rodents should be included in addition to the human multiples.
- (d) Under "Pregnancy Category C", the following wording is recommended:

Cetirizine has not been shown to be teratogenic in mice, rats or rabbits. Cetirizine has been shown to have an embryocidal effect in rats (at 225 mg/kg or 562X maximum human dose of 20 mg/day), but not in mice (at 96 mg/kg or 240X maximum human dose of 20 mg/day) or in rabbits (at 135 mg/kg or 338X maximum human dose). Adverse reproductive effects generally associated with maternal toxicity were observed at high doses or high multiples of the maximal human dose. Mating performance of male and/or female mice (delayed and reduced matings) appeared affected at 96 mg/kg (240X maximal human dose). Skeletal variants/anomalies mostly due to reduced- and/or unossification were observed at 64 mg/kg (160X maximum human dose) in mice, at 225 mg/kg (562X maximum human dose) in rats and at 135 mg/kg (338X maximum human dose) in rabbits. Nursing/lactating performance (retarded pup weight gains on Day 4-21 postpartum) was affected at 96 mg/kg (240X maximum human dose) in mice. There are no adequate and well-controlled studies in pregnant women. Cetirizine should be used during pregnancy only if potential benefit justifies the potential risk the fetus.

It was noted that the ED₅₀ values on pages 2 38 to 2 39 are different from those listed under individual studies (e.g. NP-2, NP-4, NP-8, NP-10 on pages 5 31 to 5 193). Likewise, under NP-13, the dosage for monkey was not clear (10 mg/kg on page 5 8 and 10 mg/animal on page 5 247). Please clarify the discrepancies.


Dou Huey Jean, Ph.D.
Pharmacologist

cc: NDA 19-835
HFD-160
HFD-340
CSO-Ladet
R/D DJean 4/11/89
R/D Init. by JInscoc
Typed by LGiesick 4/19/89, 9/29/89
Wang #7234P &
pgs. 99-119 7241P

 12-17-92

Statistical Review and Evaluation

NDA #: 19-835

Date: MAR 6 1989

Applicant: Pfizer Inc.

Name of Drug: Cetirizine Hydrochloride Tablets (ucb P071)

Documents Reviewed:

1. NDA Submission Volume 22 of 116.
2. NDA Submission Volume 26 of 116, pp. 1427-1432.
3. NDA Submission Volume 27 of 116.
4. NDA Submission Volume 32 of 116, pp. 1533-1552.

I. Background

Two animal carcinogenicity studies (one in rats, and one in mice) were included in this NDA submission. These two studies are intended to assess the oncogenic potential of Cetirizine hydrochloride tablets (ucb P071) in rats and mice by continuous dietary administration over 2 years. Dr. Dou Huey Jean, HFD-160 who is the reviewing pharmacologist of this NDA had requested the Division of Biometrics to perform the statistical review and evaluation of these two studies. The results of this review have been discussed with Dr. Jean.

II. The Rat Study

II. a. Design

In this study, 500 Charles River CD-1 rats of the Sprague-Dawley strain were randomly and equally distributed among 5 groups of 50 males and 50 females each. Two groups receiving normal diet served as controls. The other three groups received the test compound, ucb P071, with the diet at doses of 3, 8, or 20 mg/kg/day for 2 years. All rats, including those dying/killed moribund during the study and those killed at termination of the study, were subjected to a complete postmortem examination.

II. b. Sponsor's Analyses

The sponsor reported mortality data for every 26 weeks on page 24, Volume 27 of 116. No statistical analyses were carried out on the mortality data. Based on the survival percentage of rats in every 26 weeks, the sponsor concluded that "Neither the incidence nor distribution of mortalities indicated any pattern of deaths attributable to treatment with ucb P071."

The prevalence method for incidental tumors and death rate method for fatal tumors described in the paper of Peto et al. ("Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments", In Long-Term and Short-Term Screening Assays for Carcinogens: A Critical Appraisal, International Agency for Research on Cancer Monographs, Annex to Supplement 2, World Health Organization, 311-426, 1980) were used to analyze the tumor data. The sponsor stated that all tumor types recorded were within the normal historical control range for this strain of rat in this laboratory. Only tumors of thyroid glands, pituitary glands and liver revealed greater numbers in some treated groups when compared to the controls. These tumors were therefore subjected to detailed statistical analyses.

The sponsor's results showed that the positive dose-response relationship was significant in male rats in the incidence of benign thyroid follicular tumors (include adenoma and cystadenoma; $p = 0.009$) and benign or malignant thyroid follicular tumors (include adenoma, cystadenoma and adenocarcinoma; $p = 0.03$). In addition, the benign liver cell tumors in the female rats also showed a significant positive dose-response relationship ($p = 0.045$). Although the sponsor found that there was no significant positive dose-response relationship in pituitary gland tumors (combined, malignant and benign) in female rats, a significantly greater number of pituitary tumors was seen in female rats receiving 8 mg/kg/day ucb P071 when compared to controls (malignant: $p = 0.01$; combined: $p = 0.03$). In this review, the phrase "positive dose-response relationship" refers to the increasing linear component of the effect of treatment, and not necessarily to a strictly increasing mortality or tumor rate as dose increases.

The sponsor compared the prevalence rates of thyroid follicular tumor of the high dose group in this study with those of a historical control data from 15 studies completed in the same laboratory, and concluded that "in the light of the fact that the incidence is within the historical control values the result seen in this study was considered fortuitous.". The sponsor also stated that the incidences of pituitary tumors in female rats receiving 8 mg/kg/day and 20 mg/kg/day ucb P071 (37/50 and 35/50, respectively) are within the range of historical control values from 15 studies completed in this laboratory.

II. c. Reviewer's Analyses and Comments

The data of two control groups were combined in the reviewer's analyses. The intercurrent mortality rates for both male and female rats (see Table 1) were tested for dose-response relationship according to the death rate method given in the paper of Peto et al. (1980) using time intervals 0-26, 27-52, 53-78, 79-104, and 105-106 weeks. The actual dose levels 0, 3, 8, and 20 were the scores assigned to the control, low, medium, and high dose groups, respectively. The results of the analyses showed no significant dose-response relationship in the intercurrent mortality rates in either males ($p = 0.3263$) or females rats ($p = 0.7049$).

Since there was no significant dose-response relationship in intercurrent mortality rates, the prevalence method and the death rate method described in the paper of Peto et al. (1980) and an exact permutation trend test with the whole study period as one interval were used to test the positive dose-response relationship in the tumor data. Following Dr. Jean's suggestions, the reviewer only analyzed the data of thyroid follicular adenoma in male rats, pituitary adenoma and carcinoma and mammary fibroadenoma in female rats.

Of the tumor types tested, the thyroid follicular adenoma showed a significant (at 0.05 level) dose-response relationship in male ($p = 0.039$). However, the prevalence rate of this tumor in the concurrent control group is greater than one percent. It is considered as a common tumor in this strain of rat. For a common tumor, we consider a positive dose-response relationship not to occur by chance of variation only if the p -value is smaller than 0.01. Therefore we do not regard the positive dose-response relationship in thyroid follicular adenoma in male rats as statistically significant.

III. The Mouse Study

III. a. Design

In this study, 520 Charles River CD-1 mice were randomly and equally distributed among 5 groups of 52 males and 52 females each. The test compound, ucb P071, was administered by admixture with the diet to three groups of mice at doses of 1, 4, or 16 mg/kg/day for 2 years. The other two groups receiving normal diet served as controls. Detailed physical examinations, individual body weights and food consumption measurements were recorded weekly. Animals survived at the end of the study periods were sacrificed for postmortem examinations.

III. b. Sponsor's Analyses

The sponsor reported mortality data for every 26 weeks on page 10, Volume 22 of 116. No statistical analyses were carried out on the mortality data. Based on the survival percentage of mice in every 26 weeks, the sponsor concluded that "Neither the incidence nor distribution of mortalities indicated any pattern of deaths attributable to treatment with ucb P071."

Using the prevalence method and the death rate method described in Peto et. al. (1980), the sponsor analyzed the following tumors in male mice: the liver cell (benign and malignant combined) and malignant liver cell. the sponsor's results showed that there was a significant positive dose-response relationship in liver cell (benign and malignant combined) tumors in male mice ($p = 0.01$). The high dose group showed significantly more liver cell tumors than the control in male mice ($p = 0.02$).

III. c. Reviewer's Analyses and Comments

The data of two control groups were combined in the reviewer's analyses. The intercurrent mortality rates for both male and female mice (see Table 2) were tested for dose-response relationship according to the death rate method given in the paper of Peto et al. (1980) using time intervals 0-26, 27-52, 53-78, 79-104, and 105-106 weeks. The actual dose levels 0, 1, 4, and 16 were the scores assigned to the control, low, medium, and high dose groups, respectively. The results of the analyses showed no significant dose-response relationship in the intercurrent mortality rates in either males ($p = 0.6292$) or female mice ($p = 0.6389$).

Since there was no significant dose-response relationship in intercurrent mortality rates, the Peto's methods and an exact permutation trend test with the whole study period as one interval were used to test the positive dose-response relationship in the tumor data. Following Dr. Jean's suggestions, the reviewer only analyzed the following tumors: multiple benign liver cell tumors in male mice and lymphosarcoma in multiple organs in female mice. Of the tumor types tested, the multiple benign liver cell tumors showed a significant dose-response relationship in male ($p=0.0021$). The incidences of male mice with benign liver cell tumors are given as follows:

	Group			
	Control	Low	Medium	High
Animals with any benign liver cell tumors	27	15	15	25
Total animals examined	104	52	52	52
Percentage	25.96	28.84	28.84	48.07

The sponsor stated that the incidence of liver cell tumors in untreated control male mice of this strain is known to be variable. He also reported the historical control data from 9 studies completed in the same laboratory as follows:

	Study								
	81E	82A	82B	82C	82D	82E	82F	83A	83B
Benign liver cell tumors	2	13	15	6	16	11	12	14	9
No. of mice	52	104	104	52	88	52	52	52	52
Percentage	3.8	12.5	14.4	11.5	18.2	21.2	23.1	26.9	17.3

From the above tables, it shows that the incidence of male mice with benign liver cell tumors for the high dose group (48.07%) is well above the sponsor's historical control range (3.8% to 26.9%). The incidences for the low and medium dose group (28.84% in both groups) also fall outside the historical control range.

IV. Summary

In this review, the phrase "positive dose-response relationship" refers to the increasing linear component of the effect of treatment, and not necessarily to a strictly increasing tumor or mortality rate as dose increases.

IV. a. The Rat Study

The oncogenic potential of Cetirizine hydrochloride tablets was evaluated in this rat study when administered by admixture with the diet to both sexes at doses of 0, 3, 8, or 20 mg/kg/day for 2 years. The statistical methods given in the paper of Peto et al. (1980) and an exact permutation trend test were used to test the dose-response relationship in intercurrent mortality and incidental tumor rates.

The results of the above analyses showed that there is no significant positive dose-response relationship in mortality rate in both male and female rats, nor is there significant positive dose-response relationship in tumors tested for male or female rats.

IV. b. The Mouse Study

In this animal carcinogenicity study, Cetirizine hydrochloride tablets were evaluated for its oncogenic potential in mice when administered by admixture with the diet to both sexes at dosage levels of 0, 1, 4, or 16 mg/kg/day for 2 years. The statistical methods given in the paper of Peto et al. (1980) and an exact permutation trend test were used to test the dose-response relationship in intercurrent mortality and incidental tumor rates.

Our analyses show that there is no significant dose-response relationship in mortality rate in both male and female mice. However, there is a significant ($p = 0.0021$) positive dose-response relationship in multiple benign liver cell tumors in male mice.

Daphne Lin 3/3/89

Daphne Lin, Ph.D.
Mathematical Statistician

Concur: Karl K. Lin 3/3/89
Karl K. Lin, Ph.D., Group Leader, SARB

WR 7 3/3/89
William R. Fairweather, Ph.D., Chief, SARB

cc: Original NDA 19-835

✓ HFD-160/Dr. Walters

HFD-160/Dr. Jean

HFD-160/Mr. Ledet

HFD-710/Chron

HFD-715/Dr. Fairweather

HFD-715/Dr. Karl Lin

HFD-715/Dr. Daphne Lin

HFD-102/Dr. Chah

HFD-715/DRU 2.1.1, Cetirizine, Pfizer Inc.

Table 1
Intercurrent Mortality Rates
Male Rats

Weeks	Control			Low			Medium			High		
	Start	D	%	Start	D	%	Start	D	%	Start	D	%
0-26	100	2	2	50	1	2	50	1	2	50	0	0
27-52	98	3	3.06	49	2	4.08	49	1	2.04	50	2	4
53-78	95	19	20	47	7	14.89	48	6	12.5	48	10	20.83
79-104	76	35	46.05	40	26	65	42	16	38.09	38	22	57.89
105-106	41	2	4.87	14	0	0	26	1	3.84	16	1	6.25
Terminal	39			14			25			15		

Female Rats

Weeks	Control			Low			Medium			High		
	Start	D	%	Start	D	%	Start	D	%	Start	D	%
0-26	100	0	0	50	0	0	50	0	0	50	0	0
27-52	100	2	2	50	2	4	50	1	2	50	1	2
53-78	98	16	16.32	48	12	25	49	10	20.41	49	10	20.41
79-104	82	39	47.56	36	18	50	39	21	53.84	39	15	38.46
105-106	43	1	2.32	18	0	0	18	0	0	24	0	0
Terminal	42			18			18			24		

Notes: D: Deaths
%: Percent of death during the period

Table 2
Intercurrent Mortality Rates
Male Mouse

<u>Weeks</u>	<u>Control</u>			<u>Low</u>			<u>Medium</u>			<u>High</u>		
	Start	D	%	Start	D	%	Start	D	%	Start	D	%
0-26	104	1	0.96	52	3	5.76	52	2	3.84	52	1	1.92
27-52	103	4	3.88	49	5	10.2	50	2	4	51	5	9.80
53-78	99	20	20.20	44	9	20.45	48	5	10.41	46	4	8.69
79-104	76	31	39.24	35	13	37.14	43	19	44.18	42	18	42.85
105-106	48	0	0	22	0	0	24	0	0	24	0	0
Terminal	48			22			24			24		

Female Mouse

<u>Weeks</u>	<u>Control</u>			<u>Low</u>			<u>Medium</u>			<u>High</u>		
	Start	D	%	Start	D	%	Start	D	%	Start	D	%
0-26	104	1	0.96	52	0	0	52	0	0	52	0	0
27-52	103	4	3.88	52	1	1.92	52	3	5.76	52	0	0
53-78	99	12	12.12	51	4	7.84	49	6	12.24	52	6	11.53
79-104	87	35	40.22	47	10	21.27	43	12	27.9	46	15	32.61
105-106	52	0	0	37	0	0	31	0	0	31	1	3.22
Terminal	52			37			31			31		

Notes: D: Deaths
%: Percent of death during the period

Medical Officer's Response to Consult

NDA 19,835 Cetirizine HCL Tablets
From: R.P. Barron, Review Chemist
Subject: Appropriateness of "Reactine" as the proprietary
 name for this product
Date: August 24, 1992
Medical Officer Reviewer: Ana M. Saavedra-Delgado, M.D.

ASD
8/24/92
9 Barron
8/25/92

According to an initial review of the proposed proprietary name for this product, "Reactine", the Labeling Committee indicates that the use of this name for this product would connote a special usefulness in acute situations. They ask the Division to consider their remarks and this name in light of [201.10 (c) (3)].

Response:

This drug's proposed indications are: seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria. They are all chronic conditions. To our knowledge a special usefulness of this drug in acute conditions has not been demonstrated.

Although the onset of symptoms (sneezing, nasal and ocular pruritus, watery eyes) in seasonal allergic rhinitis may be acute, it is a chronic condition. The earliest measured clinical response to the drug in the pivotal placebo controlled studies, according to Dr. Rene A Landesman's MOR of January 29, 1990, was 12 hours post dose. Up to 1 day post dose cetirizine does not appear to be different from placebo. Even though cetirizine (5-20 mgs) once daily, appears to provide good symptomatic relief for seasonal allergic rhinitis, the complete reversal of these symptoms is not complete in any of the reviewed placebo-controlled studies.

In addition, it has been also been considered by the Division, that the use of this proprietary name could have the implication that the drug does not cause drowsiness. Reference is again made to Dr. Landesman's MOR. The incidence of reported somnolence at a dose of 5 mg once daily was statistically comparable to placebo although it was consistently larger numerically. The incidence of somnolence increases in a dose related manner and is significantly greater than placebo when the dose of cetirizine exceeds 5 mg daily. See MOR's Table 3. Therefore a proprietary name that would imply a lack of drowsiness would be inappropriate.

Table 3. Incidence of Commonly Observed Adverse Experiences Not Associated with Equivalent Incidence In Placebo-Treated Patients.

	Placebo (N = 671)	Cetirizine		
		5 mg (N= 258)	10 mg (N=636)	20mg (N=272)
Somnolence+fatigue	11.1%	16.3%	23.7%	30.9%

Recommendation:

It is felt that the use of the proprietary name "Reactine" for cetirizine HCL tablets would be inappropriate.

cc:

Orig NDA 12-835

1170-1501 20714

1170-1501 Unit, Dalgado, Bannan, Prochaska

Division of Surgical-Dental Drug Products

1. Review Number: Chemistry #1
2. Dated: November 20, 1988
3. Type and Number of Application: NDA 19-835
4. Center Therapeutic Classification: 1-C
5. Status of Application: Original submission
6. Name of Applicant: Pfizer Pharmaceuticals
7. Address: Pfizer, Inc.
235 E. 42nd Street
New York, NJ 10017
*REG. CONTACT:
PATRICIA GRABINSKI Ph.D
212-573-3412*
8. Product Names:
 - a) Proprietary: Cetirizine 5 mg Film Coated Tablet
Cetirizine 10 mg Film Coated Tablet
Cetirizine 20 mg Film Coated Tablet
 - b) established: Cetirizine Hydrochloride
USAN: Cetirizine Hydrochloride
USP: Not listed
 - c) Code Name and Number: None specified; IND utilizes
UCB-P071 for compound identification.
9. Dosage Forms, Strength/Potency, and Route of Administration:

Cetirizine Hydrochloride will be marketed as a film-coated, scored ovoid white (dye-free) tablet for oral administration. Three strengths will be available: 5 mg, 10 mg, 20 mg per tablet with the formulation of identical inactive ingredients in each tablet. Dosing regimen is one tablet daily.
10. Proposed Marketing Status: Rx
11. Pharmacological Category and Indications:

Antihistamine;

Cetirizine hydrochloride is an orally active H₁-receptor antagonist indicated for the relief of symptoms associated with seasonal allergic rhinitis and perennial allergic rhinitis and for the treatment of uncomplicated skin manifestations of chronic idiopathic urticaria.

Chemist's Part, Draft Letter to Sponsor

1. We recommend the stability protocol be revised to include:
 - a) Tests and appropriate specifications on the expected degradation and decomposition products associated with the drug product. These results may be reported in a timely manner in submissions such as annual reports.
 - b) Testing at 9 month and 18 month intervals.

Please refer to current FDA Guideline for submitting Documentation for the Stability of Human Drugs and Biologics for guidance.

2. Please provide information on the origin and identity of the HPLC response at 10.55 min retention time in the chromatogram of the 10 mg Cetirizine HCl tablet reported in Figure 9 submitted February 16, 1990. Based on the wide variations in Rt and RTT relative to cetirizine. This peak does not correspond to any of the degradation products such
3. The information submitted in support of the rework procedure is inadequate to establish the identity, strength, quality and purity of final product containing reworked material. Please provide the following information.
 - a. Specific information with regard to the type of equipment which will be utilized
 - b. The anticipated amounts and conditions requiring the addition of magnesium stearate to rework the product. Please reconcile these amounts with the proposed targeted levels.
 - c. A dissolution profile test and specifications of any rework product relative to that of an acceptable production run. The dissolution specification currently established (Q in 45 min.) for the product lacks sufficient discrimination for use to establish the quality of reworked product.
 - d. Long term and accelerated stability testing of the reworked product to establish comparability with the approved product.

- e. Finished product consisting of reworked material should bear an expiration date based on the original date of manufacture of the earliest produced batch in the composite.
4. In your response to Question 3, we require information on the limits on yields and those associated with material accountability which will trigger investigations into the manufacturing processes and procedures.
5. Please provide references to prior submissions to document that tablets under stability testing were engraved. Please submit proposed plans to provide differentiation of the three dosage strengths of the product.
6. Due ^{to} problems experienced in one of the FDA methods validation laboratories in the determination of degradation products, procedure C156.1 (included as Appendix II in your submission dated 2/16/90) will be fully validated. In this regard, Mr. Robert P. Barron will be in contact to make the necessary arrangements.

Please note the following comments from the labeling & nomenclature comm.

Reactine

Cetirizine HCl Tablets

A review did not reveal names which look or sound like the proposed name. The Committee did not have full information on the clinical usefulness of this product, but abbreviated information indicates it is primarily for chronic conditions. Yet the proprietary name REACTINE gives a connotation of special usefulness in acute situations.

The Committee suggests that the Division reviewers carefully consider our remarks and this name in light of [201.10(c)(3)]. The Committee would be willing to re-review this name if the Division contributes further background information.

TO: CDER Labeling and Nomenclature Committee
Attention: Mr. Kent Johnson, Chair, (HFD-631) Rm. 17B45

FROM: Division of CINCOLOGY & PULMONARY DRUG PROD.
Attention: P. P. BARRON

DATE: AUGUST 7, 1990

SUBJECT: Request for Assessment of the Proprietary Name of a
Proposed Drug Product

Proposed Proprietary Name: REACTIVE TABLETS

Established name, including dosage form: CETIRIZINE
HYDROCHLORIDE TABLETS

Other proprietary names by the same firm for ~~companion~~ products:
5, 10 AND 1mg STRENGTHS

Indications for Use (may be a summary if proposed statement is lengthy):
SEASONAL ALLERGIC RHINITIS; PERENNIAL ALLERGIC RHINITIS AND CHRONIC IDIOPATHIC URTICARIA.

Comments: ① ~~THE~~ PANEL OF CARTON (PROFESSIONAL SAMPLES) ATTACHED. NDA 19-835

② MARKETED AS "ZYRTEC" IN BELGIUM
③ REACTIVE IS REGISTERED TM, 9-12-89, BY PFIZER

NOTE: Meetings of the Committee are scheduled for the 1st Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Labeling Committee Recommendations

July 1990 Similar — ?

5. Consult #7 (HFD-150)

Reactine

Cetirizine HCl Tablets

A review did not reveal names which look or sound like the proposed name. The Committee did not have full information on the clinical usefulness of this product, but abbreviated information indicates it is primarily for chronic conditions. Yet the proprietary name REACTINE gives a connotation of special usefulness in acute situations.

The Committee suggests that the Division reviewers carefully consider our remarks and this name in light of [201.10(c)(3)]. The Committee would be willing to re-review this name if the Division contributes further background information.

CDER Labeling and Nomenclature Committee

Henry T. Johnson, Chair

8.30

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 19-835 **DATE REVIEWED:** 17-Oct-1995 (revised 30-Oct-1995)

REVIEW #: Chemistry #8 **REVIEWER:** Robert P. Barron

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE	
AMENDMENT BC	4-May-95	5-May-95		
AMENDMENT BZ	12-May-95	15-May-95	24-May-95	Enantiomers
AMENDMENT BC	16-May-95	17-May-95	22-May-95	Environ. Assessment
AMENDMENT BC	20-Dec-91			

NAME & ADDRESS OF APPLICANT: PFIZER, INC.
235 East 42nd Street
New York, NY 10017-5755

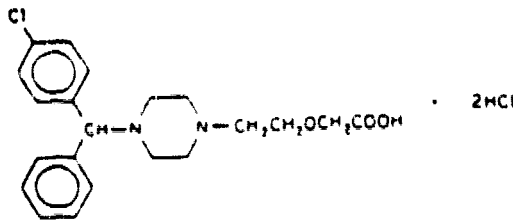
DRUG PRODUCT NAME
Proprietary: ZYRTEC TABLETS
Established: Cetirizine HCl Tablets
Code Name/#:
Chem. Type/Ther. Class: 1-S

PHARMACOL. CATEGORY/INDICATION: Antihistamine/ Seasonal allergic rhinitis
Perennial allergic rhinitis
Chronic Idiopathic urticaria

DOSAGE FORM: Film Coated Tablet
STRENGTHS: 5 and 10 mg/tablet
ROUTE OF ADMINISTRATION: Oral
Rx/OTC: xx Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Structure:



SUPPORTING DOCUMENTS: None

RELATED DOCUMENTS (if applicable): (attached) Amendment dated 24-May-1989 in Chem Rev #2
Amendment dated 15-Feb-1990
Amendment dated 29-Jan-1991
Amendment dated 20-Dec-1991
Amendment dated 19-Mar-1993 in Chem Rev #6

CONSULTS: Amendment dated 16-May-1995 (Summary EA document) was forwarded to Dr. P. Vincent on 23-May-1995 for final concurrence.

REMARKS:

SEE Pg. 3.

CONCLUSIONS & RECOMMENDATIONS:

1. Cetirizine HCl tablets is a immediate release, film coated tablet. The prospective rework procedures in this review are considered acceptable for the product with the stipulation that the firm submit all pertinent information, such as the cause of failure and validation of rework procedure on any lot which require rework to the agency at the next annual reporting period for the NDA.
2. The release specifications, i.e. Specifications R, dated 23-Jan-1995, requires revision to include the tests and specifications for degradation products as specified in the stability protocol. Release testing would be considered time zero under the stability protocol.
3. The final draft labeling for the product submitted in the amendment dated 4-May-95 requires clarification under 201.1(h)(3) of two names, Pfizer Pharmaceuticals as manufacturer and marketer and UCB Pharma as marketer of the labeling of the product. The current presentation is unacceptable under the cited regulation.

The applicant has not withdrawn the rework procedures for the NDA which has been recommended to the applicant. Therefore, with a commitment by the applicant to concur with the comments in draft letter, the NDA would be considered approved from a CMC viewpoint.


Robert P. Barron, Review Chemist


Rebecca H. Wood, Ph.D.
Supervisory Review Chemist

cc: Orig. NDA 19-835
HFD-155/Division File
HFD-150/RPBarron/30-OCT-1995
HFD-155/AMDeigado, MD
HFD-155/KLee, CSO
HFD-150/RHWood
HFD-155/GPoochikian
HFD-102/WT only

Remarks:

1. In the appended related documents and reviews, it is documented that the applicant has proposed, and thereby agrees, to the following.
 - i) The expiration dating period will be assigned to the reworked lot based on the original date of manufacture of the lot and not the date of reprocessing.
 - ii) Each reworked product will be assigned a unique lot number when a portion of a batch is reprocessed.
 - iii) Reprocessed batches will not be combined with virgin batches, but several batches which require reprocessing may be combined and reprocessed as one batch and a new lot number assigned.
 - iv) The elapsed time from the original manufacturing date to the reprocessing date will be documented and time limitations will be considered and assigned when prolong storage could adversely affect the in-process batch, such as, with a wet granulation prior to drying. Typically, review testing will be conducted at three month intervals for in-process batches.
 - v) Material held for reprocessing or under in-process quarantine will be stored under ambient (air conditioned) conditions meeting CGMP standards. Blends will be stored in LDPE lined 35 gallon plastic or fiber drums or stainless steel tote bins. Tablet cores will be stored in LDPE lined five gallon plastic or corrugated containers. Coated tablets will be stored in 24 gallon fiber drums lined with two LDPE bags and silica gel desiccants.
 - vi) A full investigation will be conducted to understand the reason why the batch does not conform to specifications. A particular batch will not reworked for the same deviation more than twice.
 - vii) During the reprocessing of a batch, labeling on the material will include specific information (e.g. product name, product code, process stage, date of manufacture, lot number, etc.) which will allow identification and traceability of the reprocessed batch. All in-process material will be clearly identified as to status (e.g. approved, quarantined, etc.)
 - viii) Reprocess batches are monitored closely. All processing plans require review and approval of responsible Production and Quality Control management before they can be implemented. (This is in compliance with the requirement of Current Good Manufacturing Practice for finished pharmaceuticals, Subpart F, 21 CFR 211.115.

2. The analytical methods associated with the product have been validated and found acceptable.

3. The amendment dated 12-May-1995 with information on the activity of enantiomers did not require a chemistry review.

4. The summary environmental assessment document, as noted above, requires final review and approval by the EA officer prior to approval of the NDA.

5. The latest EER request was issued on September 11, 1995.

Chemist's Part, Draft Letter to applicant.

1. The prospective rework procedures for granulation, tablet cores and finished tablets proposed in the amendments date May 4 1995 and December 20, 1991 are considered acceptable. As prospective procedures, we will require a commitment, as a condition of approval of the NDA, to submit complete information on any rework product in the next annual update of the NDA after completion of the actual rework.
2. Specification-R of January 23 1995 for the product should be revised to include tests and specifications for degradation products at release. This revision would bring the release specification into agreement with the stability protocol. The levels, as currently established, for degradation products will be re-evaluated based on subsequent submissions of stability data generated under the approved stability protocol.
3. The listing of both Pfizer Pharmaceuticals, as manufacturer and marketer, and UCP Pharma, as marketer of the product, is unacceptable under 21 CFR 201.1(h)(3). Pfizer Pharmaceuticals, as the applicant, should be the sole corporate name appearing on the label.

Pfizer Inc.
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 7291

☒	NDA	17-835
☐	IND	
☐	FD	
☐	M	



U.S. Pharmaceuticals

COPY / - 55 -

Rita A. Wittich
Associate Director/Group Leader
Drug Regulatory Affairs

March 19, 1993

Gregory Burke, M.D., Director
Division of Oncologic and Pulmonary
Drug Products (HFU-150)
Office of Drug Evaluation I
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: Reactine (cetirizine) Tablets
NDA #19-835

Dear Dr. Burke:

Please refer to NDA #19-835 for Reactine Tablets, to our submission of December 20, 1991, and your response date August 18, 1992.

Enclosed is our response to those questions as well as an updated stability report.

If you have any questions, please contact my office.

Sincerely,

Rita A. Wittich

CONFIDENTIAL/TRADE SECRET INFORMATION
SUBJECT TO 18-USE-1905 AND TO WHICH ALL
CLAIMS OF PRIVILEGE AND CONFIDENTIALITY
ARE ASSERTED IN BOTH STATUTORY AND
COMMON LAW.

RAW:amw
Enclosure
out-protol/14

Cetirizine Hydrochloride Tablets
Stability Update Report

1. Summary

The NDA stability program for 5, 10 mg cetirizine hydrochloride tablets has been completed. Data are now available for up to 60 months at 30°C label storage condition.

The stability program includes three batches of each dosage strength in 18 packaged lots of HDPE (high density polyethylene) bottles of 14, 100 and 500 tablets and PVC/PVdC blisters. Three lots of each dosage in HDPE bottles are with desiccant, one lot is without desiccant. The HDPE bottles of 14 tablets were evaluated up to 24 months.

Cetirizine hydrochloride potency, dissolution, water content, degradation products, friability, hardness and appearance (including color and odor) were evaluated. Based on the stability data, expiry datings requested for cetirizine hydrochloride tablets are as follows:

<u>Container Type*</u>	<u>Proposed Expiry Dating</u>
HDPE Bottles (45 ml to 290 ml size bottles)	60 months
PVC/PVdC Blisters	36 months
HDPE Bottles (30 mL Bottles)	24 months

* The sizes of the containers and descriptions of the container/closure systems are included in Appendix I, Table B.

2. Stability Program Design and Specification

For ease of reference, the Stability Program Study Design and Conditions is included in Appendix I, Table A, and the Specification-R for Cetirizine Hydrochloride tablets is included in Appendix II.

3. Stability Data Evaluation

Summaries of cetirizine hydrochloride potency, average dissolution and water content are included in Appendix III. Individual tablet lot stability data are included in Appendix IV.

a. Cetirizine Hydrochloride Potency(1) HDPE Bottles

There are no significant changes in potency after 50°C 12 weeks, 37°C/75%RH 12 weeks and 37°C 12 months storage. Average cetirizine hydrochloride potency after 36 months, 42 months and 60 months storage at 30°C remained at 97%, 96% and 96% of label claim and 97%, 97% and 96% of Initial. All individual data are within the potency specification of 90.0-110.0% of label claim. The average % of label claim are briefly summarized below:

Cetirizine Hydrochloride Potency

Dosage	Container Type	% of Label Claim (Average)					
		50°C 12 wks	37°C/75%RH 12 wks	37°C 12 mos	30°C 36 mos	30°C 48 mos	30°C 60 mos
5 mg	HDPE	99	99	98	96	94	95
10 mg	HDPE	99	100	97	97	97	96
Total Average		99	99	98	97	96	96

There is no significant difference in potency for cetirizine hydrochloride tablets stored in HDPE bottles with or without silica gel desiccants. The lots are C6107A and B for 5 mg tablets in bottles of 100's, C6181A and B for 10 mg tablets in bottles of 14's and C6182A and B for 20 mg tablets in bottles of 500's. The A lots contain desiccants and the B lots do not.

(2) PVC/PVdC Blister

There are no significant changes in potency after 50°C 12 weeks, 37°C/75%RH 12 weeks and 37°C 12 months storage. Average cetirizine hydrochloride potency after 36 months, 42 months and 60 months storage at 30°C remained at 98%, 96% and 94% of label claim and 95%, 95% and 92% of Initial. All individual data are within the potency specification of 90.0-110.0% of label claim. The average % of label claim are briefly summarized below:

Cetirizine Hydrochloride Potency

Dosage	Container Type	% of Label Claim (Average)					
		50°C 12 wks	37°C/75%RH 12 wks	37°C 12 mos	30°C 36 mos	30°C 48 mos	30°C 60 mos
5 mg	PVC/PVdC	99	99	99	100	97	94
10 mg	PVC/PVdC	99	102	97	95	95	95
Total Average		99	100	98	98	96	94

There are no significant differences in potency retention among the three (5 mg, 10 mg dosage strengths) in either HDPE bottles or PVC/PVdC blisters. A linear regression analysis has been performed on the cetirizine hydrochloride tablets 30°C potency results. 60 months potency meeting the Specification-R requirement is supported by this data for both HDPE bottles and PVC/PVdC blisters. One PVC/PVdC lot, however, approximates the lower limit. Based on this evaluation, the expiry dating for HDPE bottles will be requested for 60 months. Expiry dating for PVC/PVdC blisters will be requested for 36 months pending further stability lot evaluations to determine if such a trend truly exists. The linear regression report is presented in Appendix V.

b. Dissolution

Cetirizine hydrochloride tablets continue to meet the dissolution specification of Q = Label Claim in 45 minutes. The average dissolutions are briefly summarized below:

Dosage	Container Type	<u>Dissolution of Label Claim at 45 Minutes (Average)</u>					
		50°C 12 wks	37°C/75%RH 12 wks	37°C 12 mos	30°C 36 mos	30°C 48 mos	30°C 60 mos
5 mg	HDPE	97	98	101	97	97	100
	PVC/PVdC	100	97	102	100	95	103
10 mg	HDPE	98	100	97	97	98	96
	PVC/PVdC	99	98	95	96	99	96
Total Average		98	99	99	97	97	98

c. Water Content

Cetirizine hydrochloride tablets continue to meet the water specification of There are no significant changes in water content after 50°C/12 weeks, 37°C/12 months and 30°C/60 months storage.

As discussed in previous reports, all six lots of PVC/PVdC blisters under extreme stressed storage conditions of 37°C/75%RH after 12 weeks have increased water content with a These changes in water content have no observable effect on the potency, degradation profile and dissolution stability of cetirizine hydrochloride tablets.

There is no significant change in water content for HDPE bottles after 12 weeks at 37°C/75%RH. For HDPE bottles with and without desiccants, no significant differences in moisture content trends are discerned. The % of change from Initial for HDPE bottles, with and without desiccants, after 12 weeks 37°C/75%RH are presented below:

<u>Dosage</u>	<u>Container Type</u>	<u>12 weeks at 37°C/75%RH</u>	
		<u>With Desiccant</u>	<u>Without Desiccant</u>
5 mg	HDPE 100's	- 0.7	+ 0.7
10 mg	HDPE 14's	- 0.2	+ 1.2

d. Potential Degradation Products

No significant levels of degradation products were noted throughout this study. The potential degradation products evaluated are

e. Friability and Hardness

There is no significant friability. The maximum % of tablet weight losses are 0.18% and 0.16% for a 5 mg PVC/PVdC lot after 6 and 12 weeks 37°C/75%RH storage. The maximum % of tablet weight loss after 60 months at 30°C storage is 0.03%.

There are no significant changes in hardness after 50°C, 37°C, and 30°C storage. The maximum changes from initial are for one 10 mg PVC/PVdC lot and one 20 mg PVC/PVdC lot after 37°C/75%RH 12 week storage and 30°C/24 months storage respectively. Hardness decreased 7.3 Kp for the 10 mg lot and increased 6.4 Kp for the 20 mg lot. These changes have no observable effect on the potency and dissolution parameters studied.

f. Appearance

There are no significant changes in the appearance, color, and odor of the tablets for all the time/temperature periods studied.

4. Conclusion

Based on the stability data presented in this report, expiration datings of 60 months for 45 ml to 290 ml HDPE bottles, 36 months for PVC/PVdC blisters and 24 months for 30 ml HDPE bottles are justified when stored at or below 30°C. Stability profiles of cetirizine hydrochloride tablets in HDPE bottles are comparable with or without desiccants, supporting the packaging of cetirizine hydrochloride tablets with no desiccants. There are no significant differences in stability profiles among the three dosage strengths of 5 mg, 10 mg

Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3412

DESK COPY



Pharmaceuticals

Patricia Young, Ph.D.
Senior Associate Director
Drug Regulatory Affairs

December 20, 1991

Gregory Burke, M.D., Director
Division of Oncology and Pulmonary
Drug Products (HFD-150)
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: Reactine (cetirizine HCl) Tablets
NDA 19-835

Dear Dr. Burke:

Please refer to our pending application for Reactine (cetirizine HCl) Tablets, NDA 19-835.

Enclosed please find our response to requests for additional information regarding the chemistry/manufacturing section of the application sent to Pfizer by FAX on October 22, 1991.

Please include this information in the subject file.

Sincerely,

Patricia Young, Ph.D.

PY/ph

Enclosure

Desk Copy: Mr. Robert Barron
Chemistry Reviewer

CONFIDENTIAL/TRADE SECRET INFORMATION
SUBJECT TO 18-USC-1905 AND TO WHICH ALL
CLAIMS OF PRIVILEGE AND CONFIDENTIALITY
ARE ASSERTED IN BOTH STATUTORY AND
COMMON LAW.

Responses to Chemist's Questions 10/22/91

Question 1:

With regard to the stability protocol for the drug product please revise Section B on p. 16 to include appropriate specifications (limits) for each of the items under TEST DESCRIPTION.

Response:

The stability protocol has been revised as requested (Attachment 1). The stability limits for Assay, Dissolution and Water Content are the same as at time of release. Stability limits for Degradation Products are unchanged from the original protocol.

38
:)

Question 2:

With regard to reworked product or product containing reworked cores, please develop a dissolution profile with appropriate limits in order to demonstrate the equivalency of the reworked product with normal production material.

4 pages

PURGED

MAR 2 1994

DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS/HFD-155
Review of Chemistry, Manufacturing, and Controls

NDA #: **19-835** DATE REVIEWED: February 25, 1994 (Revised 3-1-94)

REVIEW #: Chemistry #6 REVIEWER: Robert P. Barron

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>	
AMENDMENT AC	19-MAR-93	22-MAR-93	24-MAR-93	Response to ltr 18-AUG-92
AMENDMENT EZ	25-SEP-90	1-OCT-90		enantiomer data
AMENDMENT AL	22-JUL-93	28-JUL-93	4-AUG-93	draft package insert
AMENDMENT BL	11-AUG-93	18-AUG-93	19-AUG-93	revisions to draft labeling
AMENDMENT BZ	25 AUG-93	2-SEP-93	9-SEP-93	trademark information
AMENDMENT AL	12-OCT-93	12-OCT-93		FP labeling

NAME & ADDRESS OF APPLICANT: Pfizer, Inc.
235 E. 42nd Street
New York, NY 10017

DRUG PRODUCT NAME
Proprietary: Reactine Tablets (Film Coated)
Established: Cetirizine Hydrochloride Tablets
Code Name/ #: UCB-P071
Chem. Type/Ther. Class: 1 C

PHARMACOL. CATEGORY/INDICATION: Antihistamine; H₁-receptor antagonist;
Seasonal & perennial allergic rhinitis; chronic idiopathic urticaria

DOSEAGE FORM: Immediate release film coated tablet

STRENGTHS: 5 and 10 mg/tablet

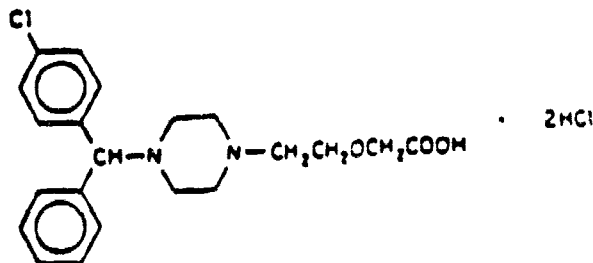
ROUTE OF ADMINISTRATION: Orally

Rx/OTC: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: (±)-(2-(2-(4-chlorophenyl)phenylmethyl)-1-piperazinyl)-ethoxyacetic acid, dihydrochloride

Molecular Formula: C₂₁H₂₆N₂O₃Cl₂ · 2 HCl Molecular Weight: 461.8



SUPPORTING DOCUMENTS: None.

LATED DOCUMENTS (if applicable): None.

CONSULTS:

1. A consult for review of environmental impact statement for this product and) was forwarded to HFD-102 on 2-FEB-93. The environmental review staff has concluded that no review is required since the document predates the Agency's position of the review of NEPA requirements.
2. A consult for establishing the dissolution specification at release and for reworked product was forwarded to the Division of Biopharmaceutics on October 7, 1993 (receipt date 10-18-93).

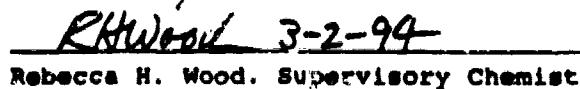
REMARKS:

1. The amendment dated 3-19-93 is in response to questions raised in the Agency letter of 18-AUG-91 and includes updated stability data on the product. Based on submitted data, revised dissolution specifications at release are proposed. Final resolution of the specifications has been completed by the Division of Biopharmaceutics
Submitted stability data are acceptable.
2. The specifications for degradation products of 0.2% individual and 1.0% total proposed in the submission under the reply to Comment #2 are acceptable. Stability data indicated the observed levels in product to be well within these limits.
3. An updated EER has found the facilities acceptable for 5 and 10 mg product

CONCLUSIONS & RECOMMENDATIONS:

1. The dissolution specification at release and for reworked material remains unacceptable. The dissolution specification has been proposed by the Division of Biopharmaceutics and will be Q - in 30 minutes. The applicant will be asked to concur with this specification.
2. The dissolution specification for reworked material remains unresolved. Due to the limited data on two different reworked batches and the failure of the applicant to propose any specification on reworked material, reworking of the product is not approvable. Rework procedures have been addressed in submissions under Chemistry Reviews 3, 4, and 5. A summary document of the applicant is required. It is recommended the rework portion of the application be withdrawn and submitted as a supplement when needed and the issue discussed at a meeting with the applicant.
3. The storage statement, as submitted, will require revision to specify the recommended storage temperature range to reflect current Division policy
(The FPL submitted 10-12-93 does have the storage temperature range.)

 3/2/94
Robert P. Barron, Review Chemist

 3-2-94
Rebecca H. Wood, Supervisory Chemist

cc: Orig. NDA 19-835
HFD-150/Division File
HFD-150/RPB/barron/4-21-93
HFD-150/CLedet
P/T RPB 2/24/94

ATT. INEP. REPORT 3274

MAR 2 1994

DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS/HFD-155
Review of Chemistry, Manufacturing, and Controls

NDA #: **19-835** DATE REVIEWED: February 25, 1994 (Revised 3-1-94)

REVIEW #: Chemistry *207* REVIEWER: Robert P. Barron

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>	
AMENDMENT AC	19-MAR-93	22-MAR-93	24-MAR-93	Response to ltr 18-AUG-92
AMENDMENT BZ	25-SEP-90	1-OCT-90		enantiomer data
AMENDMENT AL	27-JUL-93	28-JUL-93	4-AUG-93	draft package insert
AMENDMENT BL	11-AUG-93	18-AUG-93	19-AUG-93	revisions to draft labeling
AMENDMENT BZ	25 AUG-93	2-SEP-93	9-SEP-93	trademark information
AMENDMENT AL	12-OCT-93	12-OCT-93		FP labeling

NAME & ADDRESS OF APPLICANT:
Pfizer, Inc.
235 E. 42nd Street
New York, NY 10017

DRUG PRODUCT NAME
Proprietary: Reactine Tablets (Film Coated)
Established: Cetirizine Hydrochloride Tablets
Code Name/#: UCB-P071
Chem. Type/Ther. Class: 1 C

PHARMACOL. CATEGORY/INDICATION: Antihistamine; H₁-receptor antagonist;
Seasonal & perennial allergic rhinitis; chronic idiopathic urticaria

DOSEAGE FORM: Immediate release film coated tablet

STRENGTHS: 5 and 10 mg/tablet

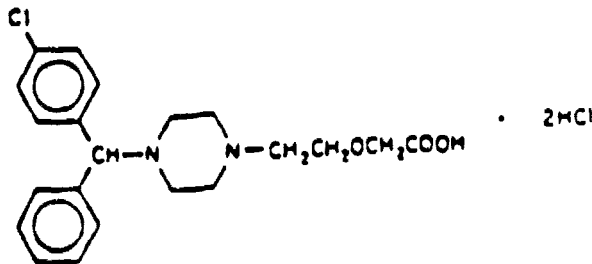
ROUTE OF ADMINISTRATION: Orally

Rx/OTC: XX Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: (±)-[2-(2-(4-chlorophenyl)phenylmethyl)-1-piperazinyl]-ethoxy]acetic acid, dihydrochloride

Molecular Formula: C₂₁H₂₅N₂O₃Cl₂ HCl Molecular Weight: 461.8



SUPPORTING DOCUMENTS: None.

RELATED DOCUMENTS (if applicable): None.

CONSULTS:

1. A consult for review of environmental impact statement for this product and was forwarded to HFD-102 on 2-FEB-93. The environmental review staff has concluded that no review is required since the document predates the Agency's position of the review of NEPA requirements.
2. A consult for establishing the dissolution specification at release and for reworked product was forwarded to the Division of Biopharmaceutics on October 7, 1993 (receipt date 10-18-93).

REMARKS:

1. The amendment dated 3-19-93 is in response to questions raised in the Agency letter of 18-AUG-91 and includes updated stability data on the product. Based on submitted data, revised dissolution specifications at release are proposed. Final resolution of the specifications has been completed by the Division of Biopharmaceutics. Submitted stability data are acceptable.
2. The specifications for degradation products of 0.2% individual and 1.0% total proposed in the submission under the reply to Comment #2 are acceptable. Stability data indicated the observed levels in product to be well within these limits.
3. An updated EER has found the facilities acceptable for 5 and 10 mg product and not

CONCLUSIONS & RECOMMENDATIONS:

1. The dissolution specification at release and for reworked material remains unacceptable. The dissolution specification has been proposed by the Division of Biopharmaceutics and will be Q = in 30 minutes. The applicant will be asked to concur with this specification.
2. The dissolution specification for reworked material remains unresolved. Due to the limited data on two different reworked batches and the failure of the applicant to propose any specification on reworked material, reworking of the product is not approvable. Rework procedures have been addressed in submissions under Chemistry Reviews 3, 4, and 5. A summary document of the applicant is required. It is recommended the rework portion of the application be withdrawn and submitted as a supplement when needed and the issue discussed at a meeting with the applicant.
3. The storage statement, as submitted, will require revision to specify the recommended storage temperature range to reflect current Division policy (The FPL submitted 10-12-93 does have the storage temperature range.)

cc: Orig. NDA 19-835
 HFD-150/Division File
 HFD-150/RPBarron/4-21-93
 HFD-150/CLmdet
 P/T RPB 2/24/94


 Robert P. Barron, Review Chemist


 Rebecca H. Wood, Supervisory Chemist

ATT. INEP. REPORT 3274

Dorsey

MAR 26 1992

DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS/HFD-150
Review of Chemistry, Manufacturing, and Controls

NDA #: 19-835 **DATE REVIEWED:** Feb. 28, 1992
Revised: Mar. 25, 1992

REVIEW #: Chemistry #6 **REVIEWER:** Robert P. Barron

SUBMISSION TYPE **DOCUMENT DATE** **CDER DATE** **ASSIGNED DATE**

This review covers the following document:

AMENDMENT N(BC) 20-Dec-91 27-Dec-91 06-Jan-92 Response
to deficiencies faxed to applicant on 10-22-91

The following was reviewed under Chemistry Review #5 dated 7-17-91:

AMENDMENT N(BC) 29-Jan-91 06-Feb-91 12-Feb-91

The following were reviewed under Chemistry Review #4 dated 8-27-90:

AMENDMENT N(AC) 16-Feb-90 27-Feb-90 02-MAR-90 Ref CR #2
AMENDMENT N(AC) 16-Feb-90 23-Feb-90 02-Mar-90 Stability
AMENDMENT N(AL) 28-Feb-90 01-Mar-90 09-Mar-90 Labeling

The following was reviewed under Chemistry Review #3 dated 7-13-90:

AMENDMENT 03-Oct-89 04-Oct-89 12-Oct-89 Draft P.I

NAME & ADDRESS OF APPLICANT: Pfizer, Inc
234 East 42nd Street
New York, NY 10017-5755

Attn: Patricia Young, Ph.D.

DRUG PRODUCT NAME
Proprietary: Reactine Tablets
Established: Cetirizine Hydrochloride Tablets
Code Name/#: n/a
Chem.Type/Ther.Class: 1-C

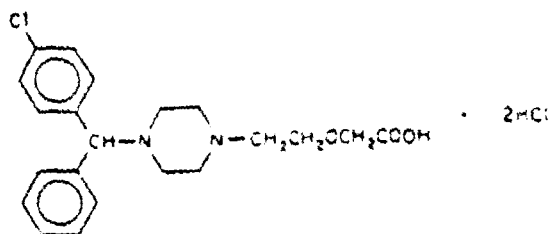
PHARMACOL. CATEGORY/INDICATION: Antihistamine

DOSAGE FORM: immediate release film coated tablets
STRENGTHS: 5, 10
ROUTE OF ADMINISTRATION: Orally
RX/OTC: XX Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: (±)-[2-[2-(4-chlorophenyl)phenylmethyl)-1-piperazinyl]-ethoxy]acetic acid, dihydrochloride
Molecular Formula: C₂₃H₂₇N₂O₃Cl₂ · 2 HCl
Molecular Weight: 461.8

Structure:



SUPPORTING DOCUMENTS: None

RELATED DOCUMENTS (if applicable):

EER Reports on facilities in Puerto Rico and Brooklyn of HFD-320 dated 2-26-92.

CONSULTS: Request for review of environmental assessment aspects and appropriateness of proprietary name forwarded with this review.

REMARKS:

1. The amendment responds to the deficiencies faxed to the applicant of 10-22-91.
2. Results of methods validation trials at DDA, St. Louis and NY Regional Laboratory were acceptable for regulatory purposes.
3. All EER's were acceptable with the exception of the Barceloneta PR facility per report of HFD-320 dated 2-26-92 (attached). EER on UCB of Belgium was found acceptable
4. Final review of the labelling is pending submission of FL by firm per chemistry review #5,
5. The applicant has submitted an EA report on pp. 3-537 to 3-540 of the original submission as noted in Chemistry Review #1 p. 40. This EA should be resubmitted and updated in light of recent changes in the requirements and submitted for review by the CDER EA officer. The Belgium facilities of UCB, are in compliance with environmental laws of Belgian Labour Authorities per DMF
6. The labeling and nomenclature committee commented on the proposed name "Reactine" and raised certain relevant clinical questions. These concerns were transmitted through a consult dated 3-24-92 to the pulmonary medical group.

CONCLUSIONS & RECOMMENDATIONS:

The chemistry, manufacturing & controls responses to the concerns as a result of Chemistry review #5 are considered unsatisfactory
The comments under Draft Letter to

Applicant should be forwarded to the firm. Additionally, EERs on the Barceloneta PR plant per report of HFD-320 dated 2-26-91 was unacceptable due to failure of firm to be prepared for inspection. Submission of FL by the firm for review is also pending.



Robert P. Barron
Review Chemist/HFD-150

cc: Org. NDA 19-835
HFD-150/Division File
HFD-150/RPBarron/2-28-92
HFD-150/CLedet
HFD-150/GPoochikian
R/D Init by: *GR* 3/26/92

DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS/HFD-150
Review of Chemistry, Manufacturing, and Controls

NDA #: 19-835

DATE REVIEWED: July 17, 1991
Revised to include Addendum 8-15-91

REVIEW #: Chemistry #5

REVIEWER: Robert P. Barron

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
This review: AMENDMENT N(AC)	29-Jan-91	06-Feb-91	12-Feb-91 Ref CR #4 and CR #3
AMENDMENT N(BC)	29-Jan-91	06-Feb-91	14-Feb-91

The following were reviewed under Chemistry Review #4 dated 8-27-90:

AMENDMENT N(AC)	16-Feb-90	27-Feb-90	02-MAR-90 Ref CR #2
AMENDMENT N(AC)	16-Feb-90	23-Feb-90	02-Mar-90 Stability
AMENDMENT N(AL)	28-Feb-90	01-Mar-90	09-Mar-90 Labeling

The following was reviewed under Chemistry Review #3 dated 7-13-90:

AMENDMENT	03-Oct-89	04-Oct-89	12-Oct-89 Draft P.I

NAME & ADDRESS OF APPLICANT:Pfizer, Inc
234 East 42nd Street
New York, NY 10017-5755

Attn: Patricia Young, Ph.D.

DRUG PRODUCT NAMEProprietary:

Reactine Tablets

Established:

Cetirizine Hydrochloride Tablets

Code Name/ #:

n/a

Chem. Type/Ther. Class:

1-C

PHARMACOL. CATEGORY/INDICATION:

Antihistamine

DOSAGE FORM:

immediate release film coated tablets

STRENGTHS:

5, 10 or 20 mg/tab

ROUTE OF ADMINISTRATION:

Orally

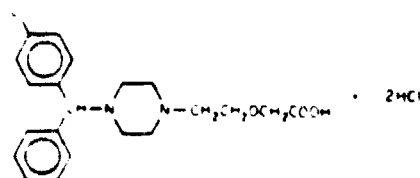
Rx/OTC:XX RX _____ OTCCHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: (±)-[2-[2-(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-ethoxy]acetic acid, dihydrochloride

Molecular Formula: C₂₁H₂₅N₂O₃Cl₂ HCl

Molecular Weight: 461.8

Structure:



SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable): None.

CONSULTS: N/A

REMARKS:

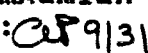
1. Amendment AC responds to the deficiencies resulting from Chemistry review #3 dated 7-14-90 and Chemistry Review #4 dated August 27, 1990.
2. Amendment provides for revised list of manufacturers (Pfizer locations in Brooklyn and Puerto Rico) and packagers (Packaging for the product including a list of DMF reference numbers.

None of the firms are listed on the current Alert List (July 15, 1991). EER on all locations were issued and found acceptable at the time of Chemistry Review #1.

CONCLUSIONS & RECOMMENDATIONS:

1. Amendment AC is not approvable. The applicant should be requested to correct the following:
 - a. Appropriate limits be added to the stability protocol under "Test Description."
 - b. A review of all labeling be performed prior to approval of the application to determine that all suggested and proposed changes have been incorporated into the labeling.
 - c. A dissolution profile with appropriate limits should be established as additional release tests for reworked product.
2. Amendment BC requires not action at this time. Appropriate EER updates have been issued to HFD-320.


Robert P. Barron, Review Chemist 9/3/91

cc: Org. NDA 19-835
HFD-150/Division File
HFD-150/RPBarron/7-11-91date
HFD-150/CLedet
HFD-150/CPHoiberg
HFD-102/CKumkumian (#1 only)
R/D Init by:  9/3/91

APPEARS THIS WAY
ON ORIGINAL

tick -
can't locate

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

REQUEST for VALIDATION of revised method for detection of degradation products.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 19, 1990

FROM: Robert P. Barron
Review Chemist
Division of Oncology and Pulmonary Drug Products, HFD-150

No report, apparently, was received from the NY Reg. Lab. THIS MUST BE REQUESTED AGAIN.

SUBJECT: NDA 19-835: Validation of revised method for degradation products.

TO: Ted M. Hopes
Director, Drug Chemistry Branch
New York Regional Laboratory HFR-NE560

Attached is a revised method for the analysis of degradation products in Ceterizine drug substance and Ceterizine film-coated tablets submitted by Pfizer Pharmaceutical in response to our ongoing review of the NDA.

Due to unacceptable results with the previous method per your memorandum of November 17, 1989 (amended), please schedule the revised method for validation trials at your earliest convenience. Contact me at (301) 443-4207 if additional supplies of standards for the degradation products, Ceterizine DS or tablets are needed. You may recall we discussed this matter sometime ago and you indicated the reserve samples for the product and drug substance were still available.

A validation of this modified method will give your lab an opportunity to possibly uncover the reasons for the previous failure and, concurrently, determine if the revised method is suitable for regulatory purposes. The previous validation package was found acceptable by DDA in St. Louis, and therefore this revised method will not be submitted to that facility.

cc:

HFD-150/Original NDA 19-835
✓HFD-150/Division File
HFC-140/Curtis Edward
HFD-102/CKumkumian
HFD-150/CPHofberg:07.16.90
R/D:RPBarron:07.16.90
F/T:kecooke:07.20.90
Wang 0833s

Enclosures

Leung

Division of Oncology and Pulmonary Drug Products

JUL 14 1990

1. Review Number: Chemistry #3
2. Dated: July 13, 1990
3. Type and Number of Application: NDA 19-835
4. Center Therapeutic Classification: 1-C
5. Status of Application: Not-approvable
6. Name of Applicant: Pfizer Pharmaceutical
7. Address: Pfizer, Inc.
235 E. 42nd Street
New York, N.Y. 10017

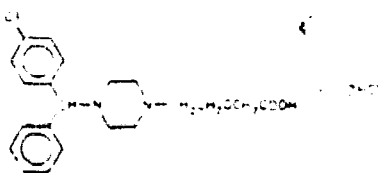
Attn: Patricia Young, Ph.D.
8. Product Names:
 - a. Proprietary: Reactine 5 mg tablets
Reactine 10 mg tablets
 - b. Established: Cetirizine Hydrochloride tablets
9. Dosage Forms, Strength/Potency and Route of Administration:

Cetirizine hydrochloride will be marketed as a white (dye-free) film-coated tablet, scored, ovoid tablet for oral administration. Three strengths will be available: 5 mg, 10 mg per tablet with the formulation of identical inactive ingredients in each tablet. Dosing regimen is one tablet daily.
10. Proposed marketing Status: Rx
11. Pharmacological Category and Indications:

Antihistamine. Cetirizine hydrochloride is an orally active H₁-receptor antagonist indicated for the relief of symptoms associated with seasonal allergic rhinitis and perennial allergic rhinitis and for the treatment of uncomplicated skin manifestations of chronic idiopathic urticaria.

12. Structural Formula, Chemical Name, Empirical Formula and Molecular Weight:

a)



b) Chemical Name: $\pm$ [2-[2-(4-chlorophenyl)phenylmethyl]-1-piperazinyloxy] acetic acid, dihydrochloride

CAS #83881-52-1
CAS #83881-52-0 (free acid)

c) Molecular Formula: $C_{21}H_{25}N_2O_3Cl \cdot 2HCl$

d) Molecular Weight: 461.8

13. Structural Formula of Related Compounds: (See Chemistry Review #1)

14. Document Date: a) Cover letter October 3, 1989
Form FDA 356h October 3, 1989

b) ~~Cover letter February 16, 1990
Form FDA 356b~~

15. CDB Date: October 4, 1989

16. Division Date: October 4, 1989

17. Assigned Date: October 12, 1989

18. Supporting Documents: None

19. Related Documents: None included

20. Remarks:

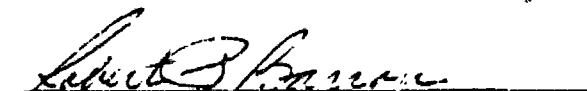
a) This submission provides a revised and annotated draft of the package insert for agency review.

b) Several pertinent comments regarding the P.I. have been made in both Chemistry Reviews #1 and #2. The applicant has failed to incorporate these changes in the current draft of the P.I.

- c) Since submission of this P.I., the applicant has selected Reactine (see amendment dated 2-28-90) as the proprietary name of the product. This name should be incorporated into the labeling for the product and another draft submitted incorporating the comments in this review.

21. Recommendation and Conclusion:

The draft Package Insert is consider inadequate and not approvable. The applicant should incorporate the comments in this review and submit another draft for review.


Robert P. Barron
Review Chemist

cc:
Orig. NDA 19-835
HFD-150/Division File
HFD-150/CPHoiberg
HFD-150/RScully
HFD-150/RBarron 7/13/90
HFD-151/CSO
HFD-80
R/D Init. by: CPHoiberg 7/14/90
F/T by: LSturdivant 7/19/90
Wang 0834s

Division of Oncologic and Pulmonary Drug Products

1. Review Number: Chemistry #2
2. Dated: (1st draft) August 3, 1989 (final) 8/11/89
3. Type and Number of Application: NDA 19-835
4. Center Therapeutic Classification: 1-C
5. Status of Application: Not approvable
6. Name of Applicant: Pfizer Pharmaceuticals
7. Address: Pfizer, Inc.
235 E. 42nd Street
New York, NJ 10017

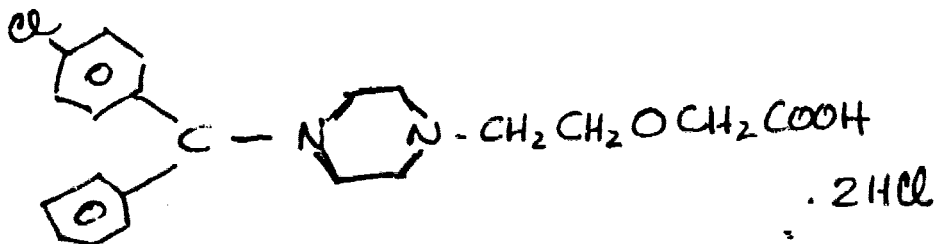
Attn: Patricia Grabinski, Ph.D.
(212) 573-3412
8. Product Names:
 - a) Proprietary: Cetirizine 5 mg Film Coated Tablet
Cetirizine 10 mg Film Coated Tablet
 - b) established: Cetirizine Hydrochloride
USAN: Cetirizine Hydrochloride
USP: Not listed
 - c) Code Name and Number: None specified; IND utilizes
UCB-P071 for compound identification.
9. Dosage Forms, Strength/Potency, and Route of Administration:

Cetirizine hydrochloride will be marketed as a white (dye-free), film-coated, scored, rectangular tablet with rounded corners for oral administration. Three strengths will be available: 5 mg, 10 mg per tablet with the formulation of identical inactive ingredients in each tablet. Dosing regimen is one tablet daily.
10. Proposed Marketing Status: Rx
11. Pharmacological Category and Indications:

Antihistamine; Cetirizine hydrochloride is an orally active H₁-receptor antagonist indicated for the relief of symptoms associated with seasonal allergic rhinitis and perennial allergic rhinitis and for the treatment of uncomplicated skin manifestations of chronic idiopathic urticaria.

12. Structural Formula, Chemical Name, Empirical Formula and Molecular Weight:

a)



b) Chemical Name: 2-(2-(4-(4-chlorophenyl)phenylmethyl)-1-piperazinyl)-ethoxyacetic acid, dihydrochloride

CAS #83881-52-1

CAS #83881-51-0 (free acid)

c) Molecular Formula: $C_{21}H_{25}N_2O_3Cl \cdot 2HCl$

d) Molecular Weight: 461.8

13. Structural Formula of related Compounds:

(see Chemistry Review #1)

14. Document Date: Form 356H: May 24, 1989
Cover letter: May 24, 1989

15. CDB Date: June 1, 1989

16. Division Date: June 1, 1989

17. Assigned Date: _____

18. Supporting Documents:

(See Chemistry Review #1)

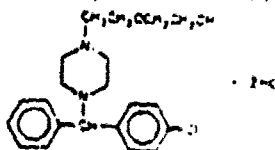
19. Related Documents:

a) C. British Journal of Dermatology, 119, 67-72, July 1988, John L. Arendt.

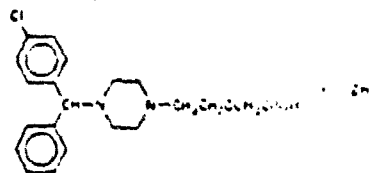
20. Remarks:

1. The active ingredient of this submission is a major human metabolite of hydroxyzine. Hydroxyzine is an approved product of Pfizer under NDA 10-392, ATARAX (HFD-120).

Hydroxyzine Hydrochloride (hydroxyzine) USP. $C_{21}H_{27}ClN_2O_2$. 447.83. [Hydroxyzine is INN] (1) Ethanol, 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-, dihydrochloride; (2) 2-[2-[4-(p-Chloro-*m*-phenylbenzyl)-1-piperazinyl]ethoxy]ethanol dihydrochloride. CAS-2192-20-3; CAS-68-93-2 [hydroxyzine] *Tranquilizer (minor)*. Atarax (Roerig); Durax (Dernik); (KV Pharmaceutical); Orgatraz (Organon); Quies (Forest); Vistaril Parenteral (Pfizer); component of Ataraxoid (Pfizer); component of Cartrax (Roerig); component of Enarax (Roerig); component of Marax (Roerig); component of Vistrax (Pfizer)



Cetirizine Hydrochloride [1995] (cetirizine) $C_{21}H_{27}ClN_2O_2$. 461.52. [Cetirizine is INN and BAN] (1) Acetic acid, [2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-, dihydrochloride, (±)-; (2) (±)-[2-[4-(p-Chloro-*m*-phenylbenzyl)-1-piperazinyl]ethoxy]acetic acid, dihydrochloride. CAS-3331-52-1; CAS-3331-51-0 [cetirizine]; *Antihistaminic*. (Pfizer) ♦P071



2. In response to deficiency 2d, the applicant has submitted a major amendment on the isolated enantiomers for Pharmacology review. This document is in the possession of the reviewing pharmacologist. No chemistry review will be necessary.
3. A consult review for a pharmacologic evaluation of the potential toxicity of residual solvents (acetone and toluene) appearing in the bulk drug substance and hence in the final dosage form has been requested.
4. Tests and specifications for individual and total levels of impurities and degradation products in the final dosage form is lacking.
5. The reprocessing procedures in this submission continue to be grossly deficient. This concern has been included in the draft letter to the applicant.

6. The allowable levels of magnesium stearate in the product require additional comments by the applicant. This is also included in the draft letter.
7. The container-closure system and draft labeling are inadequately described in the submission. Both areas may be further revised upon completion of the reviews of other disciplines, i.e., medical and biopharmaceutics.
8. One method validation report remains outstanding due to breakage of the HPLC column at the New York Regional Laboratory. The applicant has been asked to provide a replacement column per telecon with Dr. Patricia Grabinski of Pfizer on June 26, 1989.

21. Recommendations and Conclusions.

- a. The most serious remaining deficiency from a manufacturing and chemistry standpoint is the lack of specifications on impurities and degradation products in the final product.
- b. The application is not approvable at this time due to the lack of specifications on impurities and degradation products noted above.


Robert P. Barron
Reviewing Chemist

cc:
Orig. NDA 19-835
HFD-150/Division File
HFD-150/RBarron
HFD-151/CSO
R/D Init. by: CPHolberg 9/12/89
F/T by: JGuice/8/23/89 LSturdivant 9/13/89
Wang 2301M

NOV 23 1988

Division of Surgical-Dental Drug Products

1. Review Number: Chemistry #i
2. Dated: November 20, 1988
3. Type and Number of Application: NDA 19-835
4. Center Therapeutic Classification: 1-C
5. Status of Application: Original submission
6. Name of Applicant: Pfizer Pharmaceuticals
7. Address: Pfizer, Inc.
235 E. 42nd Street
New York, NJ 10017
8. Product Names:
 - a) Proprietary: Cetirizine 5 mg Film Coated Tablet
Cetirizine 10 mg Film Coated Tablet
 - b) established: Cetirizine Hydrochloride
USAN: Cetirizine Hydrochloride
USP: Not listed
 - c) Code Name and Number: None specified; IND utilizes
UCB-P071 for compound identification.
9. Dosage Forms, Strength/Potency, and Route of Administration:

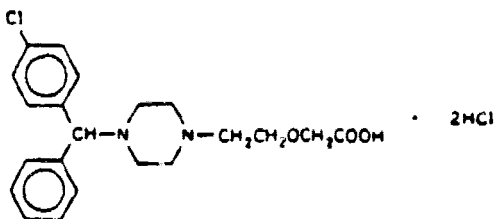
Cetirizine hydrochloride will be marketed as a film-coated, scored ovoid white (dye-free) tablet for oral administration. Three strengths will be available: 5 mg, 10 mg per tablet with the formulation of identical inactive ingredients in each tablet. Dosing regimen is one tablet daily.
10. Proposed Marketing Status: Rx
11. Pharmacological Category and Indications:

Antihistamine;

Cetirizine hydrochloride is an orally active H₁-receptor antagonist indicated for the relief of symptoms associated with seasonal allergic rhinitis and perennial allergic rhinitis and for the treatment of uncomplicated skin manifestations of chronic idiopathic urticaria.

12. Structural Formula, Chemical Name, Empirical Formula and Molecular Weight:

a)



b) Chemical Name: 2-(2-(4-(4-chlorophenyl)phenylmethyl)-1-piperazinyloxy)acetic acid, dihydrochloride

CAS #83881-52-1

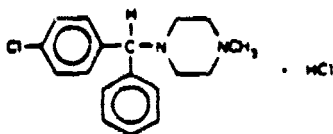
CAS #83881-51-0 (free acid)

c) Molecular Formula: $C_{21}H_{25}N_2O_3Cl \cdot 2HCl$

d) Molecular Weight: 461.8

13. Structural Formula of related Compounds:

a) Chlorcyclizine Hydrochloride (DiParalene^R by Abbott, Perazil by B-W)



Page 3
NDA 19-835

14. Document Date: Form 356H: June 30, 1988
Cover letter: June 30, 1988

15. CDB Date: July 1, 1988

16. Division Date: July 6, 1988

17. Assigned Date: July 7, 1988

18. Supporting Documents:

<u>TYPE OF</u> <u>DOCUMENT</u>	<u>DOCUMENT</u> <u>NUMBER</u>	<u>TITLE OR</u> <u>SUBJECT OF</u> <u>DOCUMENT</u>	<u>DOCUMENT</u> <u>HOLDER</u>	<u>VOLUME</u> <u>PAGE NO.</u> <u>DATES ETC.</u>
NDA	10-392	Hydroxyzine	Pfizer, Inc.	entire file

<u>TYPE OF DOCUMENT</u>	<u>DOCUMENT NUMBER</u>	<u>TITLE OR SUBJECT OF DOCUMENT</u>	<u>DOCUMENT HOLDER</u>	<u>VOLUME PAGE NO. DATE, ETC.</u>

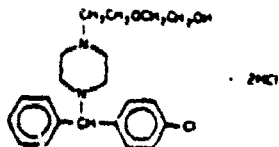
19. Related Documents:

- a) C. British Journal of Dermatology, 119, 67-72, July 1988, John L. Arendt.

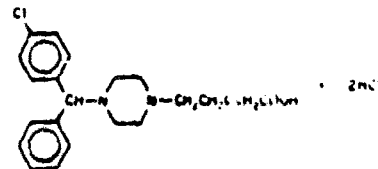
20. Remarks:

- a) The active ingredient of this submission is a major human metabolite of hydroxyzine. Hydroxyzine is an approved product of Pfizer under NDA 10-392, ATARAX (HFD-120).

Hydroxyzine Hydrochloride (hyc drox'i zeen). USP $C_{21}H_{27}ClN_2O_2$, 211Cl, 447.83. [Hydroxyzine is INN.] (1) Ethanol, 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-, dihydrochloride; (2) 2-[2-[4-(*p*-Chloro-*n*-phenylbenzyl)-1-piperazinyl]ethoxy]ethanol dihydrochloride. CAS-2192-20-3; CAS-6A-AB-2 [hydroxyzine] *Tranquilizer (minor)*; Atarax (Roerig); Durax (Dermik); (KV Pharmaceutical); Orgatrx (Organon); Quies (Forest); Vistaril Parenteral (Pfizer); component of Ataraxoid (Pfizer); component of Caritax (Roerig); component of Enarax (Roerig); component of Marax (Roerig); component of Vistarx (Pfizer)



Cetirizine Hydrochloride [1983] (seti'ri za zeen). $C_{21}H_{25}ClN_2O_2$, 211Cl, 461.82. [Cetirizine is INN and BAN.] (1) Acetic acid, [2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-, dihydrochloride, (±)- (2) (±)-[2-[4-(*p*-Chloro-*n*-phenylbenzyl)-1-piperazinyl]ethoxy]acetic acid, dihydrochloride. CAS-83881-32-1; CAS-83891-51-0 [cetirizine]. *Antihistaminic*. (Pfizer) ♦P071



- b) Cetirizine Hydrochloride was developed by UCB (Eur. Patent #58-146) and marketed in Belgium under the name Zyrtec (P-071), registered in France and Luxembourg with applications expected in a number of other European countries. The product has been licensed to Pfizer for marketing in Canada and this country. Cetirizine is a non-sedating, once daily anti-allergic.
- c) The new drug substance is manufactured by UCB of Belgium, under DMF as a racemic mixture of enantiomers for Pfizer. Pfizer formulates and manufactures the drug product at 5, 10 strengths as white (dye free), film-coated (F/C), scored ovoid tablets. The tablet size appears to be the distinguishing feature of each dosage strength. A deficiency letter has been issued UCB in associated with the review of DMF dated 9/16/88 (letter dated 10/19/88).
- d) The method of manufacture of the drug product involves formulating a Cetirizine HCl blend which is then utilized at multiples of 2 and 4 times the 5 mg dosage level. As a result, finished tablet target
-
- e) Appropriate establishment evaluation requests were forwarded to HFD-320 on August 25, 1988. UCB was found acceptable for BPC's only on 10/4/88 (EI May '88). Additional information on the establishment inspections are included under section 1 below.
- f) Methods Validation packages were processed on November 15, 1988 (New York Regional Laboratory) and November 17, 1988 (Division of Drug Analysis). The representative of the firm, Dr. Patricia Grabinski, was notified in person of the laboratory assignments on November 16th and by letter dated November 16th. Several modifications to the MV package regarding column packaging material, request for optical rotation measurements, etc. were detailed in the addendum to the memoranda to the assigned laboratories.
- g) The marketed containers for the product will include:
- i) Polyethylene bottles of 14's, 100's and 500's at all three dosage strengths.
 - ii) Blister packs of 100's, all three strengths.
 - iii) Physician's samples in blister packs, all three strengths.
- A 24 month expiration dating period is proposed for the product.

1) Summary of reviews of DMF's for product marketing:

a) Containers:

<u>DME</u>	<u>Holder</u>	<u>Type</u>	<u>Disposition</u>

Page 7
NDA 19-835

21. Conclusions and Recommendations:

Approval of the application is not recommended until the cited deficiencies in the Chemist's Draft of the Letter to the Applicant are adequately addressed.



Robert P. Barron
Reviewing Chemist

NDA 19-835
HFD-160
HFN-102/Kumkumian
Doc. Rm. 160
R/D RBarron 11/20/88
R/D init by GPoochikian 11/23/88
F/T LSturdivant 12/8/88
Wang 2301M Disk 0104M
CSO CONRAD LEDET

ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT
FOR

ZYRTEC™

(cetirizine hydrochloride)

Tablets

5 and 10 mg

NDA 19-835

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ONCOLOGY and
PULMONARY DRUG PRODUCTS
(HFD-150)

FINDING OF NO SIGNIFICANT IMPACT

NDA 19-835

ZYRTEC

(cetirizine hydrochloride)

Tablets

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for ZYRTEC, Pfizer has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Cetirizine hydrochloride is a synthetic drug which is administered as an oral tablet in the treatment of allergic rhinitis, perennial rhinitis and chronic idiopathic urticaria. The drug substance will be manufactured by UCB S^r Brussels, Belgium and the drug product will be manufactured at Pfizer, Inc., Brooklyn, NY and Pfizer Pharmaceuticals Inc., Barceloneta, Puerto Rico. The finished drug product will be used in hospitals, clinics and by patients in their homes.

Cetirizine hydrochloride is not extensively metabolized in humans and a large part of the dose will be excreted unchanged into the environment. Small quantities of drug may also enter the environment from manufacturing sites. Chemical and physical test results indicate that the drug substance will most likely be restricted to the aquatic environment and although data indicates that the substance is inherently biodegradable and susceptible to indirect photolysis, these environmental depletion mechanisms are expected to be slow.

As cetirizine is expected to persist in the aquatic environment for some time, the toxicity of cetirizine hydrochloride to aquatic organisms was characterized. Acute static toxicity studies in water fleas (*Daphnia magna*) indicate that the drug substance is generally not toxic to aquatic organisms at concentrations of at least 5 orders of magnitude greater than the maximum expected environmental concentration (MEEC). Microbial inhibition studies indicate that environmental microorganisms are not inhibited at concentrations of at least 5 orders of magnitude greater than the maximum expected environmental concentration (MEEC).

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of at a licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

6/30/95
DATE

Nancy B. Sage

PREPARED BY
Nancy B. Sage
Environmental Scientist
Center for Drug Evaluation and Research

7/5/95
DATE

Robert A. Jerussi

CONCURRED
Robert A. Jerussi, Ph.D.
Associate Director for Chemistry
Center for Drug Evaluation and Research

Attachments: Environmental Assessment (Pfizer)
 Environmental Assessment (UCB, SA)
 Material Safety Data Sheet (drug substance)
 Physico-Chemical/Fate Data Summary

ENVIRONMENTAL ASSESSMENT

Non-Confidential and Confidential Sections, As Noted

ZYRTECT™

**CETIRIZINE HYDROCHLORIDE TABLETS
NDA 19-835**

PFIZER INC

May 15, 1995

ENVIRONMENTAL ASSESSMENT

ZYRTEC™

CETIRIZINE HYDROCHLORIDE TABLETS NDA 19-835

1. **DATE:** May 15, 1995
2. **NAME OF APPLICANT/PETITIONER:** Pfizer Inc
3. **ADDRESS:** 235 East 42nd Street, New York, NY 10017
4. **DESCRIPTION OF THE PROPOSED ACTION:**

A. REQUESTED APPROVAL

Approval is requested for manufacture, packaging and marketing of tablet and formulation of cetirizine hydrochloride (ZYRTEC™), a selective competitive antagonist of the histamine H₁-receptor, for use as an antiallergic agent. The NDA for the tablet formulation of cetirizine hydrochloride was filed 5/31/88 as NDA 19-835. That filing covered 5 and 10 mg tablet formulations for indications comprising seasonal allergic rhinitis, perennial rhinitis, and chronic idiopathic urticaria. The

B. NEED FOR THE ACTION

Antihistamines find broad use in a variety of prescription and over-the-counter products. The majority of these agents are non-selective and, accordingly, have untoward side-effects. The subject agent, cetirizine hydrochloride, is highly selective and free of such side-effects. Approval of the subject NDA's will permit usage of cetirizine hydrochloride as an alternate to existing therapy in a total prescription patient population comprising an estimated 40 million allergy patients.

C. PRODUCTION AND PROCESSING LOCATIONS AND ENVIRONMENTS

Cetirizine hydrochloride drug substance is presently produced by UCB SA, Secteur Pharmaceutique, Avenue Louise 326 -- Box 7, B-1050 Brussels, Belgium, under Drug Master File No

The drug substance manufacturing site is situated at Chemin du Foriest, B-1420 Braine-l'Alleud, Belgium. The UCB Environmental Assessment, to be submitted as a supplement to the subject DMF, is provided in Appendix A and Confidential Appendix A. Formulation of the drug substance to drug products will be carried out in the existing manufacturing facilities of Pfizer Inc at 630 Flushing Ave., Brooklyn, NY 11206-5092 and Pfizer Pharmaceuticals Inc., KM 58.2 Road #2, Barceloneta, Puerto Rico 00617-0625.

The UCB facility is located in an industrial area which is surrounded by a rural/suburban environment. The UCB site has a total area of 150 acres and is surrounded on the south and east sides by single family houses and on the north and west by small factories producing a variety of products (pharmaceuticals, building materials, etc). The manufacturing facility is located in a temperate climate.

The Brooklyn facility is located in an urban environment in New York City in an area zoned for commercial use. South of the plant is a parking lot, to the east are multi-story tenements, to the west is a high-rise housing project, and to the north are vacant urban properties and industrial buildings. The Barceloneta facility is located in a mixed agricultural/industrial environment adjacent to other pharmaceutical manufacturing facilities and a food-processing plant. The Brooklyn location is in a temperate climate; the Barceloneta location is tropical.

D. USE AND DISPOSAL LOCATIONS AND ENVIRONMENTS

Cetirizine hydrochloride tablet formulations will be used as a prescription antihistamine in both hospital and home-use environments throughout the US.

Outdated or returned drug product, exclusive of samples, will be consolidated at the Pfizer Memphis Logistics Center, 1855 Shelby Oaks Drive North, Memphis, TN 38134, and shipped under manifest to either of two disposal facilities:

The permit limits under which WMI Medical Services operates are delineated in their permit (enclosed as Appendix B). The facility is located outside of Dayton, OH, in a rural/industrial area. There are no residences near the facility and the topography is flat.

(b) Environmental Healthcare, Incorporated, P.O. Box 2286 Delray Beach, FL 33447. Environmental Healthcare subcontracts the disposal to Ogden Martin Systems of Lake, Inc., which operates an incineration facility under Florida Department of Environmental Regulation, Permit A035-193817, expiry 10/25/96, at 3830 Rogers Industrial Park Road, Okahumpka, Lake County, FL 34762. The permit limits under which Ogden Martin Systems operates are delineated in their permit (enclosed as Appendix C). The facility is located in an isolated environment without neighboring residences or industrial facilities.

Outdated or returned samples are consolidated at the Pfizer Brooklyn facility and disposed of according to Item 6.D.1 below.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT OF THE PROPOSED ACTION:

A. DRUG SUBSTANCE

Chemical Name: [2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl] ethoxy]acetic acid, dihydrochloride

CAS Number: 83881-52-1

Generic Name: Cetirizine hydrochloride (USAN); Cetirizine dihydrochloride

SMILES Notation: c1cc(Cl)ccc1C(c2ccccc2)N3CCN(CC3)CCOCC(=O)O

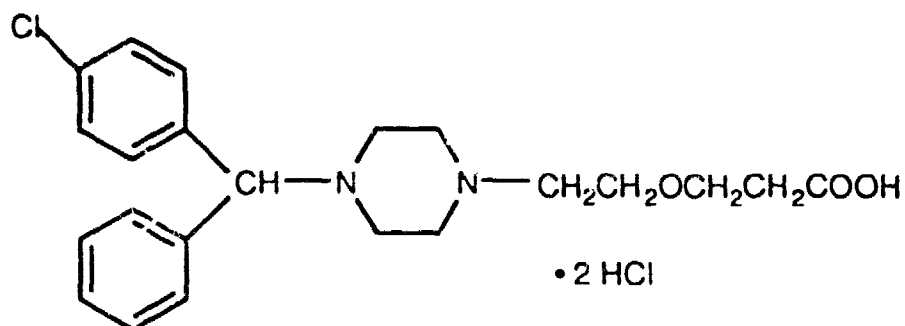
Molecular Formula: $C_{21}H_{25}N_2O_3Cl \cdot 2HCl$

Molecular Weight: 461.8

Physical Description: White or practically white powder

Impurities: Pharmaceutical Grade, purity not less than 99%

Structural Formula:



B. Drug Products

The drug products comprise (a) tablets formulated with pharmaceutically-acceptable excipients to contain 5 and 10 mg of cetirizine hydrochloride formulated to contain 5 mg cetirizine hydrochloride/mL as an aqueous formulation with pharmaceutically-acceptable excipients, pH = 4-5. Packaging of tablets will be in both HDPE bottles, with suitable closures (metal and/or plastic), or in blister packaging [Al foil and 3-component film (PVC/PE/PVDC)]; additional paper, paper board and corrugated packaging will be employed.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT:

Summary.- The manufacture of cetirizine hydrochloride drug substance is to be carried out at the above-cited UCB facility in support of the subject actions. Drug substance will be shipped from UCB to Pfizer by licenced carriers. Drug product will be manufactured and packaged at the Pfizer Brooklyn, NY and Barceloneta, Puerto Rico manufacturing facilities.

The manufacture of cetirizine hydrochloride drug substance needed in support of the UCB DMF will not have a significant impact on manufacturing emissions or controls at the UCB manufacturing site. UCB has provided certification of compliance with applicable regulations and permits in a DMF EA.

The manufacture of cetirizine hydrochloride drug product needed for the subject actions will not have a significant impact on manufacturing emissions or controls at the above-cited Pfizer manufacturing sites. Certification of compliance is provided below.

Introduction of cetirizine into the environment through use for both the tablet NDA's is projected to result in a maximum expected environmental concentration (MEEC) of cetirizine in the external aquatic environment of less than

A. BULK DRUG SUBSTANCE PRODUCTION, UCB BRAINE-L'ALLEUD SITE

The manufacture of cetirizine hydrochloride drug substance is being carried out at the above-cited UCB facility in support of other products and will be carried out at the same facility under DMF No.

in support of the subject Pfizer tablet
The UCB Environmental Assessment, to be submitted as a

supplement to the subject DMF, is provided in Appendix A and Confidential Appendix A. The UCB EA outlines the drug substance manufacturing process, identifies emissions, controls and applicable regulations and permits, and certifies that manufacture of cetirizine hydrochloride is being carried out -- and will be carried out in support of U.S. usage -- in compliance with existing Belgian regulations and permits.

B. DRUG PRODUCTS MANUFACTURE

Manufacture of cetirizine hydrochloride tablet drug products will be carried out at the Pfizer plants in Brooklyn, NY and Barceloneta, Puerto Rico. These plants are modern, multipurpose facilities designed for the efficient production of pharmaceuticals and chemicals, management of process wastes, and minimization of environmental and occupational releases. Process descriptions and flow charts are provided for the tablet manufacturing operations at both sites. Manufacturing emissions are delineated along with descriptions of controls exercised, listings of applicable site-related emissions regulations, requirements and permits, a statement of compliance with applicable emissions requirements, and a discussion of the effect of approvals on current applicable emissions requirements.

In summary, the expected increase upon current production loading from approval of the proposed actions will not have a significant impact on the controls, emissions or compliance at these facilities.

1. Process Descriptions and Flow Charts

Flow-charts outlining the manufacturing steps, defining process components, and identifying the process waste streams for both cetirizine hydrochloride tablets for both manufacturing sites is provided in Confidential Appendixes B, C, D, E and E. There are no substantive differences in the methods of manufacture between the sites.

2. Emissions

Listings of substances used in the manufacture of cetirizine hydrochloride tablets and projected components of the waste streams emitted into the occupational, atmospheric, aquatic and terrestrial environments are provided in Confidential Appendixes E and E. In summary, insignificant amounts of drug substance, drug product, and manufacturing process components will be emitted into these environments, based on the controls applied, as defined in item 6.B.3 below. There are no manufacturing side-products or intermediates. Total emissions of these materials will not be in excess of permitted levels and standards, as noted in item 6.B.4 below.

- a. Occupational.- Occupational emissions will comprise insignificant amounts of particulate cetirizine hydrochloride drug substance and excipients. Substances which could be emitted into the workplace environment -- at or below permissible levels -- are listed in Confidential Appendixes E and F in the "Occ" column.
- b. Atmospheric.- Air emissions will comprise insignificant amounts of particulate cetirizine hydrochloride drug substance and excipients. Substances which could be emitted into the atmospheric compartment -- at or below permitted or regulated levels -- are listed in Confidential Appendixes E and F in the "Air" column.
- c. Aquatic.- Liquid discharges from the manufacturing facilities, comprising insignificant amounts of cetirizine hydrochloride drug substance and excipients from equipment clean-out operations, are estimated to contain substances at or below permitted, regulated or contracted levels as listed in Confidential Appendixes E and F in the "Water" column.
- d. Terrestrial.- Solid waste terrestrial emissions will comprise excipients, packaging materials, and insignificant amounts of cetirizine hydrochloride drug substance -- at or below permitted, regulated or contracted levels -- as listed in Confidential Appendixes E and F in the "Solid Waste" column.

3. Controls

Emissions controls are used in the manufacturing processes to ensure compliance with occupational exposure limits and with general emissions requirements, specific standards (including priority pollutants and ozone depleting chemicals), permit limits, and contract requirements for the atmospheric, aquatic and terrestrial release environments, as outlined below for each of the release compartments and as applicable for both tablet and oral syrup manufacturing operations at both sites.

- a. Occupational.- Workplace exposures are controlled via appropriate equipment design, material and product transfer procedures and personal protective equipment.

Properly-designed equipment and facilities, administrative controls and personal protective equipment are used to minimize worker exposure in the handling of solids and liquids. Examples include use of closed reaction systems, pipe-line additions and transfers, local ventilation and dust collection. The use of masks, self-contained breathing apparatus, protective clothing, etc, will be prescribed as necessary when engineering and

administrative controls are insufficient to ensure worker protection.

Monitoring of work areas is carried out periodically to assure compliance with all required occupational exposure limits (eg, PEL's/STEL's). In U.S. facilities employees are informed of potential workplace hazards via a routine training program in compliance with the OSHA Hazard Communication Rule, 29 CFR 1910.1200. Material Safety Data Sheets (MSDS's) for materials used in the manufacture of drug product are provided to workers, as required. The MSDS for cetirizine hydrochloride is provided in Appendix D.

- b. Atmospheric.- Air emissions from the manufacturing process will be controlled through the use of filters (HEPA and the like) and scrubbers on powder systems; emissions from liquid-handling systems will be controlled via use of proper operational procedures.
- c. Aqueous.- Liquid discharges from the manufacturing process, comprising primarily aqueous process streams and wash waters and equipment/facilities washings, will be treated and disposed of in publicly-owned/operated WWTPs. A flow chart outlining pretreatment steps, tests performed and action limits for aqueous waste streams prior to emission to WWTPs is enclosed as Appendix G.
- d. Solid Waste.- Off-site incineration of non-hazardous wastes will be conducted at fully-licensed contract facilities. Residues emanating from incineration/ pyrolysis facilities will be disposed of by licensed contractors or at approved landfill sites.

4. Exposure/Emissions Requirements

Workplace exposure and air, aqueous and solid waste releases will be in compliance with the emissions requirements listed in Appendix E. The permit numbers, expiration dates and limits for aqueous waste stream disposal to publicly owned waste water treatment plants for the two manufacturing sites are defined in Appendix E.

5. Citation of Compliance With Applicable Emissions Requirements

The applicant certifies that emissions, discharges and wastes from the manufacture of cetirizine hydrochloride drug product for the tablet NDA's 19-835 will be in compliance with applicable occupational health and safety standards and federal, state and local emissions regulations and

permits, or with applicable consent orders and administrative orders and directives for the following Pfizer facilities: Barceloneta, PR, and Brooklyn, NY.

6. Effect of Approval of the Action on Compliance With Current Emissions Requirements

Approval of the proposed action will have no effect upon compliance with existing emissions requirements at the applicable manufacturing sites.

C. USE

Cetirizine hydrochloride tablets are to be used both in hospitals and in home-use environments. The projected quantity of cetirizine hydrochloride to be used in a mature U.S. market for both NDA's -- and the basis for this projection -- are provided in Confidential Appendix G. Assessment of potential environmental effects from cetirizine hydrochloride use (Item 8, below) are based on projected combined emissions for both tablet uses.

1. Metabolism/Excretion Summary

Clearance and excretion data indicate that cetirizine is excreted largely unchanged following oral administration to humans, with metabolism of about 20% of the administered dose (Confidential Appendix H). Note also that cetirizine is the major human metabolite from ingestion of hydroxyzine, being formed to the extent of about 40% of the oral hydroxyzine dose (Confidential Appendix I).

2. Usage Emissions -- Quantities and Concentrations

The maximum expected environmental concentration (MEEC) in the external aquatic environment of excretion products from cetirizine hydrochloride usage for both the tablet NDA's is calculated as follows (Reference 1):

$$\text{MEEC (ppm in environment)} = (\text{lb/yr production}) \times 8.9 \text{ E}^{-9} = (\text{confidential}) \times 8.9 \text{ E}^{-9} = \text{less than about 100 ppt}$$

The basis for this calculation -- and a more refined calculation based on metabolism/excretion data, corrected for the percent of total usage excreted into WWTP's, and corrected for the incremental amount of cetirizine entering the environment from hydroxyzine use -- is presented in Confidential Appendix J.

D. DISPOSAL

Rejected/off-specification bulk and/or finished product at the Brooklyn and Barceloneta production facilities will be disposed of under contract at licensed facilities, as follows:

1. Brooklyn.- Disposal is carried out under a Purchase Order Contract with BFI Pharmaceutical Services, 812 Corporate Way, Valley Cottage, NY 10989, dated 2/3/95. BFI subcontracts the disposal to American REF-FUEL Company of Hempstead, 600 Avenue C at Stewart Avenue, Westbury, NY 11590, for destruction via incineration under NY State Department of Environmental Conservation, Permits, both Number 10-86-0345, expiry 5/14/95. The American REF-FUEL facility is located in a commercial/light industrial area adjacent to a highway. The permit limits under which American REF-FUEL operates are delineated in their permits (enclosed as Appendix K). There are several residences near the facility and the topography is flat.
2. Barceloneta.- Disposal is carried out under contract with Environmental Healthcare, Incorporated, P.O. Box 2286 Delray Beach, FL 33447, dated 1/28/92. Environmental Healthcare subcontracts the disposal to Ogden Martin Systems of Lake, Inc., which operates an incineration facility under Florida Department of Environmental Regulation, Permit A035-193817, expiry 10/25/96, at 3830 Rogers Industrial Park Road, Okahumpka, Lake County, FL 34762. The permit limits under which Ogden Martin Systems operates are delineated in their permit (enclosed as Appendix C). The facility is located in an isolated environment without neighboring residences or industrial facilities.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

SUMMARY.- This Item projects the fate of excreted cetirizine, providing physico-chemical/fate data and calculations, tracing entry into sewers and wastewater treatment plants (WWTPs), outlining treatment processes, defining potential release compartments, and projecting ultimate fate in the environment.

Cetirizine is a polar substance and is very soluble in water over the range of environmental pHs. Cetirizine hydrochloride has three titrable protons and exists primarily as the neutral zwitterionic species over the range of environmental pHs, with some contribution of the anionic species at the high end of the environmental pH range. Cetirizine also exhibits very low partitioning into octanol over the range of environmental pHs. Sludge sorption data suggest that it will reside almost exclusively in WWTP hydraulics and be released to -- and remain in -- the external aquatic environment. Cetirizine has been shown to be inherently biodegradable in pure culture

and soil screening tests. Cetirizine has been shown to be photolytically unstable in the presence of humic substances. Consequently, cetirizine would not be expected to persist in the external aquatic environment. Cetirizine would not be expected to bioconcentrate based on its overall physico-chemical profile.

A. PHYSICO-CHEMICAL/FATE DATA SUMMARY AND CALCULATIONS

See Appendix H for a detailed summary of physico-chemical/fate data and calculations. An abbreviated summary of key data is presented in the Table below. See Confidential Appendices for physico-chemical/fate study reports.

CETIRIZINE HYDROCHLORIDE

KEY PHYSICO-CHEMICAL/FATE DATA

1. melting point:	222.9 ±0.9°C			
2. UV:	no UV absorption past 290nm			
3. hydrolytic stability:	stable under ambient conditions			
4. ionic form:	pKa's at 1.99, 2.82 and 8.15			
5. solubility (mg/L):	<u>pH 5</u> >10,000	<u>pH 7</u> >10,000	<u>pH 9</u> >10,000	
6. log Kow:	1.46	1.53	0.73	
7. sludge and soil sorption:	sludge soil	<u>K</u> 71.6 21.8	<u>Koc</u> 140 3090	<u>n</u> 1.09 1.15
8. volatility:	VP estimate: $H = 4.19 \times 10^{-17}$ atm-m ³ /mole			
9. biodegradation:	judged to be inherently biodegradable based on a series of screening tests			
10. photolysis:	photolysis observed in presence of humic substances, corrected environmental half-life of 20 days			

B. TREATMENT PROCESSES

Summary.- Approximately 75% of U.S. domestic waste water is processed in municipal wastewater treatment plants (WWTPs), the remainder in on-site treatment systems. A general description of the diverse WWTP processes employed in the U.S. is provided in Appendix I

along with details of the dominant processes, including treatment conditions and residence times. WWTPs, therefore, will be the major site of entry of cetirizine emitted into the environment following drug usage.

1. Excretion/Sewer Line Residency

Cetirizine excreted into sewage systems will experience a mean 24-hour sewer line residency prior to WWTP entry. This environment is anaerobic.

2. WWTP Residency

The major modes of treatment of cetirizine following entry into municipal WWTPs will be primary and secondary treatment processes. The majority of sewage in WWTP's is treated via the aerobic activated sludge process, with a mean hydraulic detention time of 8 hr and a mean sludge detention time of 1-8 days. The majority of sludge in WWTP's is then subjected to anaerobic sludge digestion (mean detention time of 30-60 days) or to incineration.

C. RELEASE COMPARTMENTS AND INITIAL RELEASE CONCENTRATIONS

Summary. The release environment for cetirizine following WWTP residency will be the external aquatic environment based on (a) vapor pressure estimate, (b) resistance to biodegradation by sludge microorganisms, and (c) sludge sorption data showing minimal removal, as detailed in Appendix H. The initial release concentration of cetirizine in the external aquatic environment is projected to be less than 100 ppt.

Data Discussion and Calculations.- Cetirizine is judged to be hydrolytically stable under conditions of WWTP residency (see Appendix H). Cetirizine is judged to be microbiologically stable under conditions of WWTP residency based on biodegradation screening data (see Appendix H and Fate discussion, item 7.D below). Sludge sorption data show negligible removal onto sludge during WWTP residency. The release environment for cetirizine following WWTP residency, therefore, is the external aquatic environment based on the "Calculation of % Removal Onto Sludge" provided below.

The projected initial release concentration of cetirizine, less than 100 ppt, is derived using projected emissions from use and accounting for negligible removal onto sludge during WWTP residency, as shown in Confidential Appendix J.

Calculation of % Removal Onto Sludge.- The basis for calculating the % removal onto sludge from sludge sorption data is detailed in Appendix J and exemplified below for the Case 2 assumptions. The Freundlich isotherm value of $K=71.5$ for cetirizine determined for secondary sludge

(Appendix H), corresponds to negligible removal onto sludge within the WWTP environment, as follows:

Assume (a) $K = 71.6$; and (b) 0.182 g of total wasted sludge solids (dry weight basis) per liter of treated effluent, said solids being comprised of primary (0.120 g/L), secondary (0.047g/L) and carried-over material (0.015 g/L).

$$\frac{(\text{amount of sludge}) (Kd)}{[(\text{amount of sludge}) (Kd) + (\text{amount of water})]}$$
$$= \text{fraction removed}$$

$$\frac{(0.182 \text{ gms}) (71.6)}{[(0.182 \text{ gms}) (71.6) + 999.8 \text{ gms}]} =$$
$$\text{fraction removed onto all sludge compartments} = 1.3\%$$

This fraction removed can be corrected for amount retained in the WWTP on primary and secondary sludge solids, and the amount released in the treated effluent, giving 1.1% removed onto retained sludge.

(The sludge amount used in the above % removal determination is derived from the quantities of primary and secondary sludge wasted, as described in Appendix J, and not on the sludge concentration in the secondary aeration chamber used for the Kd determination, which concentration is kept high via sludge recycle to ensure adequate biomass.)

The concentration of cetirizine in the hydraulic, therefore, will be about 99% of the incoming amount, with but a negligible amount wasted with the sludge.

D. FATE OF EMITTED SUBSTANCES

General Discussion.- Aqueous effluents from WWTPs are normally discharged under federally-mandated permit systems to surface waters or to groundwater by land application. Substances emitted from WWTPs into the external aqueous environment may remain in the aqueous ecosystem, sorb to sediments, and/or volatilize into the air compartment. The fate in these compartments may include biodegradative, hydrolytic, oxidative or photolytic decompositions. Sludges, following various treatment regimens as referenced above, are disposed of primarily via landfilling/trenching in sites engineered to minimize leaching to the environment. The fate of substances released from WWTPs depends on a variety of factors including biodegradability, photodegradability, hydrolystability, and physico-chemical properties (which will determine possible migration to secondary environmental compartments).

SUMMARY.- Based on the above-outlined physico-chemical/fate data and treatment processes, cetirizine would be expected to be released into -- and remain in -- the external aquatic environment following WWTP residency based on (a) vapor pressure estimate and (b) sludge and soil sorption data. Cetirizine would not be expected to persist in the external aquatic environment based on (c) biodegradation screening data showing inherent biodegradability and (d) photolysis data showing photolability in the presence of humic substances. Cetirizine would not

be expected to bioconcentrate, based on its overall physico-chemical/fate profile.

1. Air.

As a highly-water-soluble, polar, high-molecular-weight zwitterionic/partially-anionic substance at environmental pHs, cetirizine would not be expected to have appreciable volatility or to enter the atmospheric compartment from WWTPs or from aqueous effluents therefrom. A vapor pressure estimate ($H = 4.19 \times 10^{-17}$ atm-m³/mole) supports this assumption (Appendix H).

2. Soil Ecosystem.

The potential for cetirizine to be released to the soil environment via retention on sludge and sludge amendment to soil is judged unlikely based on the sludge sorption data presented in Items 7.A and 7.C above. The Freundlich Isotherm value of $K = 21.8$ ($K_{oc} = 3090$) determined for soil sorption as shown in Item 7.A indicates that cetirizine would be expected to be tightly bound to soil, were it to be contacted with soil (reference, FDA Technical Assistance Document 3.08; Appendix H).

3. Aquatic Ecosystem.

The physico-chemical/fate profile outlined in items 7.A, 7.B and 7.C and in Appendix H suggest that cetirizine will be released into -- and remain in -- the aquatic ecosystem following entry into WWTP's. The potential for cetirizine to partition to sediments has not been formally addressed, but it can be assumed that the low level of sorption to sludge ($K = 71.6$) portends minimal compartmentalization to sediments in the external aqueous environment.

The potential for cetirizine to undergo biodegradation was addressed in a series of screening studies, as outlined in Appendix H and detailed in Confidential Appendices R 1, 2, 3, 4 and 5. Based on the results of these studies cetirizine would not be expected to be mineralizable under the test criteria outlined for the aquatic biodegradation according to TAD 3.11. However, results of studies using pure cultures from diverse environmental matrices and soils under a variety of conditions suggest that cetirizine is inherently biodegradable. While these results do not relate directly to the projected aquatic release environment, they support the conclusion that cetirizine would not be expected to persist in the external aquatic environment.

The potential for cetirizine, which contains a labile benzhydryl hydrogen, to undergo photolytic degradation in the presence of synthetic humic substances has been assessed, as described in

Appendix H and detailed in Confidential Appendix S. Cetirizine showed a pseudo first-order half-life of about 20 days in this study. While this value is a theoretical half-life, uncorrected for season, latitude, cloud cover or water depth, this study indicates that cetirizine would not be expected to persist in the external aquatic environment.

The potential for cetirizine to bioconcentrate is considered negligible based on structural and log Kow-log BCF (bioconcentration factor) considerations (see Appendix H)

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES:

SUMMARY.- No adverse effects are projected to humans, animals, plants or environmental organisms from usage of cetirizine hydrochloride for the subject tablet. NDA's following excretion of cetirizine into the WWTP and ensuing aquatic release environments. Cetirizine at the projected MEEC of less than 100 ppt in WWTP and external aquatic environments would not be expected to be toxic nor inhibitory to sewage treatment or environmental microorganisms. Cetirizine would not be expected to be toxic to aquatic organisms or to show any pharmacologic activity to humans or mammals at the projected maximum levels of exposure.

These conclusions are based on data on representative mammalian and environmental organisms showing: (a) a low level of toxicity to mammals, (b) absence of toxicity to microbial species at concentrations many orders of magnitude above the MEEC; and (c) a low order of toxicity to daphnids, which are useful indicators of environmental toxicity. The mechanism of action of cetirizine, selective competitive antagonist of the histamine H₁-receptor, is a mechanism which is not likely to have a counterpart effect in non-mammalian organisms. See Confidential Appendix T (Microbial Growth Inhibition) and Confidential Appendix U (Acute Toxicity to Daphnids) for full test reports.

A. HEALTH EFFECTS (SAFETY TO ANIMALS AND HUMANS)

No effects to animals or humans are expected from the projected releases to the external aquatic environment from the projected usage of cetirizine tablets. Cetirizine hydrochloride is a substance with a low order of mammalian toxicity consonant with its anticipated therapeutic use in man at dosages up to 20 mg per day. Animal pharmacology and toxicity data on cetirizine hydrochloride are summarized in Confidential Appendix V. Assuming a therapeutic dose of 5 mg in humans, a person would have to consume more than 5×10^4 liters of WWTP effluent per day to have a pharmacologic effect.

B. ENVIRONMENTAL EFFECTS

The potential environmental effects of emitted substances from cetirizine hydrochloride use can be considered from the perspective of the two

major release compartments: (1) WWTP's and (2) external aquatic ecosystem, as outlined in Item 7 above.

1. WWTP's

MEEC levels of less than 100 ppt cetirizine within WWTP's are judged inconsequential to the assorted autotrophic aerobes and other microorganisms necessary for effective activated sludge sewage treatment based on the results of the Microbial Growth Inhibition test (FDA 4.02; see Confidential Appendix T):

<u>Species</u>	<u>Cetirizine MIC* (ppm)</u>
<i>Aspergillus niger</i>	> 1000
<i>Trichoderma viride</i>	> 1000
<i>Clostridium perfringens</i>	800
<i>Bacillus subtilis</i>	600
<i>Nostoc</i>	60

* lowest concentration that inhibited growth, as ppm cetirizine free base

- Implications: Cetirizine hydrochloride shows a safety margin to the major classes of environmental microbial organisms of 5 to 7 orders of magnitude at its projected MEEC in the WWTP release environment.

2. External Aquatic Environment

Levels of cetirizine are projected to be present at concentrations of less than 100 ppt in the immediate vicinity of the WWTP effluent release environment -- assuming no degradation and no dilution (worst case scenario). This MEEC level of cetirizine is judged inconsequential to aquatic organisms based on Microbial Growth Inhibition test results described above and Daphnia magna static acute toxicity test data (FDA 4.08; see Confidential Appendix U):

48-hour EC (effective concentration)₅₀ = 330 ppm cetirizine

NOEC (no observed effect concentration) = 93 ppm cetirizine

- Implications: Cetirizine shows a safety margin of about 6 orders of magnitude to daphnids, which are useful indicators of environmental toxicity, at its projected MEEC in the aquatic release environment.

9. USE OF RESOURCES AND ENERGY:

See Appendix A for an estimate of resources and energy usage in support of manufacture of the drug substance under the UCB DMF. The usage of resources and energy to support the production of cetirizine hydrochloride drug product in the above-cited Pfizer manufacturing facilities is negligible. No effects of manufacture are expected upon endangered or threatened species or upon property listed in or eligible for listing in the Federal Register of Historic Places.

10. MITIGATION MEASURES:

In addition to the stringent controls exercised to ensure workplace and environmental compliance, the manufacture of sertraline hydrochloride will be carried out under the supervision of pharmaceutical professionals and will entail an active equipment maintenance program. Procedures are in place providing for containment of spills or leaks and maintaining personnel training for emergency action in the event of an unusual situation which might result in an emission or occupational exposure. Employees are provided necessary personal protective equipment, and MSDS's are available, as required, for all employees who work in the manufacturing areas.

11. ALTERNATIVES TO THE PROPOSED ACTION:

An alternative to the proposed action is no action. Inasmuch as (a) no significant potential adverse environmental impacts have been identified in the manufacture and use of cetirizine hydrochloride and (b) cetirizine hydrochloride is an effective alternative to sedating and other antihistamines, no alternatives to the proposed action are needed.

12. PREPARERS:

Irving M. Goldman, Director, Environmental Sciences, Pfizer Central Research Process Research and Development Department. Organic Chemist with Ph.D. and 33 years experience in R&D on human drugs, process research, specialty chemicals, pharmaceutical research and regulatory affairs.

Charles M. Shafran, Director of Engineering, Pfizer Pharmaceuticals. Chemical Engineer with M.Eng. (Chem.) and 23 years experience in Organic Chemical Production, engineering and environmental administration.

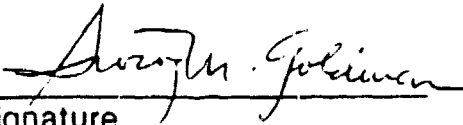
See Confidential Appendix X for Preparers involved in the development of test reports enclosed as Confidential Appendices L, M, O, P, Q, R, T, U, V and W.

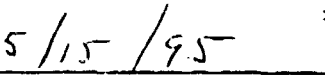
13. CERTIFICATION:

The undersigned official certifies that the information presented is true, accurate, and complete to the best of Pfizer's knowledge.

Name: Irving M. Goldman, Ph.D.

Title: Director, Environmental Sciences, Process Research and Development Department


Signature


Date

ENVIRONMENTAL ASSESSMENT (21 CFR 25.31)

For : CETIRIZINE HYDROCHLORIDE
BULK DRUG SUBSTANCE

1. Date : January 30, 1995
2. Name of Applicant : UCB S.A.
3. Corporate Address : Avenue Louise 326 - Box 7
B - 1050 Brussels
BELGIUM

4. Description of the proposed action :

A. Requested Approval

Approval is requested for the production of Cetirizine Hydrochloride bulk drug substance under the UCB S.A. D.M.F. # 8853.

B. Need for the Action

Approval will permit utilization of bulk Cetirizine Hydrochloride in the U.S. for to-be-approved uses.

C. Production and Processing Locations and Environments

Cetirizine Hydrochloride drug substance is presently produced by UCB S.A. - Pharma Sector, Avenue Louise 326 - Box 7 - B-1050 Brussels, Belgium, Chemical Plant n° 4763. Production in support of projected U.S. use will be under Drug Master File n° , for which this revised Environmental Assessment is being provided. The Drug Substance manufacturing site is located at Chemin du Foriest, B-1420 Braine-l'Alleud, Belgium. The manufacturing facility is located in an industrial area which is surrounded by a rural/suburban environment. The UCB Site has a total area of 150 acres and is surrounded on the south and east sides by single family houses and on the north and west by small factories producing a variety of products (pharmaceuticals, building materials, etc...). The manufacturing facility is located in a temperate climate.

D. Use and Disposal Locations

Not applicable.

5. Identification of Chemical Substances that are subject of the Proposed Action :5.(a) Drug Substance

Chemical Name :

[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]acetic acid dihydrochloride.
(CAS n° 83881-52-1).

Chemical abstract Registry Number :

CAS : 83881-52-1

Code Number (Laboratory Code) :

ucb P071
ucb 26071

Generic Name :

Cetirizine Hydrochloride
Cetirizine (di)Hydrochloride

Molecular Formula

$C_{21}H_{25}N_2O_3Cl \cdot 2HCl$

Molecular Weight :

461.8

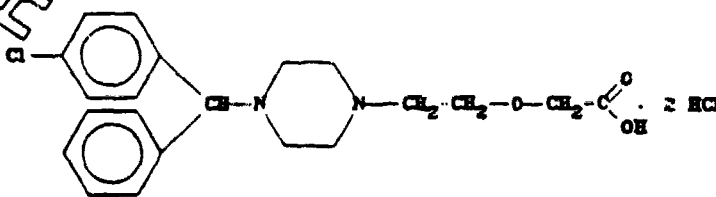
Physical Description :

White or practically white powder

Impurities :

Total impurities = Max. 1.0 %

Structural Formula :



5.(b) Drug Product

Not applicable.

6. Introduction of Substances into the Environment

The manufacture of Cetirizine Hydrochloride drug substance is being carried out in support of other products and will be carried out at the same facility under DMF _____, in support of use in the U.S.

The manufacture of bulk Cetirizine Hydrochloride in support of projected U.S. use will not have a significant impact on manufacturing emissions, controls, or compliance with emissions standards at the above-listed drug substance manufacturing site.

The applicant certifies that applicable national, regional and local environmental and occupational emissions standards and requirements are being met and will be met in support of projected U.S. use.

A. Manufacturing Emissions

A listing of components, including proprietary components, intermediates and side products, used to manufacture drug substance is provided in Confidential Appendix 1. Emissions into the occupational, atmospheric, aquatic and terrestrial environments are provided in this annex. These emissions are controlled as outlined in item 6B. Total emissions of these substances are not in excess of permitted levels and standards, as noted in item 6B and C below.

a. Occupational

Occupational emissions comprise insignificant amounts of particulate Cetirizine Hydrochloride drug substance and reaction components, solvents, intermediates and side-products. Emissions into the workplace environment at or below permissible levels are listed in Confidential Appendix 1 in the "Oc" column.

b. Atmospheric

Air emissions comprise insignificant amounts of particulates and volatiles. Emissions into the atmospheric environment at or below permissible levels are listed in Confidential Appendix 1 in the "At" column.

c. **Aquatic**

Aqueous discharges from the manufacturing facility, comprising amounts of soluble inorganic wastes and insignificant amounts of soluble organic wastes and particulates from manufacturing and equipment clean-out operations are estimated to contain substances at or below permitted, regulated or contracted levels as listed in Confidential Appendix 1 in the "Aq" column.

d. **Terrestrial**

Terrestrial emissions comprise unrecoverable solvents containing synthesis side products, non-aqueous organic wastes, aqueous waste streams not suitable for effluent and filter cakes containing adsorbed process constituents. Those emissions are collected by fully licensed contractors for off-site recovering and/or incineration.

Liquid and solid waste terrestrial emissions comprise also residues emanating from disposal at a licensed recovering and/or incineration facility (see Controls, item 6Bd, below). Emissions into the terrestrial environment at or below permissible levels are listed in Confidential Appendix 1 in the "Te" column.

B. **Controls**

Emissions controls are used in the manufacturing process to ensure compliance with occupational exposure limits, with general emissions requirements, specific standards and permit limits, and with contract requirements as indicated below. A flow chart showing the reaction sequence and the control steps/tests is provided in Confidential Appendix 2. This Appendix lists emissions resulting after controls are provided.

a. **Occupational**

Workplace exposures are controlled via appropriate equipment design, material and product transfer procedures and protective equipment. Properly designed equipment and facilities, administrative controls and personal protective equipment are used to minimize worker exposure in the handling of solids and liquids.

Examples include use of closed reaction systems, pipe-line additions and transfers, local ventilation and dust collection. Gas transfer will of necessity be carried out via close-piping systems. The use of masks, self-contained breathing apparatus, protective clothing, etc. will be prescribed as necessary when engineering and administrative controls are insufficient to ensure worker protection.

The quality of the working environment is periodically evaluated and must comply with the official "T.L.V." (Threshold limit values) which are published in the "R.G.P.T." ("Règlement Général pour la Protection du Travail") - Belgian Rules for the Labor Protection, article 148 decies 2.2.§1a. Those "T.L.V.'s" are those accepted by the "American Conference of Governmental Industrial Hygienists". (A.C.G.I.H.).

Evaluation is made by means of :

- badges worn by workers and employees
- detector tubes for air investigations

The workers and employees are informed of potential workplace hazards via a training program. Safety information sheets concerning hazards for raw materials used in the manufacture of drug substance are provided to workers and employees in the dispatching area. MSDS's for Cetirizine Hydrochloride and all intermediates in the synthesis are available to workers and employees and are provided in Appendix 3 and Confidential Appendix 1.

Workers and employees in the UCB's Chemical Plant, Site of Braine-l'Alleud, are subjected to periodic health controls which have to be made in compliance with the "R.G.P.T." ("Règlement Général pour la Protection du Travail") - (Belgian Rules for the Labor Protection) article 124§1.

In summary, the checks are :

- . Periodic clinical examination (twice a year).
- . Haematology and chemistry laboratory test ("Haemogram") (twice a year).
- . Hepatic biological evaluation (twice a year).
- . Check of the "B.E.I." (Biological Exposure Index) by urine testing.

UCB S.A. acts in compliance with R.G.P.T. regulations and has received authorization from the Provincial Government of Brabant (Walloon Region) for operation of the facility as described in the document.

b. Atmospheric

Air emissions from the manufacturing process are avoided through the use of filters and scrubbers on powder systems; emissions from liquid and gaseous handling systems will be avoided via use of proper operational procedures and properly designed condensing and scrubbing systems.

c. Aquatic

Liquid discharges from the manufacturing process, comprising primarily aqueous process streams and wash waters and equipment/facilities washings, undergo a physico-chemical treatment before being discharged into the community drain network, which flows into the river Senne. The overall synthesis waste waters approximates 700 cubic m/day.

Waste waters are controlled daily using an effluent-volume-based continuous-sampling scheme by which the effluent composition can be monitored in a representative fashion. Aqueous discharges are in compliance with the norms listed in Appendix 2.

Aqueous waste streams not suitable for effluent are collected and treated by external companies which have received approval from our governmental authorities as noted in item 6C below.

The decision has been made to construct an on-site treatment plant for biological treatment of plant aqueous wastes prior to release to the community drain network. Following pre-treatment in the existing physico-chemical plant, waters will be in compliance with the following norms :

C.O.D.	less 350 mg O2/L
B.O.D.	less 40 mg O2/L
Nitrogen Kjeldhal	less 40 mg N2/L
Suspended Solid	less 120 mg /L
Hydrocarbons	less 5 mg/L

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d. **Terrestrial**

Destruction of non-aqueous wastes comprising rejected, off-specification, unrecoverable solvents containing synthesis side products, non-aqueous organics, aqueous waste streams not suitable for effluent and filter cakes containing amounts of adsorbed process constituents are conducted at fully-licensed contract facilities :

- 1) **The Walloon Government has granted authorization to DESTRUCTO for the acquisition and transport of toxic wastes (permit issued on 27.09.1990).**

DESTRUCTO subcontracts :

- > **the disposal of non-chlorinated waste material to SCORIBEL (permit issued by the Walloon Government on 05.04.1988) for incineration in the OBOURG cementary (permit issued by the Walloon Government on 20.02.1992).**
- > **The disposal by incineration of chlorinated wastes to INDAVER (permit issued by the Flemish Government 2000 W 40007 and 2000 W 40005). The INDAVER facility is located in Antwerp Harbor area.**

- 2) **Recycling of solvents for other purposes is carried out under contract with "DENEFF CHEMICAL RECYCLING" at B-2220 HEIST o/d BERG. DENEFF is licensed by Walloon Government 30.06.1994 M-B 17669-17672.**

Waste acetone, toluene and isopropanol as well as other solvents categorized as chlorinated or non chlorinated are collected in specific and duly labelled waste containers.

A manifest is issued to accompany each disposal load intended for recycling or destruction in order to document the transfer, recycling/destruction step and, if needed, the invoice. Contract companies used for disposal of wastes are identified in item 6C.

C. Emissions Requirements

Applicable permits for the occupational, atmospheric, aquatic and terrestrial release environments are provided, including permit number, issuing agency and expiration date, as follows :

Release Environment	Regulation/ Permit #	Agency	Expiration date
Occupational	R.G.P.T. Règlement Général pour la Protection du travail (Belgian Rules for the Labour Protection)	Federal Government	Unlimited
	Permit: Authorization for exploitation of UCB Facilities June 3, 1983	Provincial Government n° 12/44.967/35.708	2013
Atmospheric	Permit: Authorization for exploitation of UCB Facilities June 3, 1983	Provincial Government n° 12/44.967/35.708	2013
Aquatic	Discharge of waste water EU/WA/E2/340/1/P.3/c April 7, 1977	Regional Ministry of Environment	Unlimited
Terrestrial disposal	Law and Royal Decree July 22, 1974 February 9, 1976	Regional Ministry of Environment	Unlimited
	Regional Decree July 5, 1985	Walloon Region	Unlimited
	Enforcement decree November 12, 1987	Walloon Region	Unlimited

Contract Companies used for the disposal of wastes are provided including permit, issuing agency and expiration date, as follows :

Company	Permit	Agency	Expiration date
DESTRUCTO B-8700 IZEGEM	Permit for transport of Toxic wastes	Ministry Order. Walloon Government	1996
INDAVER B-2030 ANTWERPEN	Permit for incineration 2000 W 40 007 2000 W 40 005	Ministry Order Flemish Government	None
SCORIBEL B-7034 OSBOURG	Permit collecting toxic wastes for incineration	Ministry Order Walloon Government March 31, 1993	2000
OSBOURG CEMENTERY B-7034 OSBOURG	Permit for incineration	Ministry Order Walloon Government February 20, 1992	1995
DENEFF CHEMICAL RECYCLING B-2220 HEIST o/d BERG	Permit for handling and transport of toxic wastes	Ministry Order Walloon Government June 30, 1994	1997

D. Citation of Compliance with Applicable Emissions Requirements

The applicant certifies that emissions, discharges and wastes from the manufacture of Cetirizine Hydrochloride drug substance are in compliance with applicable occupational health and safety standards and national, regional and local emissions regulations and permits.

E. Effect of Approval of the Action on Compliance with Current Emissions Regulations.

The applicant certifies that the incremental increase in production of Cetirizine Hydrochloride drug substance to meet the projected usage in connection with the subject DMF will not have an effect upon compliance with emissions requirements.

7. Fate of emitted substances in the environment from the Drug Product

Not applicable.

8. Environmental effects of released substances from the Drug Product

Not applicable.

9. Use of resources and energy.

A major portion of raw materials used in the manufacture of Cetirizine Hydrochloride is recovered including recoverable and recyclable solvents. About 8.8×10^6 kJ of steam and 1.4×10^9 kJ of electricity are estimated to be required to produce 1000 kilograms of Cetirizine Hydrochloride. Insignificant amount of minerals are used in the production process.

10. Mitigation measures

In addition to the controls exercised in accordance with the rules enumerated under item 6B and 6C above, the manufacture of Cetirizine Hydrochloride is carried out under the supervision of well trained professionals and entails an active equipment maintenance program.

Procedures are in place providing for containment of spills or leaks and maintaining personnel training for emergency action in the event of an unusual situation which might result in an emission or occupational exposure.

Employees and workers are provided with necessary personal protective equipment and safety information are available when required for all those who work in the manufacturing area.

11. Alternative to the proposed action

Does not apply.

12. List of preparers

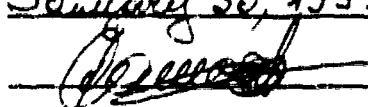
Jean-Pierre CANVAT, Bulk Pharmaceutical Chemical Plant Manager, Chemical Engineer with 31 years experience in Chemical Development, Engineering and Production.

Arthur MARSAT, Head of Environmental Department. Organic Chemist with Ph.D. and 37 years experience in R&D on specialty Chemicals, Chemical Process Research and Pharmaceutical Research.

Pierre-Olivier PLASMAN, Quality Assurance (BPC Plant). Organic Chemist with Ph.D. and 10 years experience in R&D on Pharmacology and Quality Assurance.

13. Certification

The undersigned certifies that the information presented is true, accurate, and to the best of our knowledge is complete and complies with existing Belgian regulations.

Date : January 30, 1995
 Signature : 
 Title : BPC Plant Manager

14. References

No: applicable.

15. Appendices

1. MSDS for Cetirizine Hydrochloride.
2. Aqueous discharge compliance norms.

15a. Confidential Appendices

1. Components in Manufacture of Drug Substances.
Manufacturing Emissions into the Occupational (Oc), Atmospheric (At), Aquatic (Aq) and Terrestrial (Te) Environments.
2. Cetirizine Hydrochloride Manufacture.
Flow Chart of the emissions and of the control steps/lasts.
3. MSDS's for Synthesis Intermediates.

PROPRIETE

UCB

PROPRIETY

END

A handwritten signature or set of initials in a cursive style, consisting of two large loops followed by a short horizontal stroke.

J.H.M. RESEARCH & DEVELOPMENT, INC. 5776 SECOND STREET, N.E. WASH. DC 20011

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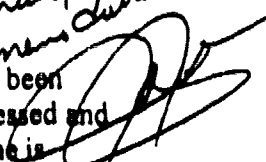
11/9/95

**I N T E R
O F F I C E**

MEMO

To: NDA# 19-835
From: Martin H. Himmel, M.D. - Acting Deputy Division Director, HFD-570
Subject: Cetirizine Tablet NDA
Date: November 9, 1995

*m Himmel
11/9/95
concur, see Director
memo dated 11/21/95.*



This memo is being written regarding the response to the approvable letter which had been submitted by the sponsor in April, 1995. As issues of efficacy have already been addressed and the Division and Office as well as an advisory committee have concluded that cetirizine is efficacious for allergic rhinitis and chronic idiopathic urticaria, this memo will only focus on safety issues. Specifically, the safety issues raised in the medical officer's reviews of 10/17/95 and 11/3/95 will be discussed. These are cardiac safety (specifically affects on the Qtc), affects on liver function tests, the reliance on hydroxyzine marketing data to support long term safety and the adverse event table in the package insert. In addition, while not a safety issue, I will also offer some comments on the medical officer review as currently written.

Cardiac Issues:

Sources of data on the cardiac affects of cetirizine in clinical trials include the 4 clinical trials designed specifically to look at the ECG effects of the drug and additional trials in which ECG's were collected at baseline and follow-up but which were not designed to look at this question and in which the timing of collection of ECG's was not specified in the protocols. The following is a summary of the data collected in the 4 ECG trials:

1. Study 92CK16-0603 - this was a double-blind, randomized, controlled, crossover trial in which subjects received placebo for 1 day (baseline) followed by 5 days of ketoconazole and a subsequent 10 days of ketoconazole + 20mg cetirizine. After a significant washout period the subjects then received 1 day of placebo followed by 5 days of placebo and then a subsequent 10 days of cetirizine 20mg. Subjects were randomized as to whether they received ketoconazole followed by the combination first or placebo followed by cetirizine first. The results from this study demonstrated a prolongation of the Qtc in subjects on cetirizine of 9.1msec. Subjects on ketoconazole demonstrated a Qtc prolongation of 8.3msec. The combination therapy resulted in an additive affect; all these values were statistically significant compared to placebo. Of note, no pharmacokinetic interaction was observed.
2. Study 92CK16-0604 - this was a double-blind, randomized, controlled, crossover trial in which subjects received placebo for 1 day (baseline) followed by 5 days of cetirizine 20mg and a subsequent 10 days of erythromycin + 20mg cetirizine. After a significant washout period the subjects then received 1 day of placebo followed by 5 days of erythromycin 500mg q8h and then

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a subsequent 10 days of cetirizine 20mg + erythromycin. Subjects were randomized as to whether they received cetirizine followed by the combination first or erythromycin followed by combination first. No significant effects on Qtc were seen and there was no pharmacokinetic interaction between cetirizine and erythromycin.

3. Study 90CK16-0497 - this was a double-blind, randomized, controlled, crossover trial in which subjects received placebo for 2 days (baseline) followed by 7 days of either placebo, cetirizine 20mg or cetirizine 60mg. Subjects were randomized as to the order in which they received these treatments. No significant affects on Qtc were seen.

4. Study 93-N-0096 - this was a double-blind, randomized, controlled, parallel trial in which subjects received placebo for 1 day (baseline) followed by either cetirizine 20mg for 5 days and a subsequent 5 days of cetirizine + azythromycin or 10 days of cetirizine 20mg or 10 days of placebo. The following results were seen in this trial:

Maximum Qtc change from baseline using Bazett formula			
Treatment Period	Placebo	Cetirizine	Combination
Baseline	426	425	429
Day 6	40	29	36
Day 11	43	42	35

As seen above, cetirizine had a smaller change in Qtc from baseline to day 6 and day 11 than placebo, although the change from day 6 to day 11 were greater in the cetirizine group. None of the differences between cetirizine and placebo were statistically significant. Also of note, there were no pharmacokinetic interactions between cetirizine and azythromycin.

The medical officer notes on pages 17-19 of her review that there were more events of prolongation of Qtc >10% in the ketoconazole interaction trial in cetirizine and combination treated subjects (12 and 40, respectively) than in subjects on placebo. In addition, in the erythromycin interaction trial there were no events on placebo v.s. 33 events on the combination of cetirizine and erythromycin. While these numbers may in fact be correct, the clinical and statistical significance of this has not been demonstrated. In addition, it is important to point out that in the ketoconazole interaction trial, subjects on cetirizine or combination therapy had 40 ECG's performed while on treatment while subjects on placebo or ketoconazole had only 20. Also, in the erythromycin trial, subjects were on placebo for only one day, thus leading to significantly fewer ECG's in subjects on placebo than other treatments. Finally, no findings of U waves on ECG's of any of the subjects in the above 4 trials was reported.

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Additional data which has been looked at to evaluate the effects of cetirizine on ECG's includes ECG's performed as part of study SAR 8 (80 subjects received cetirizine and 80 subjects received terfenadine), SAR/Lora (82 subjects received loratadine, 81 received cetirizine and 77 received placebo), 9 UCB trials performed in Europe and PEDS 4 (a 4 week allergic rhinitis study in children which included ECG's at baseline and week 2). None of these trials was designed specifically to look at effects on Qtc and thus exact timing of the performance of ECG's was not done. In addition, little is described in the medical officer review of the exact protocols of the 9 UCB trials that were combined into one data base. Studies SAR 8 and SAR/Lora were evaluated by comparing the number, across treatment arms, of subjects with a 10% or greater prolongation in Qtc. The data showed that for all treatments small numbers of subjects had such prolongations and the numbers were similar across treatment arms. The UCB trials did not have a control arm for comparison purposes and so they were just evaluated for the number of subjects with Qtc prolongation >10% and who also had a follow up Qtc >440. Two such subjects were identified, one of which also had a LBBB. For these three data sets, all ECG's with a 10% or greater prolongation in Qtc were evaluated by a cardiologist and no large T waves or U waves were identified.

The final data set evaluated comes from study Peds-4. This ECG data was analyzed using all follow-up ECG's and selecting the maximal change or by using only the ECG's performed between days 11-17 since the protocol had called for doing ECG's on day 14. The analysis only includes subjects with an ECG within 24 hours of their last dose of cetirizine.

Change from baseline Qtc (Bazett) using ECG's from days 11-17				
	Placebo	Cetirizine 5mg	Cetirizine 10mg	P value
Change from baseline	1.77	-2.52	9.94	.061

Change from baseline Qtc (Bazett) using all ECG's				
	Placebo	Cetirizine 5mg	Cetirizine 10mg	P value
Change	4.92	-2.40	10.73	.006

Of note, the significant P values are being driven by the comparison of the 5 and 10mg doses. Pairwise comparison of either dose to placebo is not significant.

In summary, the trials discussed above can be divided into two categories, those conducted specifically to evaluate the ECG affects of cetirizine and those in which ECG's were done but not for the prospective reason of evaluating the Qtc interval. The latter group of trials essentially provide individual patient use data because of lack of control on collection of ECG's as well as the lack of a control arm in the UCB trials. Perhaps the best data from this group comes from the

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Peds-4 trial which also failed to demonstrate a concern based on a evaluation of individual ECG's as well as a lack of a statistically significant difference between treatment and placebo. In addition, it would seem that since ECG collection was not tightly controlled in any case, the use of the entire ECG database rather than just those collected on days 11-17 would be more appropriate.

With regard to the trials conducted to specifically look at the ECG effects of cetirizine, only the ketoconazole interaction trial demonstrated a statistically significant prolongation in the Qtc interval in cetirizine treated subjects. The effect size, 9.1msec or about 2% over baseline, while statistically significant is not, in and of itself clinically significant. In addition, this finding was not supported by three additional trials, one of which studied a dose 6 times the highest clinical dose that would be marketed. All four of these trials were reviewed by the Division quite extensively and no rationale, based on study design or statistical analysis, could be found for why one trial demonstrated an effect while 3 others did not. To consider the finding in the ketoconazole interaction trial real would thus require considering the other 3 ECG trials false negative trials. Using a P value of .05, the probability that the ketoconazole interaction trial is a false positive trial is 5%. Assuming a power of 80% was used (the protocols actually do not specify the power that had been used for these trials) the probability of a false negative trial is 20%. However, the probability of three false negative trials (.2 x .2 x .2) would be .8%. Thus, there is greater probability that the ketoconazole interaction trial is a false positive finding than the three other ECG trials are false negatives, 5% v.s. .8%, respectively. Therefore, the ECG data in this NDA should not preclude approval of cetirizine at doses of 5 and 10mg per day, nor is a black box warning in the package insert warranted at this time.

Liver Function Tests:

With regard to effects of cetirizine on liver function tests, the following mean changes from baseline for cetirizine treated subjects v.s. placebo were seen based on the sponsor's placebo controlled database:

Lab Test	Cetirizine (%)	Placebo (%)
SGOT	.84U/L (10)	-.05U/L (6)
SGPT	1.35U/L (16)	-.189 (7)
T. Bili	-.01 (7)	-.01 (7)

Alk Phos	-.64U/L (.72)	-.14 (4)

In addition, the sponsor used a schema of categorizing lab changes in which a lab abnormality that was considered "may be related to drug" was considered a category 9 abnormality. For the 5mg dose of cetirizine 0% of subjects had an SGOT that was category 9 and 1% had an SGPT in this category. For the 10mg dose the values for SGOT and SGPT were 1 and 2%, respectively and for placebo they were 0 and 1%, respectively. No increased incidence of SGOT and SGPT elevation was seen over the duration of the clinical trials (12 weeks). The medical officer raises concerns on page 39 of her review regarding an effect on SGPT seen in the erythromycin interaction trial (see page 39 of the MO review). Based on the pattern of rise and fall in SGPT, one could attribute the effect to erythromycin, cetirizine, the combination or an unknown factor. Of importance is the fact that similar effects are not reported for SGOT or bilirubin, clinical hepatitis was not reported and the effect was reversed. On page 28-29 of the review, the medical officer has identified 4 cases of elevated SGOT and SGPT in which, in her opinion, no other cause could be identified. Of note, the review does not indicate that all other possible causes, such as viral etiologies, had been ruled out. While these cases may be associated with cetirizine use, they were not associated with clinical hepatitis or elevated bilirubin and should not preclude approval of cetirizine. One case of hepatitis, based on foreign usage of cetirizine, which could be associated with cetirizine use has been identified by the reviewer and this case has been put into the package insert.

In summary, the NDA database does not demonstrate any clinically significant differences between cetirizine and placebo in mean changes in liver function tests. Differences between the groups in category 9 values are small as well. Evaluation of individual patients has identified one case of clinical hepatitis, based on foreign marketing experience, which could be associated with cetirizine. This data does not demonstrate hepatotoxicity on the part of cetirizine and should, therefore, not preclude approval of cetirizine. Nor do they demonstrate a toxicity that requires further investigation with long term studies.

Long term safety:

The usual standard for the Division is to require long term safety data prior to approval of new molecular entities. Such data usually consists of data in 200 patients for one year or 300 for 6 months and 100 for a year. As this NDA had been submitted many years ago, such long term safety was not collected for cetirizine. The following, however, is data which compares serum levels of cetirizine following administration of cetirizine v.s. administration of hydroxyzine:

	CPK-1 bio study single dose cetirizine 10mg n=17	CPK-4 bio study multiple dose cetirizine 10mg n=18	Cimetidine interaction study, single dose of hydroxyzine 25mg, n=8 ¹	Pharmacokinetic study in elderly hydroxyzine mean dose 49mg n=9 ²
Cmax	315 ±95ng/ml	311±40ng/ml	247±118ng/ml	462±77ng/ml
AUC	2911±ng hr/ml	2503±366 ng hr/ml	4390±1502ng hr/ml	11529±2383 ng hr/ml

- 1 Simons et. al. J Allergy Clin Immunol 1995;685-93
2 Simons et. al. Clin Pharmacol Ther 1989;45:9-14

Comparing cetirizine levels from to cetirizine v.s. levels seen with administration of hydroxyzine one sees that at 25mg hydroxyzine produces somewhat lower Cmax levels and higher AUC levels. However, the more appropriate comparison would be of the daily dose of hydroxyzine v.s. the daily dose of cetirizine. Hydroxyzine is currently approved for use in chronic urticaria up to a dose of 100mg per day and in anxiety disorders up to 400mg per day. Assuming linear kinetics for hydroxyzine, an assumption supported by cross study comparison of pharmacokinetic data, one would expect a Cmax and AUC at 100mg per day of about 1000ng/ml and 17560ng hr/ml, respectively and at 400mg per day 4000ng/ml and 70240ng hr/ml, respectively. In addition, the NDA database does include 47 patients treated with 10-20mg of cetirizine out to 21-26 weeks and an additional 115 patients also treated with 10-20mg of cetirizine for 27-33 weeks. Therefore, based on the currently available cetirizine long term data as well as the pharmacokinetic comparison to hydroxyzine it would be reasonable to approve cetirizine without requiring further long term safety studies on the part of the sponsor. Regarding the reviewer's concerns that the enantiomeric mix of cetirizine from hydroxyzine would differ from what would be seen when cetirizine is administered, this is currently a hypothetical concern without data to support it. The metabolism of hydroxyzine to cetirizine does not involve the chiral center of the drug and so, while not definitively assuring that the cetirizine produced from hydroxyzine is a racemic mixture, it makes an imbalance in enantiomers less likely. In addition, the difference in expected exposure to cetirizine from the highest dose of hydroxyzine as compared to exposure from cetirizine is quite large and should mitigate concerns regarding differences in the enantiomer mix. Finally, no data has been presented demonstrating a clinical difference in the safety profile from the two enantiomers.

Adverse Event Table:

Using the medical officers suggestion of a 1% adverse event table would result in the addition of insomnia (1.4 v.s. 1.2% in placebo), epistaxis (1.2 v.s. .6% in placebo), cough (1 v.s. .6% in placebo) and abdominal pain (1 v.s. .9% in placebo) to the table. In addition, intercurrent illnesses that occurred at a rate of ≥ 1% and were more common in treated subjects only consists

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of cold (5% v.s. 4.6% in placebo). While the medical officer's approach is one possible way of constructing the table, such an approach would not add much important information. Therefore, the table as currently constructed with a 2% cutoff is acceptable.

Package Insert:

1. In the second paragraph of the pharmacodynamics section the sentence "Thus there was no significant drug effect on Qtc with the combination of ZYRTEC and ketoconazole" should be changed to "Thus there was no significant drug interaction on Qtc with the combination of ZYRTEC and ketoconazole".
2. In the last sentence of the same paragraph the second "was" should be deleted.
3. In the **ADVERSE EVENTS** section under **Central and Peripheral Nervous Systems** "cramps legs" should be changed to "leg cramps". In the same section under **Body as a Whole** "legs edema" should be changed to "leg edema".

Medical Officer Review:

The format used by the medical officer to organize her review and present the data is not considered optimal. The review includes an extensive amount of copying of parts of the NDA in situations where the data and the reviewer's conclusions could have been presented more concisely. In addition, the review is somewhat disorganized in that one needs to often look at two and even three different places in the review to find complete information about an issue. These formatting issues should be addressed by the medical officer in subsequent review of future NDA's.

Conclusions and Action Items:

Cetirizine should be approved for the treatment of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria at doses of 5 and 10mg per day. The 3 changes to the package insert discussed above can be conveyed to the sponsor in the approval letter. Finally, the sponsor should be called for a final safety update which should consist of serious adverse events which have occurred since the last update.

CC:

Original NDA 19835
HFD-570/Div. Files
HFD-570/J. Jenkins
HFD-570/C. Schumake
HFD-570/K. Lee

ORIGINAL

Medical Officer Review

NOV 9 1995

NDA 19835

Drug: Cetirizine tablets (Zyrtec)

Sponsor: Pfizer

Date: October 17, 1995

Subject: Response to the NDA approvable letter dated February 21, 1995 and proposed physician package insert included in the SU dated 4/25/95

Medical Officer Reviewer: Ana M. Saavedra-Delgado, M.D.

Correspondence:

The medical officer has completed the review of material included in the following correspondence.

Al Saavedra-Delgado MD
10/17/95
see supervisor's memo
m. Hummel
11/9/95

- SU 4/25/95 Final Safety Update, volumes 1-30
Includes response to questions 1-11 of the
cetirizine approvable letter of 2/21/95
- BZ 5/12/95 Response to items 15-22 of the 2/21/95
approvable letter
- C 5/25/95 Response to items 1 and 3 of FDA facsimile
dated 5/11/95
- N(BM) 6/7/95 Response to item 2 of FDA facsimile
dated 5/11/95
- N(BM) 6/14/95 Report of 2 deaths in a foreign
clinical study
- N(BM) 6/20/95 Additional data in response to item 2
of FDA facsimile dated 5/11/95
- N(BM) 6/29/95 Case report forms of patients
reported in correspondence dated 6/14/95
- N(BM) 7/17/95 Response to information requested in
teleconference with FDA dated 7/6/95
- C 8/8/95 Response to FDA facsimile dated
7/20/95
- BZ 8/11/95 Response to information requested in
FDA facsimile dated 8/4/95
- N BL, SU, BM 8/18/95 Draft physician package insert

labeling incorporating the pediatric data and Study Report of UCB No. A 132 (RRCE92L2503)-Efficacy and safety in children and adolescents with asthma. The medical officer has completed the review of the draft physician package insert included in this correspondence as it refers to the tablet.

N (BM) 8/11/95 Case Report Forms and patient identifiers requested in FDA facsimile dated 8/1/95

Response to consult by Epidemiology on ketoconazole and hydroxyzine dated 6/23/95

C 9/12/95 Response to FDA facsimile dated 8/25/95.

CC: Orig. NOA 19-835
HFD-570/D.V. Files
HFD 570/A. Suvredra-Delgado
HFD-570/M. Himmel

Outline and Table of Contents of this review:

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- I. Draft review of the proposed package insert included in the SU 4/25/95

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- II. Appendices

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Section 3

- I. Revised package insert faxed to the sponsor September 29, 1995.

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- II. Reviewer's general comments and regulatory recommendations.

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Section 1.

I. Response to our clinical requests on the February 21, 1995 NDA approvable letter.

In the following section the requests submitted to the sponsor in the approvable letter are presented in small font followed by a summary of their response in regular (10cpi Courier) font. Unless otherwise specified, these responses are found in the sponsor's submission dated April 25, 1995.

1. As discussed at the meeting of December 21, 1994, all ECG's in SAR-8, SAR/LORA, the UCB controlled trial and the azithromycin interaction trial in which there is a 10% or greater prolongation in QT_c from baseline should be evaluated by a cardiologist for changes in T-U wave morphology. The change in QT_c on the ECG's of the UCB, SAR-8, and SAR/LORA trials should be evaluated for age, gender, race, dose, dose adjusted for weight, duration of treatment related effects and concurrent therapy, if any. Because of possible diurnal effects on QT_c, the analysis should incorporate a description of how the ECG's included in the analysis compare with regard to the time they were collected. If serum drug concentrations are available, an analysis of change in QT_c by drug level should be performed. Please compute the QT_c according to the Bazett formula. For the UCB data and the azithromycin study, in addition to mean changes an analysis should also be performed comparing active treatment to placebo with regard to subjects with <10% increase in QT_c from baseline, 10-15%, 15-20% and >20% increase over baseline.

Response:

- a. "All ECGs from SAR-8, SAR/LORA, and azithromycin studies were evaluated by a cardiologist. The ECGs from SAR-8 and SAR/LORA were evaluated and interpreted by Daniel B. Goodman (Medical Director), Cardiology for Clinical Trials. This interpretation was submitted in the March 3, 1994 safety update. The ECGs from the azithromycin interaction study were interpreted by Raymond Woosley, M.D. and they form part of this response. The ECGs from the UCB studies were evaluated by a physician trained in cardiology."

The specific occurrences of QT_c(Bazett's) prolongation of greater than or equal to 10% over baseline for the SAR-8, SAR/LORA and the UCB studies were included in Vol 1 pages 2-17. Since these studies were not specifically designed to study QT_c prolongations, only the data from individual patient results in terms of QT_c prolongation are included in this document.

The results from the cetirizine-azithromycin interaction study where QT_c evaluation was part of the study protocol are discussed separately as part of **Section 2** on the

proposed labeling, in Appendix 1.

SAR-8 (L-048) - ECG cardiology evaluation of the following ECGs- blinded

Clarification by the sponsor following telephone conversation of 5/24/95:

There were two treatment arms in this study and the following number of patients were considered to be safety evaluable: 80 cetirizine and 80 terfenadine. Reference was made to Table F1.B, vol. 3 of this submission (4/25/95).

Patients with a 10% or greater prolongation in QTc from baseline. Table 1.1

From a total of 160 patients in this study a total of 12 patients had a prolongation in QTc 10% or greater over baseline. These were 4 males and 8 females between the ages of 26 to 51 yrs of age.

cetirizine=8	terfenadine=4
females=5	3
males=3	1

Of the eight cetirizine treated patients with a 10% or greater prolongation in QTc over baseline, five had a QTc >440msec in the ECG. Table 1.2:

#90S0026-10	sinus rhythm 51 y/o w/female pt on estrogen progesterone and thyroxine
#90S0029-2	sinus rhythm 43 y/o w/female
#90S0030-11	sinus tachycardia/ early repolarization pattern 32 y/o w/male
#90S0030-14	sinus rhythm/ sinus arrhythmia 26 y/o w/female on triphasil (BCP)
#90S0030-19	sinus rhythm/T wave inversions/ abnormal ECG clinically significant 30 y/o female on Sudafed 30 mg and Trileven (BCP)

Of the four terfenadine patients with a 10% or greater prolongation in QTc over baseline, two had a QTc >440msec in the ECG. Table 1.2:

TABLE 1-1
 SABB: ONE WEEK STUDY OF CETIRIZINE AND TERFENADINE IN SEASONAL ALLERGIC RHINITIS
 PROTOCOL L-6108
 LISTING OF PROPORTIONS OF 12% OR GREATER THAN BASELINE QTC
 QTC COMPUTED USING BAZETT'S FORMULA

SITE	PAT NUM	AGE	SEX	WEIGHT	RACE	TREATMENT GROUP	TREATMENT DURATION (DAYS)	QTC (BAZETT) BASE POST 1	CHANGE CONCOMITANT MEDICATIONS
96S0026	1								
96S0027	7								
	23								
96S0028	11								
	14								
	17								
	19								
96S0029	2								
96S0030	9								
	11								
	14								
	19								

TABLE 1.2: CARDIOLOGIST REVIEW OF ECGS WITH QTc >= 10% INCREASE FROM BASELINE: SAR-0 (PROTOCOL L-0140)

SITE	SUBJECT	TREATMENT GROUP	MEDICATION START	STOP	ECG DATE	Z	QTc CHANGE (MZZETT)	ECG INTERPRETATION
9630026	10							
9630027	7							
	23							
9630028	11							
	14							
	17							
	19							
9630029	2							
9630030	9							
	11							
	24							
	19							

* CET = CATHETERIZATION YEP = TEMPORARY

***** - CTR - PENDING DATA

#9CS0028-19 sinus rhythm
37 y/o other/female

#90S0030-9 sinus rhythm, poor R wave
progression V1-V3/ borderline ECG
41 y/o w/female on Ibuprofen 600 mg and
Afrin nasal spray

SAR/LORA (C91-0001) cardiology evaluation blinded

Clarification by the sponsor following telephone
conversation of 5/24/95:

There were three treatment arms in this study and the following number of patients were considered to be safety evaluable: 82, loratadine, 81 cetirizine and 77 placebo. Reference is made to Table F1.B, vol. 3 of this submission (4/25/95).

Patients with a 10% or greater prolongation in QTc from baseline. Table 1.3

From the total number of patients in this study 6 patients had a prolongation in QTc 10% or greater over baseline. These were 5 males and 1 female between the ages of 14 to 38 yrs of age.

cetirizine=4	placebo=2	loratadine=0
females=1	0	
males=3	2	

Of the four cetirizine treated patients with a 10% or greater prolongation in QTc over baseline, two had a QTc >440msec in the ECG. Table 1.3 and 1.4:

#91C0002-91 sinus bradycardia/ early
repolarization pattern
25 y/o w/male

#91C0005-190 sinus rhythm
14 y/o w/male

No placebo or loratadine patient had a 10% or greater change in QTc over baseline and a QTc >440msec in the ECG (Tables 1.3 and 1.4).

UCB studies

Clarification by the sponsor following telephone

SAR/LORA: TWO WEEK STUDY OF CETIRIZINE AND LORATADINE IN SEASONAL ALLERGIC RHINITIS
 TABLE 1.3
 PROTOCOL CTR CAN 21-001
 LISTING OF PROBLEMS OF 102 OR GREATER THAN BASELINE QTC
 QTC COMPUTED USING BAZETT'S FORMULA

SITE	PAT NUM	AGE	SEX	WEIGHT	RACE	TREATMENT GROUP	TREATMENT DURATION (DAYS)	QTC (BAZETT) BASE	QTC (BAZETT) POST 2 CHANGE CONCOMITANT MEDICATIONS
91C0002	97								
91C0005	100								
	190								
	195								
91C0006	103								
	153								

TABLE 1.4: CARDIOLOGIST REVIEW OF ECGS WITH QTc >= 10% INCREASE FROM BASELINE: SAR/LORA (PROTOCOL C-91-0001)

SITE	SUBJECT	TREATMENT GROUP	MEDICATION START	STOP	ECG DATE	% CHANGE (BAZETT)	QTc	ECG INTERPRETATION
91C0002	91							
91C0005	100							
	190							
	195							
91C0006	141							
	163							

BY CET - CERTIFIED

CONTRACT - 010 - 000000 0000

conversation of 5/24/95:

There is an error in the original submission (4/25/95). The total number of patients from these 9 studies was 247. In these 9 trials, three types of protocol were conducted: pts. received cetirizine 10 mg for 1 yr (168), another group received cetirizine for 9 months and then were switch to cetirizine 20 mg and the third type of protocol consisted of patients that received 20 mg of cetirizine for 1 year. From the total number of patients evaluated 72 patients had ECGs done at baseline and on follow up. From these 72, 66 had received cetirizine for 12 months, 3 for 10 months, 2 for 9 months and 1 for 8 months. Of these 72 patients with pre and post ECGs, 49 were over 64 years of age.

The individual QT intervals for these 72 patients entered in Pfizer's database had their QTc recalculated using Basset's formula. Of these, 2 patients had QTc prolongations of $\geq 10\%$ over baseline. These were interpreted by Dr. Goodman.

From Table 1.6 the two patients with $>10\%$ prolongation in QTc that also had a QTc >440 msec were:

Pt# Buyse-7 "compared to previous tracing, there are no changes except a slight lowering of the T wave an AVF but still within normal limits"
62 y/o ?m/f, 12 mo of treatment

Buyse-15 "complete left bundle branch block since the previous tracing the non specific IVCD has progressed to LBBB"
88 y/o ?m/f, 12 mo of treatment, on Digitalis

- b. Cetirizine blood levels were not obtained for the SAR-8 and SAR/LORA studies. "The number of patients with a 10% prolongation or greater in QTc" was given by time interval post dose for these studies:

SAR-8, SARA/LORA

Within:	
1.5 hrs	5
1'56" and 3'7"	5
4'20" and 5'	3
7'15" and 10'15"	3
24'15"	1
32'15"	1

Of the above a total of 13/18 (72%) were noted within 6 hrs

post dose.

2. Please analyze the ECG data from the PED-4 study as requested above, using the Bazett's formula for patients who received post ECGs within 24 hours of the last cetirizine dose. The QT_c analysis of this data should include a comparison by dose adjusted for weight, by gender and race. This should be done for both change from baseline as well as by percentage increase or decrease from baseline. As above, all ECG's with a 10% or greater prolongation of QT_c from baseline should be evaluated by a cardiologist for changes in T-U wave morphology.
- a. A summary of the data from the PEDs-4 response that the reviewer considered to be relevant to the labeling was summarized in the Appendix 2 to the reviewer's comments to the proposed labeling in Section 2.

Analyses assessing the effect of weight, gender or race on change from baseline QT_c .

Statistical methods used:

"An ANOVA was performed on the change from baseline QT_c introducing weight class and weight by treatment interaction, as terms in the model, in addition to treatment and baseline QT_c . Similar analyses were performed for gender and race. For each factor an analysis was conducted for the three groups (1: QT_c recorded between 11-17 days, 2: all patients for endpoint change, 3: all patients for maximum change), Tables 2.9 to 2.11. In addition, Pearson correlation of change in QT_c and patient weight in KG was computed by treatment groups, Table 2.12.

The change in QT_c is not correlated for patient weight for either the placebo or the cetirizine groups. The analysis of variance shows that neither the overall effect of weight nor the interaction with treatment is significant in analysis grouping.

Similar results are seen for race.

With respect to gender effects (Table 2.10), overall differences between males and females were significant for the 11-17 day, endpoint change and maximum change analysis ($p < .047$ in each case), but the gender by treatment interaction was not significant."

No statistically significant positive correlations were observed for these three parameters for the ECGs obtained in this study.

It should be noted that these analyses were not part of the original protocol design. The study was a multicenter study and it can be assumed that there were differences in techniques and instruments used between centers.

The following data is noted although no statistical significant differences were demonstrated:

Weight:

CETIRIZINE-PEDIATRIC SEASONAL ALLERGIC RHINITIS IV (PROTOCOL #91CE16-0573)

TABLE 2.9 (ADDENDUM)

SUMMARY STATISTICS FOR CHANGE FROM BASELINE QTc BY WEIGHT CLASS

ANALYSIS GROUPING	OBSERVED MEAN ± STANDARD DEVIATION					
	< 25 kg Patients			≥ 25 kg Patients		
	PLACEBO	CETIR 5 MG	CETIR 10 MG	PLACEBO	CETIR 5 MG	CETIR 10 MG
11-17 DAYS (No. Pats)	(7)	(8)	(10)	(33)	(27)	(34)
Baseline QTc	430.2 ± 29.96	423.0 ± 16.65	421.8 ± 21.22	424.0 ± 24.81	415.7 ± 27.07	420.2 ± 22.95
Change	2.66 ± 16.69	-8.64 ± 27.52	3.87 ± 23.95	-1.52 ± 25.46	2.76 ± 37.72	12.21 ± 25.56
ENDPOINT (No. Pats)	(13)	(11)	(12)	(51)	(53)	(53)
Baseline QTc	423.0 ± 23.99	423.6 ± 17.58	418.5 ± 20.82	417.9 ± 25.23	420.5 ± 27.51	421.8 ± 21.57
Change	6.76 ± 26.80	-7.10 ± 18.73	6.70 ± 22.92	4.93 ± 27.74	-2.67 ± 32.61	9.84 ± 24.68
MAXIMUM (No. Pats)	(13)	(11)	(12)	(51)	(53)	(53)
Baseline QTc	423.0 ± 23.99	423.5 ± 17.58	418.5 ± 20.82	417.9 ± 25.23	420.5 ± 27.51	421.8 ± 21.57
Change	6.76 ± 26.80	-7.10 ± 18.73	7.21 ± 23.86	5.66 ± 27.57	-1.85 ± 33.64	10.90 ± 25.26

CETIRIZINE-PEDIATRIC SEASONAL ALLERGIC RHINITIS IV (PROTOCOL #91CE16-0573)

TABLE 2.11 (ADDENDUM)

SUMMARY STATISTICS FOR CHANGE FROM BASELINE QTc BY RACE

ANALYSIS GROUPING	OBSERVED MEAN ± STANDARD DEVIATION					
	NON-WHITES			WHITES		
	PLACEBO	CETIR 5 MG	CETIR 10 MG	PLACEBO	CETIR 5 MG	CETIR 10 MG
11-17 DAYS (No. Pats)	(8)	(3)	(8)	(34)	(32)	(35)
Baseline QTc	421.3 ± 25.00	429.8 ± 38.65	426.1 ± 17.59	425.7 ± 25.87	416.2 ± 24.51	418.1 ± 23.41
Change	1.79 ± 34.76	-17.52 ± 47.72	14.19 ± 25.45	-1.24 ± 22.80	1.58 ± 34.87	8.32 ± 25.39
ENDPOINT (No. Pats)	(6)	(4)	(9)	(58)	(60)	(56)
Baseline QTc	421.3 ± 25.00	427.7 ± 30.21	426.1 ± 17.59	418.7 ± 25.08	420.6 ± 25.90	420.4 ± 21.88
Change	7.93 ± 44.15	-14.53 ± 39.42	14.19 ± 25.45	5.03 ± 25.59	-2.69 ± 30.20	8.28 ± 24.17
MAXIMUM (No. Pats)	(6)	(4)	(9)	(58)	(60)	(56)
Baseline QTc	421.3 ± 25.00	427.7 ± 30.21	426.1 ± 17.59	418.7 ± 25.08	420.6 ± 25.90	420.4 ± 21.88
Change	7.93 ± 44.15	-14.53 ± 39.42	14.19 ± 25.45	5.67 ± 25.43	-2.05 ± 31.17	9.58 ± 24.81

4-96

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The sponsor provided us with the summary statistics for the above cited Table 2.9, on the telephone facsimile dated June 13, 1995.

In the Table 2.9 (addendum) for change from baseline QTc by weight class, no numerical differences are observed for the patients in the <25 kg group that had been treated with cetirizine when it is compared to placebo. However, the largest difference for the >25 kg group was a mean change in QTc of 12.21 msec from baseline in the 10 mg cetirizine group (N=34) compared to -1.52 msec in the placebo group (N=33) for those patients whose ECGs were obtained 11-17 days post treatment initiation.

At per our original request, a separate analysis was provided by the sponsor using mg/kg of body weight in the submission dated May 25, 1995. The dose adjusted for weight was computed as the patient's daily dose divided by the patient's weight in kg. The analyses were performed using the analysis groups defined above. There were no positive statistical significant correlations between change from baseline QTc and dose adjusted for weight. In Table 2 (2/25/95), the largest numerical difference in values for mean adjusted change in QTc from baseline between cetirizine and placebo was 6 msec observed at 0.221-0.294 mg/kg (N=14 patients) and 5.8 msec in the 0.294-0.368 mg/kg (N=17 patients) for the 11-17 day group analysis. At >0.368 mg/kg doses the mean adjusted change in QTc between cetirizine and placebo was 1.4 msec.

Gender:

The sponsor provided us with the summary statistics for the above cited Table 2.10 on the telephone facsimile dated June 13, 1995.

In the summary statistic Table 2.10 (addendum) for change from baseline QTc by gender, a numerical change in mean QTc is observed in females for ECGs obtained on days 11-17. The **change in QTc from baseline for the females** from this analysis group that included ECGs for 34 females and 85 males are as follows: placebo 4.38 msec prolongation (N=13), 5 mg cetirizine 12.96 msec prolongation (N=8) and 10 mg cetirizine 16.24 msec (N=13), in the other two groups that were considered for analysis, endpoint and maximum change, there was no appreciable change in QTc observed between cetirizine and placebo.

For male patients, a numerical difference in mean QTc from baseline was observed at each one of these analysis groups (11-17 days, endpoint and maximum change), with the largest difference observed for QTc measured 11-17 days post

CETIRIZINE-PEDIATRIC SEASONAL ALLERGIC RHINITIS IV (PROTOCOL #91CE16-0573)

TABLE 2.10 (ADDENDUM)

SUMMARY STATISTICS FOR CHANGE FROM BASELINE QTc BY GENDER

ANALYSIS GROUPING	OBSERVED MEAN ± STANDARD DEVIATION					
	FEMALES			MALES		
	PLACEBO	CETR 5 MG	CETR 10 MG	PLACEBO	CETR 5 MG	CETR 10 MG
11-17 DAYS (No. Pats)	(13)	(8)	(13)	(27)	(27)	(31)
Baseline QTc	429.1 ± 28.96	413.3 ± 27.20	416.1 ± 18.79	423.1 ± 23.96	418.6 ± 25.17	422.4 ± 23.70
Change	4.38 ± 24.89	12.96 ± 39.17	16.24 ± 22.55	-3.28 ± 24.01	-3.94 ± 34.39	7.83 ± 26.15
ENDPOINT (No. Pats)	(26)	(21)	(17)	(38)	(43)	(48)
Baseline QTc	418.6 ± 27.73	424.2 ± 31.23	415.4 ± 19.60	419.2 ± 23.12	419.5 ± 23.24	423.2 ± 21.71
Change	12.33 ± 29.94	3.13 ± 31.07	12.57 ± 26.58	0.49 ± 24.69	-6.63 ± 30.21	7.87 ± 23.52
MAXIMUM (No. Pats)	(26)	(21)	(17)	(38)	(43)	(48)
Baseline QTc	418.6 ± 27.73	424.2 ± 31.23	415.4 ± 19.60	419.2 ± 23.12	419.5 ± 23.24	423.2 ± 21.71
Change	12.33 ± 29.94	3.13 ± 31.07	13.51 ± 25.55	1.48 ± 24.61	-5.75 ± 31.68	8.05 ± 24.75

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treatment initiation, 7.83 msec for 10 mg cetirizine (N=31) versus -3.26 msec for placebo treated patients (N=27).

In this table, the change in QTc in male patients was always negative or reduced for male patients treated with 5 mg of cetirizine and (positive or prolonged) for female patients.

Race:

The sponsor provided us with the summary statistics for the above Table 2.11 on the telephone facsimile dated June 13, 1995.

In the summary statistic Table 2.11 (addendum) for change from baseline QTc by race, there were a total of 18 non-white patients in the analysis compared to 101 white patients. In the white patients that had the ECG recorded 11-17 days post treatment initiation, the largest mean difference from baseline in mean QTc was a mean prolongation of 9.32 msec for the 10 mg cetirizine patients (N=35) versus a decrease of 1.24 msec in the placebo treated group (N=34). However, the largest numerical change from baseline in mean QTc by race was observed in the 11-17 days group analysis for the non-white patients. The mean prolongation in QTc for 9 patients treated with 10 mg cetirizine was 14.19 msec and 1.79msec for 6 placebo treated patients.

In terms of gender, even though the numerical differences are more prominent in females for the 11-17 days, a numerical difference between 10 mg cetirizine and placebo is seen for males, across the different groups used for the analyses: 11-17 days, endpoint and maximum. The range for this difference between 10 mg cetirizine versus placebo treated males in these three analysis groups is 7.38 to 11.11 msec.

There are larger or more noticeable numerical differences in mean QTc from baseline in the 11-17 day period analysis for the 10 mg cetirizine treated group versus placebo than in the other analysis groupings (maximum change and endpoint) for comparisons made by gender, race and for the over 25 kg in body weight.

Because the number of non-white and under 25 kg patients studied is small compared to their counterparts, very little can be said in terms of a particular effect on mean QTc prolongation.

To explain the larger numerical differences in QTc that are reported in Table 2.2 for change from baseline QTc in endpoint and maximum ECG (see following page, from vol. 35.1 page 23) between treatment groups using the Bazett correction as compared to the Hodges correction reported in the 9/3/93 submission to NDA 20346, the sponsor states that it is related to a higher heart rate observed in the 10 mg cetirizine treated group. However

CETIRIZINE - PEDIATRIC SEASONAL ALLERGIC RHINITIS IV (PROTOCOL 091CE16-0573)
 TABLE 2.2 : SUMMARY OF ANALYSIS OF CHANGE FROM BASELINE IN HEART RATE AND QT INTERVAL
 FOR LAST OR MAXIMUM ECG RECORDED ON TREATMENT
 (EXCLUDING ANY ECG RECORDED MORE THAN 24 HOURS POST LAST DOSE)

	MEAN ± STANDARD DEVIATION			P-VALUE
	PLACEDO	5MG CETIRIZINE	10MG CETIRIZINE	
NUMBER OF PATIENTS	64	64	65	
HEART RATE				
BASELINE	79.05± 11.45	80.47± 15.09	78.40± 12.05	
CHANGE	0.89± 11.67	0.63± 12.81	4.08± 11.34	
(P-VALUE WITHIN)	0.677	0.135	0.026	
ADJUSTED CHANGE ¹	0.79	1.09	3.72	0.241
QT (UNCORRECTED)				
BASELINE	367.14± 26.33	366.92± 26.09	371.15± 27.20	
CHANGE	2.83± 10.56	-8.16± 16.09	-0.76± 19.45	
(P-VALUE WITHIN)	0.226	0.011	0.890	
ADJUSTED CHANGE ¹	2.50	-5.54**	-0.09+	0.026
QTc (BAZETT)				
BASELINE	418.93± 24.08	421.02± 25.98	421.15± 21.31	
CHANGE	5.30± 27.35	-3.43± 30.60	9.10± 24.23	
(P-VALUE WITHIN)	0.192	0.735	0.008	
ADJUSTED CHANGE ¹	4.39	-3.02*	9.59++	0.008
MAX QT (UNCORRECTED)				
BASELINE	367.14± 26.33	366.92± 26.09	371.15± 27.20	
CHANGE	3.13± 10.56	-5.00± 17.30	0.08± 19.49	
(P-VALUE WITHIN)	0.130	0.016	0.515	
ADJUSTED CHANGE ¹	2.80	-5.38**	0.77++	0.021
MAX QTc (BAZETT)				
BASELINE	418.93± 24.08	421.02± 25.98	421.15± 21.31	
CHANGE	5.09± 27.21	-2.04± 31.52	10.22± 24.04	
(P-VALUE WITHIN)	0.107	0.687	0.002	
ADJUSTED CHANGE ¹	4.92	-2.40*	10.73++	0.006

¹ ADJUSTED FOR BASELINE DIFFERENCES.
 * STATISTICALLY SIGNIFICANTLY DIFFERENT FROM PLACEDO (P<.10)
 ** STATISTICALLY SIGNIFICANTLY DIFFERENT FROM PLACEDO (P<.05)
 + STATISTICALLY SIGNIFICANTLY DIFFERENT FROM 5MG CETIRIZINE (P<.10)
 ++ STATISTICALLY SIGNIFICANTLY DIFFERENT FROM 5MG CETIRIZINE (P<.05)

according to the sponsor's Table 2.2, even though there is a numerical difference in heart rates observed between treatment groups in terms of change from baseline, no statistical differences are seen, $p=0.241$.

The following references were reviewed to ascertain to what extent the Bazett would over correct the QT at high heart rates:

In: Morganroth J. (ed). QTc interval prolongation: is it beneficial or harmful? The American Journal of Cardiology, vol 72, No. 6, 1993.

Funk-Brentano C and Jaillon P. Rate-Corrected QT interval: Techniques and limitations, p17B-p22B.

Rautaharju PM, Warren JW. Estimation of QT prolongation. A persistent, avoidable error in computer electrocardiography. Journal of Electrocardiography. 1990: 23(suppl):111-117.

Macfarlane PW, Coleman EN, Devine E et al. A new 12-lead pediatric ECG interpretation program. Journal of Electrocardiography. 1990: 23(suppl):76-81.

The authors in the review from the American Journal of Cardiology suggest reporting the QT at defined heart rates in preference to using one of the corrections; the article briefly discusses the future importance that using repolarization parameters may have in predicting arrhythmic events. However, the authors state that for studies where QTc is a major end-point they prefer the Fridericia correction. In this article differences between the Fridericia and Bazett are emphasized at RR intervals of 1000 msec and above. These would correspond to a heart rate of 60 beat/min and below.

Rautaharju's article points out that the traditional Bazett's fails at low heart rates and the Fridericia at high heart rates. According to the reported figures in this article, the cut off for the Bazett would be HR <60 b/min and for the Fidericia HR greater the 100 b/min. This article also points out that the fact that the QTc (Bazett) for normal women is longer than for normal men appears to be due to QT shortening in males after puberty and a gradual linear increase in adult males, with no significant age trends in females between puberty and menopause. For this purpose the authors propose a correction for QT prediction in males 15-50 years of age.

The Macfarlane article uses the Hodges correction in

the pediatric population, and 460 msec as the upper limit of normal. The authors report that for this correction there is a small but significant correlation between age and QTc, but that for the first 7 days of life, the QTc decreases. They point out that there is a need of a more satisfactory equation to improve sensitivity in detecting prolonged QTc in the pediatric population. The article also emphasizes the need to use ECG machines that take 500 samples/sec rather than 250 samples/sec, to achieve acceptable accuracy. From reading this article this reviewer considers that the authors concerns in terms of the sensitivity of QTc correction were related more to the neonatal period than to the rest of the pediatric age group.

In Table 8, Appendix 1 from Friedman's Diagnostic Electrocardiography and Vectocardiography, McGraw Hill, 1985, the following values, using the Bazett formula are given:

Age	# cases	Mean	Range
0-24 hr	32	0.42	0.37-0.53
0-2 years	16	0.40	0.37-0.42
2-4	16	0.40	0.38-0.42
8-10	16	0.41	0.39-0.42
11-14	15	0.41	0.40-0.42
Adults	48	0.38	0.35-0.44

Only two patients that had a 10% or greater prolongation in QTc from baseline and a QTc post treatment >440 also had a heart rate greater than 100 beats/min. These were placebo patient #186 and 10 mg cetirizine patient #275.

From reviewing the above references it does not appear that the need to use a QTc correction other than the Bazett would be justified in this study. In other studies where there are patients with a mean heart rate of < 60 b/sec other QTc corrections may be justified.

The following individual data from the PEDs-4 study is noted:

The following table looks at the individual data from patients that had the ECGs recorded on days 11-17 days of treatment that had an increase of 10% or greater over baseline QTc with a QTc that was > 440 msec:

Patients with a 10% or greater change from baseline in QTc (Bazett) and QTc > 440 msec for ECGs recorded on days 11 to 17 of treatment, in parenthesis, baseline QTc followed by prolonged QTc:

Placebo	5 mg cet	10 mg cet
92N0036-298 (408-452)	92N0038-264 (416-469)	92N0036-299 (425-472)
	92N0040-219 (377-450)	92N0037-275 (405-458)
	92N0038-282 (393-457)	92N0037-278 (402-458)

Patients with a 10% or greater change from baseline in QTc (Bazett) and QTc > 440 msec for ECGs recorded post day 17 of treatment in parenthesis, baseline QTc followed by prolonged QTc:

Placebo	5 mg cet	10 mg cet
92N0041-50 (380-454)	92N0043-179 (398-457)	92N0043-169 (395-442)
92N0042-57 (404-454)		92N0044-144 (403-445)
92N0042-186 (386-457)		

The following are the patients with a 10% or greater increase in QTc from baseline and a QTc greater than 440 msec when the patients with post treatment recorded ECGs at heart rates of 100 b/min or greater are excluded:

Patients with a 10% or greater change from baseline in QTc (Bazett) and QTc > 440 msec for ECGs recorded on days 11 to 17 of treatment:

Placebo	5 mg cet	10 mg cet

92N0036-298 (B,F)	92N0038-264 (W,M, 0.09 mg/kg) 92N0040-219 (W,M, 0.15 mg/kg) 92N0037-282 (W,F, 0.16 mg/kg)	92N0036-299 (W,F, 0.29 mg/kg) 92N0037-278 (B,F, 0.32 mg/kg)

The following additional patients have a change in QTc of 10% or greater (Bazett) and a post treatment QTc > 440 msec when ECGs were recorded beyond 17 days of treatment. When the patients with ECGs recorded beyond the above time frame of 11-17 days are included, :

Placebo	5 mg cet	10 mg cet
92N0042-50 (B,F) 92N0042-57 (W,M)	92N0040-179 (W,M, 0.17 mg/kg)	92N0043-169 (W,F, 0.36 mg/kg) 92N0044-144 (W,M, 0.32 mg/kg)

3. Using the Bazett formula, please list the QT_c prolongations that are more than 10% over baseline, for the three studies: 90CK16-0497, 92CK16-0603 and 92CK16-0604, by patient, indicating study phase, day, and hour.

The listing requested for the QT_c prolongations that are more than 10% over baseline for studies 90CK16-0497, 92CK16-0603 and 92CK16-0604 are provided in Tables 3.1, 3.2 and 3.3 respectively.

The following reviewer's tables depict the information provided in the submission grouping patients by treatment and listing the number of events with a QT_c prolongation that is 10% or greater and the maximum % prolongation in QT_c (+=or > 10%) for that patient, under that treatment.

Study 90CK16-0497

Multiple dose, placebo controlled crossover study, third party blinded and a wash-out of 5 days.
 Subjects (24, males, 24 white 1 black) received placebo for 2 days before receiving either 20 or 60 mg of cetirizine for 7 days.

Placebo Pt.# (# events, max. %prolongation, * = >440 msec)	Cet 20 mg Pt.#(# events, max. % prolongation, * = >440 msec)	Cet 60 mg Pt.# (# events, max. %prolongation, * = >440 msec)
Totals: 6 patients, 8 events 15.6%- max prolongation	Totals: 4 patients, 8 events 19.0%- max prolongation	Totals: 6 patients, 11 events 15.4%- max prolongation

Study 92CK16-0603

Multiple dose, randomized, open (cardiologist-blinded), two way crossover with a 20 day wash-out period. Subjects (16, male: 12 hispanics, 2 black, 2 white) received 1 day placebo followed by 400 mg ketoconazole or placebo for 5 days, and then for 10 days the combination of ketoconazole and cetirizine for those that had received ketoconazole or 20 mg cetirizine for those that had only received placebo.

Placebo Pt.# (# events, max. %prolongation, * = >440 msec)	Cet 20 mg Pt.# (# events, max. %prolongation, * = >440 msec)	Ketoconazole 400 mg Pt.# (# events, max. %prolongation, * = >440 msec)	Combination Pt.# (# events, max. %prolongation, * = >440 msec)
Totals: 2 patients, 2 events, 11.3 (max % prolongation)	Totals: 7 patients, 12 events, 12.6 (max % prolongation)	Totals: 3 patients, 6 events, 14.2 (max % prolongation)	Totals: 9 patients, 40 events, 15.7(max % prolongation)

Study 92CK16-0604

Multiple dose, randomized, open (cardiologist-blinded), two-way cross-over with a 20 day wash-out period. Subjects (16, male 9 hispanics, 7 white) received placebo for one day, followed by cetirizine (20 mg) or erythromycin (500 mg) alone for five days each before each group received the combination for 10 days.

Placebo Pt.# (#events, max. %prolongation, * >440 msec)	Cet 20 mg Pt.# (#events, max. %prolongation, * >440 msec)	Erythro 500mg Pt.# (#events, max. %prolongation, * >440 msec)	Combination Pt.# (#events, max. %prolongation, * >440 msec)	
			Cetirizine given first	erythro given first
Totals: 0 patients, 0 events, 0, max % prolongation	Totals: 1 patient, 1 event, 11.1, max % prolongation	Totals: 3 patients, 3 events, 11.7, max %prolongation	Total: 6 patients 16 events 20.1, max % prolongation	Total: 7 patients, 17 events, 20.6, max % prolongation

In the ketoconazole-cetirizine interaction study 92CK16-

0603, there is an increased frequency of events of QTc prolongation (10% or greater) per subject receiving the combination than when this drugs are taken by themselves. This effect is more readily apparent here using the Bazett correction than with the Hodges correction that was used in the original study report. Using the Hodges correction there were: no event while on placebo, 2 subjects receiving 20 mg of cetirizine with 3 events (10% or greater prolongation in QTc from baseline), 1 ketoconazole with 2 events and 5 receiving the combination with 18 events (MOR date 2/27/94). With the Bazett correction the numbers are: 1 subjects with 2 events while on placebo, 7 subjects receiving 20 mg of cetirizine with 12 events (10% or greater prolongation in QTc from baseline), 3 ketoconazole with 6 events and 9 receiving the combination with 40 events. Even though the QTc prolongations in this study were generally not in the 15-20% range the frequency of these particularly using the combination is of concern.

For study 92CK16-0604 the above individual data suggests an effect for the erythromycin-cetirizine combination and a clinical concern for the patients with prolongations around 18-20% over baseline.

The above discussed effects are not seen for study 90CK16-0497. The 19% prolongation in QTc (absolute=481 msec) for subject # 22 while on 20 mg of cetirizine (Day 1 hour 6) is of concern even though it is apparently a single event.

4. Please explain the discrepancies between the results for the requested ECG analysis regarding the number of patients with more than 10% increase in QT_c in SAR/LORA and SAR-8 studies provided to us in the March 12, 1993 submission and the data submitted on March 3, 1994 in the safety update. An explanation of why the overall numbers of subjects in the treatment groups differ between the two submissions should also be given.

Response: The results of patients with prolonged QTc in the March 12, 1993 submission were based on the measurements provided by each participating investigator. The results submitted in the March 12, 1994 safety update represent the standardized QTc measurement done on all ECGs by Cardiology Clinical Trials. The total number of patients with ECGs differ in both submissions because in the first one all patients with ECGs were included and in the second submission (3/12/94) only those patients with baseline and posttreatment ECGs were included.

5. In reference to Table 1, Appendix 2 of the July 15, 1993 submission, please list the terms that were included under "psychiatric disorders" and update the corresponding frequencies per term. Please report these results by dose and duration of treatment.

Response: Section D.5.b.1.a.; Tables F8 B1-B4.

The cumulative database in placebo controlled studies included 2679 patients treated with cetirizine and 1671 placebo treated patients. The incidence of adverse experiences in cetirizine and placebo treated patients in the cumulative database are shown in Tables F8 A-B. These trials are in adult patients treated with the tablet and the capsule formulations and include 2 trials conducted in Canada. These are referred in the submission as U.S. sponsored trials. The cumulative safety data includes data in NDA 19835 filed on June 30, 1988 and the post NDA data through February 26, 1994.

The most common adverse experiences by body systems are Central and Peripheral Nervous system Disorders (which includes headache), Psychiatric Disorders (which includes somnolence) and Body as a Whole (which includes fatigue).

From Table F8.B1

Adverse experience	cetirizine No. Pts (%)	placebo No. PTS (%)
Total No. of Pts	2679	1671
N. of Pts with any AE	1158 (43.2%)	610 (36.5%)
Centr and Periph Nervous Syst Disorder	504 (18.8%)	324 (19.4%)
Psychiatric Disorders	464 (17.3%)	143 (8.6 %)
Body as a whole	225 (8.4%)	86 (5.1%)

As shown in Table F8.B2, somnolence accounts for the majority of the incidence of all terms which are included under psychiatric disorders.

The incidence of the specific terms are shown in Table F8.B2 from placebo controlled adult studies.

Adverse experience	cetirizine No. Pts (%)	placebo No. PTS (%)
Total No. of Pts	2679	1671
N. of Pts with Psychiatric Disorders	464 (17.3%)	143 (8.6%)

Somnolence	405 (15.1%)	105 (6.3%)
Nervousness	26 (1.0%)	14 (0.82 %)
Concentration impaired	6 (0.2%)	1 (0.1%)
Emotional liability	5 (0.2%)	0 (0.0%)
Depression	4 (0.1%)	1 (0.1%)
Thinking abnormal	4 (0.1%)	0 (0.0%)

The incidence by dose of the Psychiatric Disorder are shown in Table F8.B3 for placebo-controlled fixed dose studies.

Adverse experience	Combined Cet No. Pts (%)	cet 5 mg	cet 10 mg	cet 20 mg	placebo No. PTS (%)
Total No. of Pts	2532	430	1489	554	1531
N. of Pts with Psychiatric Disorders	428 (16.9%)	58 (13.5%)	243 (16.3%)	119 (21.5%)	123 (8.1%)
Somnolence	373 (14.7%)	49 (11.4%)	205 (13.8%)	112 (20.2%)	90 (5.9%)
Nervousness	23 (0.9%)	2 (0.5%)	13 (0.9%)	8 (1.4%)	11 (0.7 %)
Concentration impaired	6 (0.2%)	0 (0%)	6 (0.4%)	0 (0%)	1 (0.1%)
Emotional liability	5 (0.2%)	3 (0.7%)	1 ((0.1%)	1 (0.2%)	0 (0.0%)
Depression	4 (0.2%)	1 (0.2%)	3 (0.2%)	0 (0%)	1 (0.1%)
Thinking abnormal	4 (0.2%)	1 (0.2%)	3 (0.2%)	0 (0%)	0 (0.0%)

Incidence of psychiatric disorders adverse experiences in placebo controlled studies by duration of treatment.

Adverse experience	cet up to 2 wks No. Pts (%)	cet 3-4 wks	cet 5-12 wks	placebo up to 2 wks	placebo 3-4 wks	placebo 5-12 wks
Total No. of Pts	2676	1835	957	1671	1147	586
N. of Pts with any Psychiatric Disorders	425 (15.9%)	160 (8.7%)	82 (8.6%)	133 (8.0%)	45 (3.9%)	22 (3.8%)
Somnolence	374 (14.0%)	135 (7.4%)	71 (7.4%)	96 (5.8%)	32 (2.8%)	17 (3.0%)
Concentration impaired	5 (0.2%)	0 (0%)	1 (0.1%)	1 (0.1%)	0 (0%)	0 (0%)
Emotional lability	3 (0.1%)	2 (0.1%)	3 (0.3%)	0 (0%)	0 (0%)	0 (0%)
Depression	4 (0.2%)	2 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.2%)
Thinking abnormal	4 (0.2%)	3 (0.2%)	2 (0.2%)	0 (0%)	0 (0%)	0 (0.0%)

* A patient can have an adverse experience reported for more than one interval of cetirizine therapy.

Agree with the sponsor's conclusion that somnolence accounts with the majority of the incidence of the reports in this category. The above series of tables also demonstrate that at doses of 5 and 10 mg it is approximately double the reported incidence in placebo treated patients (Table F8. B2-B3) and that this incidence persists at the different time intervals: up to 2 weeks, 3-4 weeks and 5-12 weeks of treatment (Table F8. B-4).

The reported incidence rates of other adverse events such as: concentration impaired, emotional lability and thinking abnormal are less than 1% but they are reported more frequently and for a longer duration than in placebo treated patients.

6. Please provide an integrated safety update. As discussed, the cutoff date of February 1994 can be used. Intercurrent illnesses must be included in the adverse event database for the new patients. Any reports of serious adverse reactions after February 1994 should also be submitted; please include manufacturer number of the reports.

The following issues should be addressed in the integrated safety update. If the new database is small and will not be integrated into your previous database, these issues should be addressed for the March 3, 1994 integrated safety update.

- a. Please analyze and submit duration of exposure by dose, gender and race.

Response: Section D.5.f.3. Tables F-16.A F16.N

Tables F16.A and C summarize the incidence of adverse experiences in patients treated with cetirizine maximum dose of 5 and 10 mg respectively by duration of treatment in the cumulative database. In these tables the total number of patients that discontinued due to adverse events was also included. Copy of these tables follow.

The percentage of patients reporting adverse events for the time periods selected are about the same for both doses, except for the 13 wk to 6 mo interval. Here the % of patients treated with the 5 mg dose reporting adverse events was greater, 11/34 (32.4%) than those on the 10 mg dose 13/69 (19.0%).

The majority of the patients treated with the 5 and 10 mg dose discontinued the study during the first two weeks of treatment. The percent of patients that discontinued due to adverse events for the two doses was about the same over the first four weeks of treatment. Five patients on the 10 mg dose discontinued the study during the 5-12 weeks of treatment whereas only 1 that was treated with the 5 mg did. The specific reasons for study discontinuations are not listed in these tables.

In **Tables F16.B and D** the detailed incidence of adverse events of patients (cumulative database) treated with cetirizine 5 and 10 mg respectively are shown. There are approximately 70 different adverse event terms reported for the 5 mg treated patients and 130 for the 10 mg treated patients in these tables.

Fatigue is reported at higher frequency in the 10 mg dose in the first 4 wks of treatment.

TABLE FIG.A: SUMMARIZED INCIDENCE OF ADVERSE EXPERIENCES IN PATIENTS TREATED WITH CETIRIZINE MAXIMUM DOSE 5 MG BY DURATION OF TREATMENT (CUMULATIVE DATABASE)* BY MAXIMUM DOSE

TREATMENT: CETIRIZINE MAXIMUM DOSE 5 MG

ADVERSE EXPERIENCES ¹	CETIRIZINE			
	UP TO 2 WKS NO. PTS. (%)	3-4 WKS NO. PTS. (%)	5-12 WKS NO. PTS. (%)	13 WKS-6 MOS. NO. PTS. (%)
TOTAL NO. OF PATIENTS ²	589	397	273	34
TOTAL NO. OF PTS. WITH ADVERSE EXPERIENCES	214 (36.33%)	98 (24.69%)	75 (27.47%)	11 (32.35%)
TOTAL NO. OF PATIENTS DISCONTINUED DUE TO ADVERSE EXPERIENCES	12 (2.04%)	3 (0.76%)	1 (0.37%)	0 (0.00%)
TOTAL NO. OF ADVERSE EXPERIENCES	332	141	106	14

*CUMULATIVE DATABASE INCLUDES NDA, UPDATE AND NEW STUDIES

¹A PATIENT CAN HAVE AN ADVERSE EXPERIENCE REPORTED FOR MORE THAN ONE INTERVAL OF CETIRIZINE THERAPY.

THEREFORE, THE PATIENT INCIDENCE IS NOT NECESSARILY EQUAL TO THE SUM OF ENTRIES FOR ALL TIME INTERVAL COLUMNS.

²FOR 84 PATIENTS (84N0055 PATIENT 71,85N0051 PATIENT 8 AND 86N0199, PATIENT 8, PROTOCOL C-89001: 78 PATIENTS AND PROTOCOL L-0103: 3 PATIENTS) THE START DATE OF MEDICATION COULD NOT BE DETERMINED. THESE PATIENTS ARE EXCLUDED FROM THIS TABLE.

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TABLE F16.C: SUMMARIZED INCIDENCE OF ADVERSE EXPERIENCES IN PATIENTS TREATED WITH CETIRIZINE MAXIMUM DOSE 10 MG BY DURATION OF TREATMENT (CUMULATIVE DATABASE)* BY MAXIMUM DOSE

TREATMENT: CETIRIZINE MAXIMUM DOSE 10 MG

ADVERSE EXPERIENCES ¹	CETIRIZINE			
	UP TO 2 WKS NO. PTS. (%)	3-4 WKS NO. PTS. (%)	5-12 WKS NO. PTS. (%)	13 WKS-6 MOS. NO. PTS. (%)
TOTAL NO. OF PATIENTS ²	1961	1223	529	69
TOTAL NO. OF PTS. WITH ADVERSE EXPERIENCES	750 (38.65%)	312 (25.47%)	139 (26.28%)	13 (18.84%)
TOTAL NO. OF PATIENTS DISCONTINUED DUE TO ADVERSE EXPERIENCES	40 (2.04%)	7 (0.57%)	4 (0.76%)	1 (1.45%)
TOTAL NO. OF ADVERSE EXPERIENCES	1236	439	185	18

*CUMULATIVE DATABASE INCLUDES NDA, UPDATE AND MFW STUDIES

¹A PATIENT CAN HAVE AN ADVERSE EXPERIENCE REPORTED FOR MORE THAN ONE INTERVAL OF CETIRIZINE THERAPY.

THEREFORE, THE PATIENT INCIDENCE IS NOT NECESSARILY EQUAL TO THE SUM OF ENTRIES FOR ALL TIME INTERVAL COLUMNS.

²FOR 84 PATIENTS (84N0055 PATIENT 71, 85N0051 PATIENT 8 AND 86N0199, PATIENT 8, PROTOCOL C-89001: 78 PATIENTS AND PROTOCOL L-0103: 3 PATIENTS) THE START DATE OF MEDICATION COULD NOT BE DETERMINED. THESE PATIENTS ARE EXCLUDED FROM THIS TABLE.

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Even though the % of patients reporting increase in appetite is greater for those treated with 5 mg, the % of patients reporting a weight increase is greater for those patients that had been treated with the 10 mg tablet.

Adverse experience	Cet 5 mg up to 2 wks	Cet 5 mg 3-4 wks	Cet 5 mg 5-12 wks	Cet 5 mg 15wks to 6 mo
Total No. of pts	589	397	273	34
Total No. of pts with adverse experiences	214 (36.3%)	98 (24.7%)	75 (27.5%)	11 (32.4%)
fatigue	18 (3.1%)	9 (2.3%)	8 (2.9%)	0 (0%)
weight increase	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)
Adverse experience	Cet 10 mg up to 2 wks	Cet 10 mg 3-4 wks	Cet 10 mg 5-12 wks	Cet 10 mg 15wks to 6 mo
Total No. pts.	1961	1225	529	69
Total No. of pts with adverse experiences	758 (38.7%)	312 (25.5%)	139 (26.3%)	13 (18.9%)
fatigue	102 (5.2%)	48 (3.9%)	14 (2.7%)	1 (1.5%)
weight increase	9 (0.5%)	11 (0.9%)	10 (1.9%)	3 (4.4%)

The reports of weight increase during longer duration of treatment are more apparent in the higher dose group.

In these listings, the following are noted, in parenthesis, duration of exposure:

Diabetes Mellitus: 5mg dose at the 5-12 week interval (1)
 Polyuria: 10 mg (up to 2 wks) (4), 3-4 wks) (1)
 Purpura: 5 mg dose at the 3-4 week interval (1) and 5-12 wk interval (1)
 Purpura: 10 mg (up to 2 weeks) (1)
 Hematuria: 10 mg (3-4 weeks) (1)
 Ocular hemorrhage: 10 mg (up to 2 weeks) (1)
 visual field defect: 10 mg (up to 2 weeks) (1)
 vision abnormal: 5 mg (up to 2 wks) (2), (3-4 weeks) (1)
 vision abnormal: 10 mg (up to 2 wks) (2), (3-4 weeks) (1)
 Ptosis: 10 mg (up to 2 weeks) (1) and (3-4 weeks) (1)
 Tinnitus: 5 mg (up to 2 weeks) (1)
 Tinnitus: 10 mg (up to 2 weeks) (1), (3-4 wk) (1), 5-12 wks) (1)

Deafness: 10 mg (up to 2 weeks) (1) and (3-4 weeks) (1)
 Ototoxicity: 10 mg (up to 2 weeks) (1)
 Ataxia: 10 mg, (up to 2 wks) (1), (3-4 wks) (1)
 Melena: 10 mg (up to 2 weeks) (1)
 Gastritis: 10 mg (up to 2 wks) (1), (3-4 weeks) (1)
 Cardiac failure: 10 mg (up to 2 weeks) (1)

Gender

Females. From Sponsor's Table F16.G

Adverse experience	cet up to 2 wks No. Pts (%)	cet 3-4 wks	cet 5-12 wks	cet 13 wks -6 mo
Total No. of Pts	2072	1211	640	139
N. of Pts with Adverse Experiences	873 (42.1%)	398 (32.9)	210 (32.8%)	59 (42.5%)
Pts. discontinued due to adverse experiences	54 (2.6%)	8(0.7%)	5 (0.8%)	2 (1.4%)
total number of adverse experiences	1427	569	309	81

Males. From Sponsor's Table F16.E

Adverse experience	cet up to 2 wks No. Pts (%)	cet 3-4 wks	cet 5-12 wks	cet 13 wks -6 mo
Total No. of Pts	1819	1147	577	98
N. of Pts with Adverse Experiences	629 (34.6%)	256 (22.3%)	130 (22.5%)	24 (24.5%)
Pts. discontinued due to adverse experiences	29 (1.6%)	6(0.5%)	1 (0.2%)	0 (0%)
total number of adverse experiences	965	359	170	34

"Table F13 summarizes the adverse experiences by race in placebo-controlled studies. The majority of the patients treated with cetirizine were white (88%-2358/2679), compared to 8% (223/2679) black patients, and 4% (98/2679) patients in the "other" category. The "other" group is composed of Hispanics and Oriental patients. Among the placebo group there were 86% (1440/1671) white patients, 9% (147/1671) black patients and 5% (84/1671) "other" patients.

The incidence of adverse experiences for white patients were: 44.4% cetirizine, 37.2% placebo; for black patients: 35.9% cetirizine, 32.7% placebo; for "other" patients 32.7% cetirizine and 32.1% placebo.

For the cetirizine treated patients, there were 2.9% discontinuations among white patients, 3.6% among black patients and 1% among "other" patients.

Regarding the most frequent adverse experiences reported by cetirizine treated patients, 9% of blacks reported headaches compared to 17.6% of whites and 17.3% of "other" patients. Somnolence was reported by 19.3% of black patients, 14.9% of white patients and 10.2% of "other" patients.

There were no statistically significant differences in relative incidence of discontinuation or incidence of overall adverse events. The relative incidence were also compared among races for the common adverse experiences of headache, somnolence, fatigue and dry mouth. Except for fatigue, race is not a significant factor in determining the risk of these events beyond the expected incidence in the general population. The observed incidence of fatigue is slightly higher for the "other" race category. However, in the absence of significant dependence on race on any other cetirizine-related adverse experience, this single finding is probably related to very low incidence in a small subgroup of patients, and therefore it is difficult to draw any meaningful conclusion."

- b. Please analyze and submit adverse event rates by use of oral contraceptives. U.S. and foreign studies should be analyzed separately.

Response: SU 4/25/95 vol. 2, D.5.b.1.c. and vol 3 Tables F8.E-F.

"A total of 185 cetirizine treated patients and 141 placebo treated patients received concomitant oral contraceptives. In comparison 1116 and 736 placebo treated patients did not receive concomitant oral contraceptives."

"There are no significant differences in the relative incidence of the most common adverse experiences, headaches, somnolence, fatigue and dry mouth in cetirizine patients treated concomitantly with oral contraceptives and cetirizine patients who did not receive concomitant oral contraceptives."

From Table F8.F, for patients on cetirizine that are not using oral contraceptives the reported incidence of

TABLE F8.E: SUMMARIZED INCIDENCE OF ADVERSE EXPERIENCES IN FEMALE PATIENTS TREATED WITH CETIRIZINE OR PLACEBO IN PLACEBO-CONTROLLED STUDIES

	INCIDENCE IN SAFETY EVALUABLE FEMALE PATIENTS			
	BIRTH CONTROL USER		NON-BIRTH CONTROL USER	
	CETIRIZINE NO. PTS. (%)	PLACEBO NO. PTS. (%)	CETIRIZINE NO. PTS. (%)	PLACEBO NO. PTS. (%)
TOTAL NO. OF PATIENTS	185	141	1116	736
TOTAL NO. OF PTS. WITH ADVERSE EXPERIENCES	84 (45.41%)	59 (41.84%)	526 (47.13%)	303 (41.17%)
TOTAL NO. OF PATIENTS DISCONTINUED DUE TO ADVERSE EXPERIENCES	5 (2.70%)	5 (3.55%)	41 (3.67%)	20 (2.72%)
TOTAL NO. OF ADVERSE EXPERIENCES	143	96	952	501

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TABLE 8.F: INCIDENCE OF ADVERSE EXPERIENCES IN FEMALE PATIENTS TREATED WITH CETIRIZINE OR PLACEBO IN PLACEBO-CONTROLLED STUDIES

ADVERSE EXPERIENCES	INCIDENCE IN SAFETY EVALUABLE FEMALE PATIENTS			
	BIRTH CONTROL USER		NON-BIRTH CONTROL USER	
	CETIRIZINE NO. PTS. (%)	PLACEBO NO. PTS. (%)	CETIRIZINE NO. PTS. (%)	PLACEBO NO. PTS. (%)
TOTAL NO. OF PATIENTS	185	141	1116	736
NO. OF PTS. WITH ADVERSE EXPERIENCES	84 (45.41%)	59 (41.84%)	526 (47.13%)	305 (41.17%)
HEADACHE	31 (16.76%)	36 (25.53%)	216 (19.35%)	153 (20.79%)
SOMNOLENCE	26 (14.05%)	11 (7.80%)	101 (16.22%)	40 (5.43%)
FATIGUE	11 (5.95%)	1 (0.71%)	70 (6.27%)	19 (2.58%)
MOUTH DRY	5 (2.70%)	5 (3.55%)	71 (6.36%)	23 (3.13%)
NAUSEA	7 (3.78%)	6 (4.26%)	40 (3.58%)	27 (3.67%)
DIZZINESS	4 (2.16%)	2 (1.42%)	25 (2.06%)	14 (1.90%)
PHARYNGITIS	7 (3.78%)	4 (2.84%)	20 (1.79%)	16 (2.17%)
COUGHING	2 (1.08%)	0 (0.00%)	16 (1.43%)	7 (0.95%)
NERVOUSNESS	2 (1.08%)	1 (0.71%)	14 (1.25%)	8 (1.09%)
RESPIRATORY DISORDER	1 (0.54%)	1 (0.71%)	15 (1.34%)	10 (1.36%)
INSOMNIA	2 (1.08%)	0 (0.00%)	13 (1.16%)	13 (1.77%)
RHINITIS	4 (2.16%)	2 (1.42%)	10 (0.90%)	3 (0.41%)
BACK PAIN	2 (1.08%)	0 (0.00%)	11 (0.99%)	7 (0.95%)
EPISTAXIS	2 (1.08%)	1 (0.71%)	11 (0.99%)	2 (0.27%)
EARACHE	0 (0.00%)	0 (0.00%)	12 (1.08%)	4 (0.54%)
ABDOMINAL PAIN	0 (0.00%)	2 (1.42%)	11 (0.99%)	6 (0.82%)
DYSPEPSIA	3 (1.62%)	0 (0.00%)	8 (0.72%)	14 (1.90%)
WEIGHT INCREASE	3 (1.62%)	1 (0.71%)	8 (0.72%)	3 (0.41%)
DYSMENORRHEA	2 (1.08%)	3 (2.13%)	8 (0.72%)	3 (0.41%)
PARESTHESIA	3 (1.62%)	0 (0.00%)	6 (0.54%)	2 (0.27%)
APPETITE INCREASED	2 (1.08%)	1 (0.71%)	6 (0.54%)	2 (0.27%)
DIARRHEA	1 (0.54%)	1 (0.71%)	7 (0.63%)	6 (0.82%)
MALAISE	1 (0.54%)	0 (0.00%)	7 (0.63%)	4 (0.54%)
PRURITUS	2 (1.08%)	3 (2.13%)	6 (0.54%)	13 (1.77%)
EYE ABNORMALITY	1 (0.54%)	1 (0.71%)	6 (0.54%)	1 (0.14%)
PALPITATION	1 (0.54%)	0 (0.00%)	6 (0.54%)	4 (0.54%)
VOMITING	1 (0.54%)	2 (1.42%)	6 (0.54%)	4 (0.54%)
CHEST PAIN	0 (0.00%)	0 (0.00%)	6 (0.54%)	3 (0.41%)

-- (CONTINUED) --

somnolence is 16.2% whereas in those that are is 14.1%. The incidence of patients reporting dry mouth not using oral contraceptives is 6.4% and for those that are not is 2.7%.

"There were no significant differences in discontinuation rates due to adverse experiences in cetirizine treated patients who were treated concomitantly with oral contraceptives and those who were not receiving oral contraceptives."

- c. Lab data (change from baseline, percent of subjects with abnormal labs), should be analyzed by treatment, dose, age, gender and race. Please submit the list of patients whose pre-treatment lab values were within normal limits and who had any of the following lab values post initiation of treatment with cetirizine: SGOT > 65 U/L, SGPT > 60 U/L, BUN > 25 mg/dl, or serum creatinine > 1.5mg/dl. Please provide a brief summary of the above outliers: age, gender, race, dose, duration of treatment prior to the event, concomitant medication used, reported adverse events and dates of reports.

Response: SU 4/25/95, vol.2:D.6.a., D.6.b. and D.6.c.; vol 3: Tables F21-F23F and F-Figures.

The incidence of abnormal hepatic transaminases in all cetirizine treated patients that were considered to be clinically significant and possibly related to study medication (Category 9), according to the sponsor was: SGOT (1%) 27/2979 and SGPT (2%) 52/2926 (SU 4/25/95, vol 35.2, page 9 58). For placebo treated patients these incidence were: SGOT (0%) 6/1525 and for SGPT (1%) 12/1480, (Table F 23.B in SU 4/25/95, vol 35.3, page 9 322).

The majority of the SGOT and SGPT abnormalities regardless of attributable causality were generally less than twice the upper limit of normal. For these, the incidence of abnormal SGOT of more than twice the upper limit of normal appears to be similar in cetirizine and placebo treated patients (0.4%), for SGPT the incidence is (0.3%) versus (0.1%)-SU 4/25/95, vol 35.2 page 9 60.

a. Scatter plots

Scatter plots of pre-therapy values versus end of therapy values were plotted for the hematology and serum chemistry tests. These included: Hct, Hgb, RBC, WBC, neutrophils, bands, lymphocytes, monocytes, basophils, eosinophils, platelets, BUN, creatinine, SGOT, SGPT, T. bilirubin, alkaline phosphatase, and LDH. There were no clear trends in the test results after treatment with cetirizine as compared to placebo.

Scatterplots of BUN, creatinine, SGOT and SGPT by age, gender, race and dose did not reveal a clear trend between cetirizine and placebo.

Further information was requested from the sponsor regarding specific outliers in these scatterplots. The sponsor's response dated August 11, 1995 was reviewed. A alternative explanation as to the possible cause of lab abnormality was not found after review of the CRF for the following patients. These patients were required to have a baseline value within the normal range and at least one abnormal value after the start of treatment:

N-0047 84N0060/49

54 y/o white, female patient in SAR study. In CFR no record of concomitant drugs or illness. Patient received 10 mg cetirizine treatment from 9/19/84 to 9/26/94. Patient completed the study.

Prior to treatment 9/18/84	SGOT=31
	SGPT=27
	LDH=246
	T. bili=0.2
End of treatment 9/26 '84	SGOT=80
	SGPT=108
	LDH=272
	T. bili=0.3
10/3/84	SGOT=40
	SGPT=89
	LDH=235
	T. bili=not available in CFR
10/9/84	SGOT=17
	SGPT=26
	LDH=not available in CFR
	T. bili=not available in CFR

N-0050 85N0044/5

35 y/o hispanic female patient in a 4 week chronic idiopathic urticaria study. In the CFR there is no record of concomitant drugs or illness. Patient received 10 mg cetirizine treatment from 9/19/84 to 9/26/94. Patient had received Benadryl for 9 mo. prior to study.

Prior to treatment 6/9/86	SGOT=23
	SGPT=24
	LDH=188
	T. bili=0.5
First Day of treatment 6/11/86	
End of week two 6/25/86	
	SGOT=82
	SGPT=70

LDH=235
T. bili=0.6

End of Week 4, end of therapy, 7/9/86

SGOT=68
SGPT=168
LDH=211

T. bili=0.7

7/14/86

SGOT=49
SGPT=61

LDH=not available in CFR
T. bili=not available in CFR

N-0356 88-N0053/48

26 y/o white, female patient in an 8 week SAR study. In the CFR there is no record of concomitant drugs or illness.

Patient received 5mg cetirizine treatment from 7/29/88 to 9/23/88 and completed the study.

Prior to treatment 7/29/88

SGOT=17
SGPT=13
LDH=not available in CFR

T. bili=0.8

End of treatment 9/26/88

SGOT=311
SGPT=92
LDH=not available in CFR

T. bili=not available in CFR

10/11/88

SGOT=17
SGPT=17
LDH=not available in CFR

T. bili=not available in CFR

L-230 92-S0013/100

23 y/o white, female patient in a 2 week SAR study. In the CFR there is a record of asthma as a concomitant illness and the use of Ventolin inhaler 2 puffs qd and of Ortho Novum qd. Patient received 10mg cetirizine treatment from 9/24/92 to 10/08/92 and completed the study.

Prior to treatment 9/10/92

SGOT=21
SGPT=17
LDH=not available in CFR

T. bili=0.4

End of treatment 9/26/88

SGOT=105
SGPT=170
LDH=not available in CFR

T. bili=0.3

10/12/92

SGOT=71
SGPT=129
LDH=not available in CFR

10/22/92 T. bili=not available in CFR
 SGOT=51
 SGPT=70
 LDH=not available in CFR
 T. bili=not available in CFR

b. Mean changes in laboratory results

"Mean changes in laboratory results for patients treated with cetirizine and placebo in placebo controlled studies were analyzed and are shown in **Table 22.A**. There were statistically significant differences between treatment groups for change from baseline in SGOT, SGPT, and creatinine. The mean change for SGOT was 0.84 U/L for the cetirizine group compared to -0.05 U/L for placebo ($p < 0.02$). The mean change for the SGPT from baseline for the cetirizine treatment group was 1.35 U/L compared to -0.19 U/L for placebo ($p < 0.001$). The creatinine mean change from baseline was 0 for creatinine treated patients and 0.13 mg/dl for placebo treated patients."

According to the sponsor's **Table 22.A** (cumulative database), these mean changes from baseline represent the following mean percent changes from baseline:

N	Cetirizine	N	Placebo
2488	SGOT=11.64%	1511	SGOT=5.96%
2421	SGPT=15.6%	1451	SGPT=6.85%
2500	T.bili=6.9%	1527	T.bili=6.8%
2497	creatinine=1.84%	1523	creatinine=2.85%
2423	BUN=3.80%	1448	BUN=4.53%

Table 22.B summarizes the changes in laboratory results by dose as found in the NDA versus the cumulative database. When the cumulative database is compared to the NDA database, in the cumulative database the mean percent changes from baseline decreased for SGOT and SGPT for the 5 and 10 mg dose but not for the 20 mg dose where the mean percent change from baseline increased or stayed the same.

For **SGPT**, not considering the 15 mg treated group (N=58), the following are the mean percent changes from baseline in the cumulative database for cetirizine treated patients:

Dose	N	Mean % change
5 mg	559	15.86%
10 mg	1560	12.69%
20 mg	671	19.04%

TABLE F22.A: ANALYSIS OF CHANGES IN LABORATORY RESULTS IN PLACEBO-CONTROLLED STUDIES (CUMULATIVE)

LABORATORY TEST	CETIRIZINE				PLACEBO				P-VALUE OF MEAN BASELINES	P-VALUE OF MEAN CHANGES
	MEAN N BASELINE	CHANGE FROM BASE MEAN	S.D.	MEAN % CHANGE	MEAN N BASELINE	CHANGE FROM BASE MEAN	S.D.	MEAN % CHANGE		
HEMATOLOGY										
HCT (HEMATOCRIT)	2487 42.71	-.322	2.295	-.585	1514 42.4	-.305	2.314	-.558	0.020	0.824
HGB (HEMOGLOBIN)	1692 14.54	-.164	.7967	.5332	1097 14.4	-.127	.7243	-.724	0.017	0.151
WBC (WHITE BLOOD COUNT)	1691 7.029	-.142	1.574	.4493	1096 6.929	-0.06	1.569	1.652	0.171	0.179
RBC (RED BLOOD CELLS)	1675 4.837	-0.06	.2988	-1.05	1078 4.776	-.042	0.282	-.697	0.001	0.119
NEUTROPHILS	1605 57.86	-.399	9.479	.8595	1011 57.76	-.114	9.56	1.437	0.808	0.456
LYMPHOCYTES	1599 31.93	0.369	8.402	5.891	1003 31.82	0.022	8.205	4.098	0.752	0.302
EOSINOPHILS	1591 3.516	0.145	2.555	27.88	1009 3.547	0.126	2.606	21.82	0.796	0.855
MONOCYTES	1582 5.281	-.187	2.689	18.74	1005 5.381	-.043	2.765	17.95	0.996	0.565
BASOPHILS	1567 .6932	0.038	.8041	12.94	989 .6613	0.025	.8364	18.43	0.245	0.707
PLATELETS	1600 273.9	-2.79	39.61	0.257	1048 273.7	-1.05	38.99	.7984	0.928	0.266
BANDS	886 1.114	0.003	2.788	11.06	592 1.252	-.124	2.887	1.427	0.288	0.409
SERUM CHEMISTRY										
SGOT UNITS	2408 22.24	0.84	11.64	9.939	1511 21.89	-.054	11.62	5.963	0.299	0.018
SGPT UNITS	2421 13.15	1.353	15.14	15.6	1451 22.5	-.189	11.41	6.849	0.240	0.001
ALK PHOSPHATASE	1450 84.19	-.636	14.12	.7219	865 85.2	-.663	16.37	.5505	0.657	0.966
BUN	2423 13.31	0.034	3.419	3.798	1448 13.95	-.144	3.914	4.525	0.824	0.138
T/BILIRUBIN	2588 0.549	-.007	.2145	6.924	1527 .5598	-.008	.2148	6.888	0.249	0.941
CREATININE	2497 .9981	0	.1526	1.84	1523 .9815	0.013	.1568	2.845	0.013	0.020
LDH	1338 167.3	1.607	37.56	3.76	772 168.8	0.696	36.74	2.493	0.552	0.589

CHANGE OF FINAL VISIT FROM BASELINE AND % CHANGE FROM BASELINE WERE CALCULATED FOR EACH PATIENT AND THE MEANS OF THESE CHANGES DETERMINED.

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TABLE F22.B: SUMMARY OF CHANGES IN LABORATORY RESULTS IN CETIRIZINE (NDA & CUMULATIVE) - BY DOSE AT FINAL DETERMINATION

LABORATORY TEST	CETIRIZINE-NDA				CETIRIZINE-CUMULATIVE			
	MEAN N BASELINE	CHANGE FROM BASE MEAN	S.D.	MEAN % CHANGE	MEAN N BASELINE	CHANGE FROM BASE MEAN	S.D.	MEAN % CHANGE
CETIRIZINE 5 MG								
SERUM CHEMISTRY								
SGOT UNITS	314 21.89	-.494	12.71	6.203	559 21.87	-.049	13.25	7.594
SGPT UNITS	314 23.74	-.100	21.05	10.81	559 23.10	0.19	21.11	15.86
BUN	310 13.7	0.195	3.31	4.975	555 13.7	-.055	4.786	3.774
CREATININE	313 1.024	0.014	.1696	3.271	558 1	0.012	.1497	2.69
CETIRIZINE 10 MG								
SERUM CHEMISTRY								
SGOT UNITS	704 21.74	0.588	9.219	11	1634 21.99	0.688	12.39	9.266
SGPT UNITS	690 23.43	0.95	14.79	14.34	1560 22.16	0.861	14.93	12.69
BUN	694 14.36	-.026	3.458	2.817	1563 13.93	0.071	3.453	3.892
CREATININE	701 1.023	0.002	.1574	2.765	1643 0.992	0.003	.1473	2.125
CETIRIZINE 15 MG								
SERUM CHEMISTRY								
SGOT UNITS	58 24.48	-.259	8.405	4.48	58 24.45	-.259	8.405	4.48
SGPT UNITS	58 25.1	3.034	11.21	25.61	58 25.1	3.034	11.21	25.61
BUN	58 14.64	-.724	3.797	.1482	58 14.64	-.724	3.797	.1482
CREATININE	57 1.023	-.020	.1424	-2.11	57 1.023	-.020	.1424	-2.11
CETIRIZINE 20 MG								
SERUM CHEMISTRY								
SGOT UNITS	410 23.21	0.239	12.37	8.981	672 23.23	0.94	11.46	10.58
SGPT UNITS	410 25.25	1.885	14.53	19.72	671 25.02	1.988	13.24	19.84
BUN	361 13.74	-.027	3.413	4.231	623 13.62	-.006	3.216	3.428
CREATININE	408 1.014	0.016	.1752	3.461	670 1.003	0.006	.1617	1.903

PATIENTS TO BE INCLUDED IN THIS TABLE REQUIRED A BASELINE AND AT LEAST ONE TREATMENT VALUE WITH A CORRESPONDING CET. DOSE CHANGE OF FINAL VISIT FROM BASELINE AND % CHANGE FROM BASELINE WERE CALCULATED FOR EACH PATIENT AND THE MEANS OF THESE CHANGES DETERMINED.

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For the NDA database the mean percent change in baseline for SGPT was:

Dose	N	Mean % change
5 mg	314	18.81%
10 mg	690	14.34%
20 mg	410	19.72%

For the cumulative database the mean percent change in SGOT from baseline, excluding the 15 mg dose data, was 7.59%, 9.27% and 10.58% for the 5, 10 and 20 mg dose respectively.

Table 22.C summarizes the changes in laboratory results by **gender** as found in the NDA versus the cumulative database; no apparent differences between genders were observed.

Table 22.D summarizes the changes in laboratory results by **age (<65 and >65)** as found in the NDA versus the cumulative database. The range of number of patients with lab results for the population >65 years of age is 119-120 patients for the NDA database and 141-144 patients for the cumulative database versus a range of 1307-1369 in the NDA database and 2686-2815 patients in the cumulative database for patients <65 years of age. When the results of the two age groups are compared, the patients >65 years of age have a lower mean percent change from baseline than those that are younger, including the serum creatinine.

Table 22.E summarizes the changes in laboratory results by **race** as found in the NDA versus the cumulative database. Although the numbers for non-white patients are small compared to the white patient population in the cumulative database, for SGPT, the mean percent change from baseline in the cumulative database is larger for blacks, 17% (N=228) and "others", 17.5% (N=109) versus 14.8% in the white population (N=2546). In addition, the mean percent change from baseline in SGPT in black patients increased from 12.7% to 17% from the NDA to the cumulative database, which was opposite to the decrease in the other two groups; twice the number of patients were studied in the cumulative database versus the NDA database.

C. Clinically significant and possibly drug related abnormalities.

Results falling outside the normal range were reviewed by the investigator for clinical significance and relationship to study drug. The abnormal results that were later computer categorized as Category 9 were those that were considered to be clinically significant and possibly related to study medication. These in turn were blindly reviewed by a Pfizer physician and were either left as Category 9 or

TABLE F22.C: SUMMARY OF CHANGES IN LABORATORY RESULTS IN CETIRIZINE (NDA & CUMULATIVE) - BY GENDER

LABORATORY TEST	CETIRIZINE-NDA				CETIRIZINE-CUMULATIVE			
	MEAN N BASELINE	CHANGE FROM BASE MEAN	S.D.	MEAN % CHANGE	MEAN N BASELINE	CHANGE FROM BASE MEAN	S.D.	MEAN % CHANGE
MALE								
SERUM CHEMISTRY								
SGOT UNITS	839 23.67	0.142	10.89	7.923	1480 24.38	0.609	14	9.541
SGPT UNITS	832 26.41	1.622	13.8	16.34	1441 26.62	1.724	14.95	15.12
BUN	811 14.76	0.083	3.462	3.492	1419 14.94	0.056	3.547	3.282
CREATININE	835 1.114	0.002	.1651	2.461	1481 1.1	0.003	.1537	1.953
FEMALE								
SERUM CHEMISTRY								
SGOT UNITS	650 20.47	0.338	10.95	10.75	1474 20.21	0.461	10.3	8.702
SGPT UNITS	643 21.03	0.337	10.72	10.29	1437 19.52	0.369	16.84	14.97
BUN	615 13.10	-.137	3.387	3.507	1411 12.71	-.051	3.86	4.114
CREATININE	647 0.9	0.013	.1645	3.499	1478 0.895	0.006	.1478	2.241

CHANGE OF FINAL VISIT FROM BASELINE AND % CHANGE FROM BASELINE WERE CALCULATED FOR EACH PATIENT AND THE MEANS OF THESE CHANGES DETERMINED.

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TABLE F22.D: SUMMARY OF CHANGES IN LABORATORY RESULTS IN CETIRIZINE (NDA & CUMULATIVE) - BY AGE

LABORATORY TEST	CETIRIZINE-NDA				CETIRIZINE-CUMULATIVE					
	N	MEAN BASELINE	MEAN CHANGE FROM BASE MEAN	S.D. S.D.	MEAN % CHANGE	N	MEAN BASELINE	MEAN CHANGE FROM BASE MEAN	S.D. S.D.	MEAN % CHANGE
< 65 YRS										
SERUM CHEMISTRY										
SGOT UNITS	1369	22.38	0.205	11.21	9.361	2809	22.34	0.544	12.52	9.288
SGPT UNITS	1358	24.35	1.23	16.47	18.11	2737	23.18	1.138	16.12	15.44
BUN	1307	13.76	0.019	3.37	3.684	2686	13.63	0.03	3.688	3.821
CREATININE	1365	1.015	0.009	.1655	3.165	2815	0.993	0.005	.1584	2.159
>= 65 YRS										
SERUM CHEMISTRY										
SGOT UNITS	128	21.08	0.483	6.675	6.832	145	21.53	0.379	6.441	5.921
SGPT UNITS	117	20.78	-.892	11.48	6.582	141	21.12	-.699	11.61	7.317
BUN	119	17.6	-.349	4.041	1.461	144	17.6	-.316	4.034	1.384
CREATININE	119	1.085	-.011	.1572	.0374	144	1.073	-.004	0.158	.8846

CHANGE OF FINAL VISIT FROM BASELINE AND % CHANGE FROM BASELINE WERE CALCULATED FOR EACH PATIENT AND THE MEANS OF THESE CHANGES DETERMINED.

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TABLE F22.E: SUMMARY OF CHANGES IN LABORATORY RESULTS IN CETIRIZINE (NDA & CUMULATIVE) - BY RACE

LABORATORY TEST	CETIRIZINE-NDA				CETIRIZINE-CUMULATIVE					
	N	MEAN BASELINE	CHANGE FROM BASE MEAN	S.D. S.D.	MEAN % CHANGE	N	MEAN BASELINE	CHANGE FROM BASE MEAN	S.D. S.D.	MEAN % CHANGE
WHITE										
SERUM CHEMISTRY										
SGOT UNITS	1353	22.25	0.295	10.43	0.936	2613	22.32	0.556	12.28	9.07
SGPT UNITS	1348	24.17	1.116	16.41	17.36	2546	23.35	1.07	16.48	14.77
BUN	1297	14.16	0.02	3.412	3.739	2502	13.96	0.01	3.769	3.609
CREATININE	1347	1.019	0.006	.1629	2.794	2619	0.994	0.005	.1503	2.119
BLACK										
SERUM CHEMISTRY										
SGOT UNITS	110	22.42	-.773	16.12	10.51	232	22.15	0.418	14.44	10.86
SGPT UNITS	109	22.94	0.312	13.40	12.73	220	20.66	0.405	11.59	17
BUN	103	12.73	-.156	3.396	2.467	225	12.10	-.039	3.119	3.123
CREATININE	109	1.043	0.025	.1011	4.953	231	1.039	-.003	.1599	1.305
OTHER										
SERUM CHEMISTRY										
SGOT UNITS	26	22.54	0.923	7.975	14.99	109	22.14	0.303	6.15	6.668
SGPT UNITS	26	23.42	1.305	12.34	27.00	104	21.72	1.731	9.017	17.49
BUN	26	15.30	-1.04	4.377	-4.42	103	14.23	0.2	3.351	5.127
CREATININE	26	1.015	-.015	.1933	0.573	109	0.982	0.016	.1433	3.239

CHANGE OF FINAL VISIT FROM BASELINE AND % CHANGE FROM BASELINE WERE CALCULATED FOR EACH PATIENT AND THE MEANS OF THESE CHANGES DETERMINED.

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recategorized to one of the following: 5=documented lab error, 6=likely due to concurrent illness, 7=likely due to concomitant medication.

"Among the patients treated with maximum doses of 5, 10, 15 and 20 mg of cetirizine, there were no significant differences between placebo, 5 mg and 10 mg treated patients for SGOT and SGPT, but there were significantly more abnormalities in patients treated with doses higher than 10 mg." (SU 4/25/95, vol.35.2 9 58)

"For serum creatinine, the relative incidence of abnormalities was significantly more in elderly patients than in patients less than 65 years ($p < 0.033$). " (SU 4/25/95, vol.35.2 9 58)

"There is no apparent change from baseline in mean creatinine levels for either the elderly or the younger group of cetirizine treated patients. Therefore, the clinical significance of the different incidence of abnormal serum creatinine is questionable" (SU 4/25/95, vol.35.2 9 59)

Table 23.A In this table the number of patients and percent of total number of patients with abnormal laboratories are reported from the cumulative database, not limited to placebo controlled studies. Only the number of patients with category 9=may be related to drug, will be highlighted.

Cetirizine treated patients:

For SGPT: 52 out of 2932 (2%)
For SGOT: 27 out of 2926 (1%)

Table 23.B. The number of patients and percent of total number of patients with abnormal laboratories are reported from the cumulative database by **maximum dose** in placebo controlled studies. From these, only the number of patients with category 9=may be related to drug, will be highlighted:

SGOT	N	Cetirizine 5 mg	N	Placebo
	453	0 (0%)	1525	6 (0%)
		Cetirizine 10 mg		
	1445	13 (1%)		
		Cetirizine 20 mg		
	553	8 (1%)		
SGPT	N	Cetirizine 5 mg	N	Placebo
	453	6 (1%)	1480	12 (1%)
		Cetirizine 10 mg		

TABLE F23.B: SUMMARY OF LABORATORY TEST ABNORMALITIES BY CATEGORY FOR PBO-CONTROLLED STUDIES - BY MAXIMUM DOSE

LAB TEST	TOTAL NUMBER PATIENTS	NORMAL RESULTS (Z#)	NUMBER OF PATIENTS BY ABNORMAL CATEGORY									TOTAL
			1	2	3	4	5	6	7	8	9(Z##)	
CETIRIZINE												
CETIRIZINE MAXIMUM DOSE: 5 MG												
SERUM CHEMISTRY												
SGOT UNITS	453	436(96)	4	6				1	1	5		17
SGPT UNITS	453	411(91)	13	10				3	1	9	6(1)	42
BUN	453	427(94)	10	14						2		26
CREATININE	453	430(97)	5	9							1(0)	15
TOTAL			32	39				4	2	16	7	100
CETIRIZINE MAXIMUM DOSE: 10 MG												
SERUM CHEMISTRY												
SGOT UNITS	1445	1306(96)	15	15	1			2		13	13(1)	59
SGPT UNITS	1392	1260(91)	55	23	5			2	1	23	23(2)	132
BUN	1300	1290(94)	23	46	2			1	1	9		82
CREATININE	1459	1300(95)	30	37					1	3		79
TOTAL			131	121	8			5	3	48	36	352
CETIRIZINE MAXIMUM DOSE: 15 MG												
SERUM CHEMISTRY												
SGOT UNITS	50	52(98)	4	1						1		6
SGPT UNITS	50	39(67)	5	6				1		6	1(2)	19
BUN	50	54(93)	1	2						1		4
CREATININE	50	55(95)	1	2								3
TOTAL			11	11				1		8	1	32
CETIRIZINE MAXIMUM DOSE: 20 MG												
SERUM CHEMISTRY												
SGOT UNITS	553	514(95)	8	12	2		1		1	7	2(1)	39
SGPT UNITS	554	480(87)	27	16	4		1		1	16	9(2)	74
BUN	553	525(95)	12	13				1		2		28
CREATININE	553	526(95)	5	10				1		3		27
TOTAL			52	59	6		2	2	2	28	17	168
PLACEDO												
SERUM CHEMISTRY												
SGOT UNITS	1525	1470(96)	21	14	5			1	1	7	6(0)	55
SGPT UNITS	1480	1346(91)	61	20	4			2	1	34	12(1)	134
BUN	1463	1374(94)	33	43	2					11		89
CREATININE	1539	1451(94)	27	49				1		11		88
TOTAL			142	126	11			4	2	63	18	366
LABORATORY TEST CATEGORIES ARE -												
1:BASELINE VALUE ABNORMAL			4:NORMAL WITH CONT. THERAPY			7:MAY BE DUE TO CONC. DRUGS						
2:DEVIATION INSIGNIFICANT			5:DOCUMENTED LAB ERROR			8:INSIG, NOT DUE TO RX, BY PHYSICIAN						
3:SINGLE ABNORMAL VALUE			6:EVIDENCE OF CONC. ILLNESS			9:MAY BE RELATED TO DRUG						

* PERCENTAGE OF TOTAL PATIENTS WITH NORMAL TEST RESULTS
 ## PERCENTAGE OF TOTAL PATIENTS WITH CATEGORY 9 ABNORMALITY
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9
332

1392 23 (2%)
 Cetirizine 20 mg
 554 9 (2%)

D. Liver Function Tests Results

"Evaluation of the incidence of abnormal liver function tests in patients with normal baseline tests in placebo-controlled studies show that cetirizine is associated with elevations in SGOT and SGPT but not total bilirubin or alkaline phosphatase. Abnormalities are generally less than twice the upper limit of normal. The incidence of abnormal SGOT and SGPT more than twice the upper limit of normal appear to be similar in cetirizine and placebo-treated patients." (SU 4/25/95, vol 32, 9 60).

The sponsor's statement needs to be taken in the context of the mean duration of exposure (30.1 days-cumulative database) for these populations.

- d. The integrated safety summary should also address weight gain, by duration of treatment, age and gender. Submit a scatter plot of the pre- versus post-study weight of subjects enrolled in clinical trials. The scatter plot should be based on the trials for which mean weight data are reported in the updated integrated safety summary.

Response: SU 4/25/95, vol 2: D.7.b., vol 3 Tables F25.A-F25.B and F-Figures.

"It should be noted that no placebo controlled studies were of greater than 8 weeks duration."

"Based on the mean weight changes in the placebo controlled studies, cetirizine treatment up to eight weeks is associated with a statistically significant weight increase of 1.1 +/- 4.5 lbs. There are no statistically significant differences between age subgroups, between the sexes, or among races with respect to the amount of weight increase, indicating that these are not determining factors of risk for this effect. However, there is a significant relation of weight gain to duration of treatment, with mean weight changes indicating increased weight gain with longer duration of treatment."

- e. Please submit any available clinical data regarding the enantiomers of cetirizine.

Response: SU 4/25/95, vol 2: D.9.c vol 17 and 18: K.2.a.

The response regarding non-clinical data was reviewed by Pharmacology. The PK of study UCB-101 was reviewed by Biopharm. The following comments pertain only to clinical

findings.

"UCB 101: Double blind crossover comparison at random between cetirizine (5 mg, single oral intake), ucb 28556 (2.5 mg, single oral intake), and ucb 28557 (2.5 mg, single oral intake) on the histamine induced wheal and flare skin reaction in normal healthy volunteers." "wash-out period 7 days between doses"

"A total of 19 healthy male volunteers entered this study. Histamine-induced wheal and flare were induced by the prick test using a high concentration of histamine (100 mg/ml). Responses were recorded pre-dose and at 4 and 8 hours after dosing. Eighteen subjects completed the study; one subject discontinued for personal reasons. Results show that cetirizine and ucb 28556 produced comparable effects on inhibition of both the wheal and flare reaction induced by histamine, including onset of activity and extent of maximal inhibition with the exception of the 0-32 hour AUC for inhibition of the wheal reaction, where cetirizine was less active than ucb 28556. There was no significant effect of ucb 28557 on either the wheal or flare reaction."

"No serious adverse reaction and no withdrawals due to adverse experiences occurred in the study. Of the 19 volunteers that received cetirizine, 4 volunteers reported the following mild adverse experiences: blocked sinuses and dry cough, headache, blocked nose, and raised rash over the lower back."

"Of the 18 volunteers who received ucb 28556, only one volunteer reported one adverse experience: headache; assessed as mild."

"Of the 18 volunteers who received ucb 28557, 2 volunteers reported a total of 3 adverse experiences: red, raised itchy, spot above the buttocks (mild), urticarial patches (moderate severity) and headache (mild)."

"In conclusion, cetirizine and ucb 28556 were active in blocking histamine induced wheal and flare but ucb 28557 had no significant activity."

"UCB-102: Double blind cross-over comparison at random between cetirizine (10 mg, single oral intake), ucb 28556 (5 mg, single oral intake) ucb 28557 (5mg, single oral intake) and placebo in a nasal provocation test with histamine in adult healthy volunteers." (wash-out period 7-14 days)

"A total of 28 healthy adult volunteers entered this study. A histamine nasal provocation test was performed 4 hours after treatment. A total of 24 volunteers completed the

study per the protocol."

"The results of this study show that ucb 28556 and cetirizine significantly increased the median histamine nasal threshold concentration and this result was significantly different from ucb 28557 and placebo. Nasal pressure was also significantly reduced by ucb 28556 and cetirizine as compared with ucb 28557 and placebo. Both ucb 28556 and cetirizine reduced the number of histamine-induced sneezes compared with placebo and ucb 28557."

"One adverse experience was observed. One volunteer experience bronchitis which started 8 days after treatment with ucb 28556. This event was assessed as severe and the relationship to study drug was considered as unlikely."

- f. As discussed at the meeting of December 21, 1994, please submit a listing of intercurrent illnesses by treatment reported by patients in your trials. Also please note which illnesses resulted in premature withdrawal from the study.

Response: In 4/25/95 SU, vol 2. Sections D.5.a.2., D.5.b.1.b., D.5.h. In vol 3, F7A-B, F8.C-D and F 19.A.

"Intercurrent illnesses, defined as those which first appeared at the start of therapy, were recorded for all patients and are presented separately from the adverse event database. Illnesses which began prior to treatment were not included."

NDA versus cumulative database. " In general, the incidence of intercurrent illnesses for cetirizine treated patients was similar between the NDA and cumulative databases....In the cumulative database, respiratory illnesses were the most common illnesses reported (11.6%) followed by neurological (3.2%) and gastrointestinal (2.2%) which were similar to the NDA database (except neurological, which includes headache, was somewhat higher in cumulative vs NDA database."

From review of Table F7.B, the term headache is reported by 10/1568 (0.6%) for the NDA database and by 114/3982 (2.9%) for the cumulative database. In the same table headache (sinus) is reported by 1/1568 (0.1%) and in the cumulative database by 29/3982 (0.7%); sinus infection is (0.1%) for the NDA database and (0.7%) in the cumulative database.

In Table F8.D, the individual incidence listing, although the term chronic sinus infection is similar for placebo and cetirizine treated

patients in both the NDA and cumulative database, the incidence for the term sinus infection are different:

For NDA database: cetirizine 1 (0.1%) placebo 0 (0.0%)

For Cumulative database: cetirizine 11 (0.4%) placebo 0 (0%)

The incidence of menstrual cramps also increased 0-0.7% from the NDA to the cumulative database presumably due to the increased number of women enrolled in the cumulative database.

The CRF and additional information was requested from the sponsor regarding three patients listed as having intercurrent illnesses. The reported events for these patients were: abnormal EKG, premature cardiac beats, and syncopal episode. The sponsor response (BM-7/17/95) was reviewed.

Patient 87-N-0017/36: 44 y/o asian male, in seasonal asthma study, symptomatic premature beats. These decreased after rinsing mouth after using a beta agonist inhaler. ECG reported normal by investigator.

Patient 91-S-0033/304: 18 y/o hispanic female in SAR and asthma study; syncopal episode 4 days post treatment initiation, patient continued treatment; no recurrent events reported by the investigator.

Patient 89-N-0103/74: 51y/o caucasian female in PAR study, according to patient's primary physician, this patient had prior history of heart palpitations and shortness of breath not related to exercise, with 80% PFTs and was referred to the study investigator for asthma evaluation. The study investigator did not record any CV signs or symptoms in the initial screening hx and physical exam. During the course of treatment a routine ECG was done prior to a bunion operation which was abnormal: with T wave inversions and multiple PVCs. Echo revealed mitral prolapse and regurgitation as well as tricuspid regurgitation. The patient discontinued the study early.

Placebo controlled studies. "The overall incidence of intercurrent illnesses in the cumulative database in cetirizine treated patients (16.5%) and placebo treated patients (19.2%) were similar."

From **Table F8.C**, the number of patients with intercurrent

STUDY : COMBINED CETIRIZINE PROTOCOLS.

TABLE 80C : INCIDENCE OF ILLNESS CATEGORIES EMERGENT DURING PLACEBO-CONTROLLED STUDIES.

ILLNESS CATEGORIES	MDA		CUMULATIVE	
	CETIRIZINE (N=1369)	PLACEBO (N=821)	CETIRIZINE (N=2679)	PLACEBO (N=1671)
NO. OF PTS WITH CONCURRENT ILLNESSES *	160 (11.7%)	142 (17.3%)	441 (16.5%)	320 (19.2%)
RESPIRATORY	95 (6.9%)	75 (9.1%)	236 (8.8%)	162 (9.7%)
NEUROLOGICAL	8 (0.6%)	18 (2.2%)	55 (2.1%)	50 (3.0%)
GASTROINTESTINAL	16 (1.2%)	16 (1.9%)	52 (1.9%)	36 (2.2%)
IMMUNOLOGICAL	11 (0.8%)	10 (1.2%)	41 (1.5%)	34 (2.0%)
MISCELLANEOUS	18 (1.3%)	14 (1.7%)	48 (1.5%)	29 (1.7%)
MUSCULO-SKELETAL	9 (0.7%)	15 (1.8%)	35 (1.3%)	34 (2.0%)
GENITO-URINARY	8 (0.6%)	10 (1.2%)	33 (1.2%)	28 (1.7%)
DERMATOLOGICAL	11 (0.8%)	8 (1.0%)	26 (1.0%)	21 (1.3%)
ODONTOLOGICAL	7 (0.5%)	5 (0.6%)	14 (0.5%)	12 (0.7%)
OTOLOGICAL	3 (0.2%)	2 (0.2%)	12 (0.4%)	8 (0.5%)
PROCEDURES	3 (0.2%)	2 (0.2%)	11 (0.4%)	5 (0.3%)
OPHTHALMOLOGICAL	5 (0.4%)	2 (0.2%)	11 (0.4%)	4 (0.2%)
CARDIOVASCULAR	3 (0.2%)	3 (0.4%)	8 (0.3%)	4 (0.2%)
ENDOCRINOLOGICAL	2 (0.1%)	0 (0.0%)	4 (0.1%)	1 (0.1%)
HEMATOLOGICAL	0 (0.0%)	2 (0.2%)	2 (0.1%)	4 (0.2%)

PATIENTS MAY BE INCLUDED IN MORE THAN ONE CATEGORY.

* EACH PATIENT IS COUNTED ONLY ONCE ON THIS LINE.

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STUDY : COMBINED CETIRIZINE PROTOCOLS.
 TABLE F8D : INCIDENCE OF ILLNESSES EMERGENT DURING PLACEBO-CONTROLLED STUDIES.

ILLNESSES	NDA		CUMULATIVE	
	CETIRIZINE (N=1369)	PLACEBO (N=821)	CETIRIZINE (N=2679)	PLACEBO (N=1671)
NO. OF PTS WITH CONCURRENT ILLNESSES *	169 (11.7%)	142 (17.3%)	441 (16.5%)	320 (19.2%)
"COLD" WITH NASAL AND SINUS CONGESTION	59 (4.3%)	41 (5.0%)	133 (5.0%)	77 (4.6%)
SORE THROAT	21 (1.5%)	10 (2.2%)	49 (1.8%)	30 (1.8%)
HEADACHE	7 (0.5%)	13 (1.6%)	46 (1.7%)	40 (2.4%)
DIARRHEA(FLU)	9 (0.7%)	5 (0.6%)	23 (0.9%)	11 (0.7%)
ASTHMA	7 (0.5%)	4 (0.5%)	22 (0.8%)	17 (1.0%)
CHRONIC SINUSITIS	9 (0.7%)	6 (0.7%)	21 (0.8%)	13 (0.8%)
FLU SYMPTOMS	9 (0.7%)	6 (0.7%)	20 (0.7%)	20 (1.2%)
ELEVATED TEMPERATURE	7 (0.5%)	8 (1.0%)	17 (0.6%)	12 (0.7%)
VIRAL SYNDROME	1 (0.1%)	2 (0.2%)	17 (0.6%)	9 (0.5%)
COUGHING	7 (0.5%)	9 (1.1%)	16 (0.6%)	13 (0.8%)
CRAMPS(MENSTRUAL)	0 (0.0%)	1 (0.1%)	14 (0.5%)	10 (0.6%)
BRONCHITIS	8 (0.6%)	7 (0.9%)	12 (0.4%)	12 (0.7%)
NAUSEA	5 (0.4%)	9 (1.1%)	12 (0.4%)	12 (0.7%)
PROCEDURES (POOLED)	3 (0.2%)	2 (0.2%)	11 (0.4%)	5 (0.3%)
SINUS INFECTION	1 (0.1%)	0 (0.0%)	11 (0.4%)	0 (0.0%)
CRAMPS, ABDOMINAL	3 (0.2%)	0 (0.0%)	10 (0.4%)	3 (0.2%)
ACHES AND PAINS	4 (0.3%)	2 (0.2%)	9 (0.3%)	4 (0.2%)
BACK PAIN	2 (0.1%)	5 (0.6%)	8 (0.3%)	13 (0.8%)
HEADACHE (SINUS)	1 (0.1%)	0 (0.0%)	8 (0.3%)	11 (0.7%)
GI VIRUS	1 (0.1%)	1 (0.1%)	8 (0.3%)	7 (0.4%)
DENTAL PROBLEMS	3 (0.2%)	1 (0.1%)	8 (0.3%)	6 (0.4%)
UTI	5 (0.4%)	3 (0.4%)	7 (0.3%)	7 (0.4%)
GASTRITIS	1 (0.1%)	1 (0.1%)	7 (0.3%)	3 (0.2%)
JOINT PAIN	0 (0.0%)	0 (0.0%)	7 (0.3%)	2 (0.1%)
OTITIS MEDIA	1 (0.1%)	0 (0.0%)	7 (0.3%)	2 (0.1%)
MUSCLE SORENESS	3 (0.2%)	1 (0.1%)	6 (0.2%)	3 (0.2%)
CONJUNCTIVITIS	3 (0.2%)	1 (0.1%)	6 (0.2%)	2 (0.1%)
RESPIRATORY DISTRESS	2 (0.1%)	1 (0.1%)	5 (0.2%)	5 (0.3%)
STRESS	0 (0.0%)	1 (0.1%)	5 (0.2%)	3 (0.2%)
FATIGUE	2 (0.1%)	0 (0.0%)	5 (0.2%)	2 (0.1%)
MIGRAINE	1 (0.1%)	1 (0.1%)	5 (0.2%)	1 (0.1%)
PRURITUS AND REDNESS OF SKIN	3 (0.2%)	0 (0.0%)	5 (0.2%)	0 (0.0%)
HIVES	1 (0.1%)	2 (0.2%)	4 (0.1%)	6 (0.4%)
CONGESTION IN EAR	2 (0.1%)	2 (0.2%)	4 (0.1%)	5 (0.3%)

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STUDY : COMBINED CETIRIZINE PROTOCOLS.
 TABLE F0D : INCIDENCE OF ILLNESSES EMERGENT DURING PLACEBO-CONTROLLED STUDIES.

ILLNESSES	NDA		CUMULATIVE	
	CETIRIZINE (N=1369)	PLACEBO (N=821)	CETIRIZINE (N=2679)	PLACEBO (N=1671)
UPPER RESPIRATORY VIRUS	0 (0.0%)	0 (0.0%)	4 (0.1%)	3 (0.2%)
ALLERGIC RHINITIS	0 (0.0%)	0 (0.0%)	4 (0.1%)	2 (0.1%)
CHEST PAIN	3 (0.2%)	1 (0.1%)	4 (0.1%)	1 (0.1%)
DERMATITIS,CONTACT (POISON IVY)	1 (0.1%)	3 (0.4%)	3 (0.1%)	3 (0.2%)
BLOODSHOT EYES	2 (0.1%)	1 (0.1%)	3 (0.1%)	2 (0.1%)
LARYNGITIS	1 (0.1%)	1 (0.1%)	3 (0.1%)	2 (0.1%)
HEARTBURN	0 (0.0%)	1 (0.1%)	3 (0.1%)	1 (0.1%)
CANDIDIASIS	1 (0.1%)	0 (0.0%)	3 (0.1%)	0 (0.0%)
STIFF NECK	0 (0.0%)	0 (0.0%)	3 (0.1%)	0 (0.0%)
ARTHRITIS	0 (0.0%)	1 (0.1%)	2 (0.1%)	3 (0.2%)
COLD SORES	2 (0.1%)	0 (0.0%)	2 (0.1%)	3 (0.2%)
DERMATITIS	0 (0.0%)	1 (0.1%)	2 (0.1%)	3 (0.2%)
HERPES SIMPLEX	1 (0.1%)	2 (0.2%)	2 (0.1%)	2 (0.2%)
LEG ACHE	0 (0.0%)	0 (0.0%)	2 (0.1%)	3 (0.2%)
FLU	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)
TENDONITIS	1 (0.1%)	2 (0.2%)	2 (0.1%)	2 (0.1%)
BRONCHITIS,ACUTE	1 (0.1%)	0 (0.0%)	2 (0.1%)	1 (0.1%)
BURSITIS	2 (0.1%)	1 (0.1%)	2 (0.1%)	1 (0.1%)
DRUG REACTION	1 (0.1%)	1 (0.1%)	2 (0.1%)	1 (0.1%)
NOSE BLEED	1 (0.1%)	0 (0.0%)	2 (0.1%)	1 (0.1%)
PAIN,SWELLING MOUTH	2 (0.1%)	0 (0.0%)	2 (0.1%)	1 (0.1%)
RASH-CONTACT DERMATITIS	2 (0.1%)	1 (0.1%)	2 (0.1%)	1 (0.1%)
ABDOMINAL PAIN	1 (0.1%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
ACNE CYST	0 (0.0%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
ALLERGIES	0 (0.0%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
FURUNCULOSIS	1 (0.1%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
INGROWN TOENAIL	0 (0.0%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
MENSTRUAL ABNORMALITY	0 (0.0%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
NECK MUSCLE SPASM	1 (0.1%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
OTITIS EXTERNA	0 (0.0%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
STREP THROAT	0 (0.0%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
SWOLLEN GLANDS	1 (0.1%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
VAGINAL YEAST INFECTION	0 (0.0%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
DIZZINESS	0 (0.0%)	2 (0.2%)	1 (0.0%)	5 (0.3%)
ANEMIA	0 (0.0%)	1 (0.1%)	1 (0.0%)	3 (0.2%)
SNEEZING	0 (0.0%)	2 (0.2%)	1 (0.0%)	3 (0.2%)

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STUDY : COMBINED CETIRIZINE PROTOCOLS.
 TABLE F8D : INCIDENCE OF ILLNESSES EMERGENT DURING PLACEBO-CONTROLLED STUDIES.

ILLNESSES	NDA		CUMULATIVE	
	CETIRIZINE (N=1569)	PLACEBO (N=821)	CETIRIZINE (N=2679)	PLACEBO (N=1671)
BLADDER INFECTION	0 (0.0%)	0 (0.0%)	1 (0.0%)	2 (0.1%)
MOOD-CHANGES	0 (0.0%)	1 (0.1%)	1 (0.0%)	2 (0.1%)
VAGINITIS	1 (0.1%)	2 (0.2%)	1 (0.0%)	2 (0.1%)
BEE STING	1 (0.1%)	0 (0.0%)	1 (0.0%)	1 (0.1%)
CANKER SORES IN MOUTH	0 (0.0%)	0 (0.0%)	1 (0.0%)	1 (0.1%)
DIAPHORESIS	0 (0.0%)	0 (0.0%)	1 (0.0%)	1 (0.1%)
DYSURIA	1 (0.1%)	0 (0.0%)	1 (0.0%)	1 (0.1%)
FINGER INFECTION	0 (0.0%)	1 (0.1%)	1 (0.0%)	1 (0.1%)
FOOT, INJURY	1 (0.1%)	0 (0.0%)	1 (0.0%)	1 (0.1%)
GINGIVITIS	0 (0.0%)	1 (0.1%)	1 (0.0%)	1 (0.1%)
IRRITABLE BOWEL	0 (0.0%)	0 (0.0%)	1 (0.0%)	1 (0.1%)
TMJ(TEMPOROMANDIBULAR JOINT DISEASE)	0 (0.0%)	0 (0.0%)	1 (0.0%)	1 (0.1%)
TOOTH INFECTION	1 (0.1%)	1 (0.1%)	1 (0.0%)	0 (0.0%)
ABNORMAL EKG	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
ANGINA	1 (0.1%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
ANOREXIA(NERVOSA)	1 (0.1%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
ARTHRITIS, KNEE	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
BONE SPUR	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
CHIPPED TOOTH	1 (0.1%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
CRAMPS, UNSPECIFIED	1 (0.1%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
DEPRESSION	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
DIABETES MELLITUS	1 (0.1%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
DRY THROAT	1 (0.1%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
EPIDIDIMITIS	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
ESOPHAGEAL REFLUX	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
EYE INFECTION	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
FLUSHING	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
GALLSTONES	1 (0.1%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
HERNIA, AXIAL	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
HERPES ZOSTER	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
HYPEREXTENSIVE JOINT	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
HYPOTHYROIDISM	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
IMPACTED WISDOM TEETH	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
INFLAMATION, KNEE	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
KIDNEY STONES	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
MONONUCLEOSIS	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)

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STUDY : COMBINED CETIRIZINE PROTOCOLS.
 TABLE F0D : INCIDENCE OF ILLNESSES EMERGENT DURING PLACEBO-CONTROLLED STUDIES.

ILLNESSES	NDA		CUMULATIVE	
	CETIRIZINE (N=1569)	PLACEBO (N=821)	CETIRIZINE (N=2679)	PLACEBO (N=1671)
NASAL CONTUSION	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
NEURO-DERMATITIS	1 (0.1%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
PAIN, FACIAL	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
PHLEBITIS, SUPERFICIAL	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
PINCHED NERVE	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
PITYRIASIS ROSEA	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
PNEUMONIA	1 (0.1%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
PREMATURE CARDIAC BEATS	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
PREMENSTRUAL SYNDROME	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
PRESSURE TO MAXILLARY	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
RECTAL BLEEDING	1 (0.1%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
SALIVARY GLAND INFECTION	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
SCRATCH ON EYE	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
SPUTUM YELLOW	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
SUNBURN	1 (0.1%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
SWOLLEN BREASTS	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
SYNCOPE EPISODE(S)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
TORN MENISCUS	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
URINARY FREQUENCY	1 (0.1%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
VAGINAL MONILIA	1 (0.1%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
SPRAINS & STRAINS	0 (0.0%)	1 (0.1%)	0 (0.0%)	3 (0.2%)
CONSTIPATION	0 (0.0%)	1 (0.1%)	0 (0.0%)	2 (0.1%)
ENLARGED LYMPH NODE	0 (0.0%)	1 (0.1%)	0 (0.0%)	2 (0.1%)
JAW PAIN	0 (0.0%)	1 (0.1%)	0 (0.0%)	2 (0.1%)
KNEE INJURY	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)
LOW BACK SPASH	0 (0.0%)	2 (0.2%)	0 (0.0%)	2 (0.1%)
NERVOUSNESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)
PAIN, ABSCESS TOOTH	0 (0.0%)	1 (0.1%)	0 (0.0%)	2 (0.1%)
PALPITATIONS	0 (0.0%)	2 (0.2%)	0 (0.0%)	2 (0.1%)
ABSCESS, TOE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
ATAXIA	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
BACTERIAL INFECTION	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
BLOATED FEELING	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
BRONCHOSPASH	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
BRUISING	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
BURNS, ARM	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)

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STUDY : COMBINED CETIRIZINE PROTOCOLS.
 TABLE F08 : INCIDENCE OF ILLNESSES EMERGENT DURING PLACEBO-CONTROLLED STUDIES.

ILLNESSES	NDA		CUMULATIVE	
	CETIRIZINE (N=1369)	PLACEBO (N=821)	CETIRIZINE (N=2679)	PLACEBO (N=1671)
COXSACKIE VIRUS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
CYST ON WRIST	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
CYST, OVARIAN	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
DENTAL CARIES	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
DERMATITIS, ATOPIC	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
DRY SKIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
FALLOPIAN TUBE INFECTION	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
FINGER, INJURY	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
FOOT PAIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
FRACTURE, CLAVICLE	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
HAIRY CELL LEUKEMIA	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
HERNIA, INGUINAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
HYPOGLYCEMIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
INCONTINENCE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
INCREASED HEART RATE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
INNER EAR PROBLEMS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
ITCHY EUSTACHIAN TUBES	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
KIDNEY INFECTION	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
KNEE (PAIN & SWELLING)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
KNEES LOCKING	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
LEG CRAMPS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
NEURALGIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
PAIN/STIFFNESS IN NECK	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
PAIN, RIB	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
RUBELLA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
TONGUE SWELLING	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
TRAUMA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
TROUBLE SLEEPING	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
URINARY HESITANCY	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)

PATIENTS MAY BE INCLUDED IN MORE THAN ONE ILLNESS.

* EACH PATIENT IS COUNTED ONLY ONCE ON THIS LINE.

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TABLE 3.1: MATCHING ADVERSE EXPERIENCE AND INTERCURRENT ILLNESS¹ EVENT TERMS: CETIRIZINE TREATED ADULT PATIENTS

Number of safety evaluable patients	3982		
Number of patients with adverse experiences (AE)	1743	(1743/3982)	43.8%
Number of patients with intercurrent illnesses	826	(826/3982)	20.7%
Number of patients with matching AE and intercurrent illness terms	71	(71/1743)	4.1%
Number of patients with matching terms who discontinued due to AE	2		
Number of patients with matching terms who discontinued due to intercurrent illness	2		

<u>Event Terms*</u>	<u>Number of Patients</u>
Headache	24
Pharyngitis/sore throat	10
Respiratory disorder/upper respiratory virus/cold/upper respiratory infection/bronchitis	7
Diarrhea	6
Fever/elevated temperature	6
Nausea	4
Earache/otitis media/ear congestion	4
Bronchospasm/respiratory distress/asthma	3
Coughing	2
Rash/contact dermatitis-rash	2
Eye Abnormality/conjunctivitis	1
Eczema/dermatitis	1
Infection fungal/vaginal yeast infection	1
Chronic sinusitis/sinusitis	1
Palpitations/premature cardiac beats	1
Conjunctivitis/blood shot eyes	1
Epistaxis/nose bleed	1
Herpes simplex/cold sores	1
Back pain	1
Hemorrhage rectum/rectal bleeding	1
Furunculosis	1
Migraine	1
Polyuria/urinary frequency	1
Chest pain	1
Anorexia	1
Myalgia/muscle soreness	1

¹ Intercurrent illness includes all illnesses which emerged after the onset of treatment with study drug
*Event terms separated by a slash (/) were considered similar terms by a Pfizer physician

TABLE 3.2: MATCHING ADVERSE EXPERIENCE AND INTERCURRENT ILLNESS¹ EVENT TERMS: PLACEBO TREATED ADULT PATIENTS

Number of safety evaluable patients	1671		
Number of patients with adverse experiences (AE)	610	(610/1671)	36.5%
Number of patients with intercurrent illnesses	320	(320/1671)	19.1%
Number of patients with matching AE and intercurrent illnesses terms	32	(32/610)	5.2%
Number of patients with matching terms who discontinued due to AE	4		
Number of patients with matching terms who discontinued due to intercurrent illnesses	1		

<u>Event Terms*</u>	<u>Number of Patients</u>
Headache	13
Nausea	1
Pharyngitis/sore throat	5
Respiratory disorder/cold	4
Urinary incontinence/incontinence	1
Urinary retention/urinary hesitancy	1
Bronchospasm/asthma	1
Back pain/low back spasm	1
Heartburn/dyspepsia	1
Fever/elevated temperature	1
Rash/contact dermatitis	1
Coughing	1
Myalgia/muscle soreness	1
Conjunctivitis	1
Infection/finger infection	1
Palpitations	1
Diarrhea	1
Chest pain	1
Urticaria/hives	1

¹ Intercurrent illness includes all illnesses which emerged after the onset of treatment with study drug
*Event terms separated by a slash (/) were considered similar terms by a Pfizer physician

illnesses:

For NDA database: cetirizine 11.7%, placebo 17.3%

For Cumulative database: cetirizine 16.5%, placebo 19.2%

There is a greater increase in the incidence patients reporting intercurrent illnesses during treatment with cetirizine than during placebo treatment when the cumulative database is compared to the NDA database.

The incidence of patients that discontinued the study due to intercurrent illnesses in placebo controlled studies (cumulative database) was 1.6% in cetirizine treated patients and 2.3% in placebo treated patients.

In response dated 5/25/95, the sponsor clarifies the following: "Of the 1743 cetirizine treated patients who reported one or more adverse experiences, 71 (4.1%) reported one or more intercurrent illnesses using the same or similar event terms. Of the 610 placebo treated patients who reported one or more adverse experiences, 32 (5.2%) reported one or more intercurrent illnesses using the same or similar event terms. Table 3.1, 3.2 (C-5/25/95)

7. Please submit the complete medical records for the adverse event report with Mnf. number 9300233.

Response: After numerous attempts the physician refuses to give further information on this case to the sponsor. The hand written copy of the physician report and the statement to the sponsor " I have no further information, I have already given info to FDA "is included. This information had been faxed to Dr. Ravitz, Division of Epidemiology, on February 16, 1994.

Reviewer's comments: The hand-written copy of the report follows. The physician report, as this reviewer reads it, states that:

78 y/o female with long history of HTN, DM, atrial fibrillation. She was started on Vistaril 10 hs for the last 2-3 days -stopped it then when restarted had multiple syncopal episodes with rib fractures. Documented torsades de pointes at hospital.

The recorded concomitant medication included the following medications for years:

Lanoxin po, Procainamide, Coumadin,
Hydrochlorothiazide, Potassium chloride, Bumex, and
Zantac.

The report notes that the patient required inpatient hospitalization. Relevant test: QT prolongation on EKG to

52 msec?. The patient took the vistaril for inability to sleep. The dose: 1 capsule po q hs. The therapy dates: 12/25. Therapy duration 12/31. Event onset:12/31/92. Event duration: 1 day. Did event abate after stopping drug?: Yes. Did event reappear after reintroduction?:N/A. Date of report: 2/7/93. Physician: Dr. Keneth Ellenbogen, Medical College of Virginia, Box 53 Richmond Va, 23298, 804-786-7565. Stamped: Received on 93 Feb 16.

The patient had tolerated the concomitant medication regimen which included procainamide, lanoxin, diuretics and potassium supplements without a history of adverse events. We do not know the status of the patient's electrolytes at the time of torsades. In view that no additional information will be available in this case, it cannot be ruled out that hydroxyzine at normal doses did not contribute to the QT prolongation and torsades in this patient.

8. Please address the increased frequency of Category 9 adverse events (liver enzymes) in the erythromycin-cetirizine study for 4 out of 16 patients receiving the combination.

"Results falling outside the normal range were reviewed by the investigator for clinical significance and relationship to study drug. The abnormal results were later computer categorized as Category 9 were those that were considered to be clinically significant and possibly related to study medication. These in turn were blindly reviewed by a Pfizer physician and were either left as Category 9 or recategorized to one of the following: 5=documented lab. error, 6=likely due to concurrent illness, 7=likely due to concomitant medication."

See attached photocopy. (SU 4/25/95, vol 35.2, p9 61)

SGPT (U/L) Values

Pt.	Base line	Cet Day 5	Comb Day 6	Comb Day 8	Comb Day 10	Wash Day 2	Wash Day 4	Wash Day 7	Wash Day 19	Eryth Day 5	Comb Day 6	Wash Day 7	Wash Day 7
6	32	41	119	222	178	131	94	34	34	48	82	59	---
16	27	43	170	286	226	167	116	100	DC'd	DC'd	DC'd	DC'd	DC'd
102	10	45	92	79	67	57	---	---	22	71	115	91	48

Pt.	Base line	Ery Day 5	Comb Day 6	Comb Day 8	Comb Day 10	Wash Day 2	Wash Day 4	Wash Day 7	Wash Day 19	Cet Day 5	Comb Day 6	Wash Day 2
1	21	21	81	88	87	67	---	---	24	20	40	51

One of the subjects demonstrated a maximal elevation of SGPT < 2x the upper limit of normal, another subject showed a maximal SGPT elevation between 2 and 4 times the upper limit of normal, and the other two subjects had maximum elevations >4X the upper limit of normal. All subjects were asymptomatic, and no subject discontinued for abnormal liver function tests. Two subjects (nos. 6 and 102) experienced elevations of SGPT on the combination of drugs following single administration of both cetirizine and erythromycin; subject 102 experienced an elevated SGPT on erythromycin alone as well. One patient (no. 16) experienced an abnormal SGPT on the combination following cetirizine, but he discontinued from the study prior to the second regimen for personal reasons. Subject 1 had an abnormal SGPT on combination treatment following initial treatment with erythromycin, but not on cetirizine alone or on the combination following initial treatment with cetirizine. In general, the SGPT returned to normal when the combined drugs were stopped during the three week washout phase.

Both cetirizine and erythromycin are known to be associated with abnormal transaminases in a small percent of patients. It is difficult to attribute the abnormalities observed in the small number of volunteers in this study to either the combination, cetirizine alone or erythromycin alone because of the sequential nature of the design and lack of concurrent placebo, erythromycin, and cetirizine controls. In addition, the abnormalities resolved during the washout period when both drugs were withdrawn. Therefore, we cannot attribute these abnormalities to concomitant administration of cetirizine and erythromycin. //

- As previously advised, your proposed name "Reactine" connotes usefulness in acute situations and implies lack of drowsiness. Your alternate proposed names "Ultreon" implies maximum strength or effectiveness as compared to related products and "Alacrin" appears to be derived from "alacrity" which denotes quickness and alertness. These three tradenames are not acceptable. Your alternate proposed name, "Zyrtec", is acceptable.

The sponsor accepted the trade name Zyrtec. Refer to proposed package insert.

- Your proposed annotated package insert has been revised. Please refer to the attachment and note that our recommended additions to the labeling are underlined and in bold typeface and our comments are in brackets, caps, and bold typeface.

The proposed package insert was included in this submission. Specific comments regarding the proposed labeling are included in Section 2 of this review.

In addition, we have the following comments and requests for information.

15. Please provide a summary of the population variability of cetirizine kinetics. This should include presentations of histograms by dose of cetirizine, C_{max} and AUC after single and multiple (steady-state) dosing.

The response to this question was included in the correspondence dated 5/12/95-BZ. Biopharm was consulted for the review of this section.

16. Which enantiomer form of cetirizine is formed when hydroxyzine is given to humans?

Response: BZ-5/12/95. "UCB Pharma has indicated that no chiral analysis has been performed to determine which enantiomer of cetirizine is formed in either blood or urine samples obtained from humans who have received single or multiple doses of hydroxyzine."

17. Does each one of the cetirizine enantiomers bind to the same plasma protein?

Response: BZ-5/12/95. "Plasma protein binding studies have not been conducted with individual enantiomers of cetirizine, according to UCB Pharma."

18. What is known about the pharmacokinetics of the enantiomers in humans? Does interconversion occur?

Response: BZ-5/12/95. "Pharmacokinetic monitoring of the cetirizine enantiomers (UCB 28556 and UCB 28557) was conducted in humans after a single oral dose of 2.5 mg of UCB 28556 or UCB 28557 or a single oral dose of 5 mg of cetirizine (NDA-Report UCB101; filed 4/25/95, vol 17 pages 11 1314-11 1736). ... The mean plasma concentration of cetirizine was similar to the summed concentration of the two enantiomers when the enantiomers were given alone, indicating that there was no apparent interaction between the two isomers. ... The cumulative urinary excretion of each of the individual enantiomers following the administration of cetirizine was approximately equal to the cumulative urinary excretion of each of the respective enantiomers when they were administered alone... In urine samples, there was no evidence of interconversion of the enantiomers of cetirizine."

19. Has cetirizine binding to H_1 receptors ever been tested? If so, what are the results?

Response: BZ-5/12/95. "Draft data from UCB exists. An audited result is not available. The affinity of cetirizine and hydroxyzine was tested for H3 receptors in the guinea pig cerebral cortex. In this study, [3H]-N-alpha-methylhistamine was used as the radioligand and thioperamide was the positive control. Neither cetirizine nor hydroxyzine (both tested at 10 microM) inhibited significantly (<20%) the radioligand specific binding, whereas thioperamide (a selective H3 histamine antagonist) displayed an affinity of 15 nanoM, according to UCB Pharma."

20. What is the CNS and cardiac activity of cetirizine's metabolite? We note that in mice, the metabolite influences its general behavior at 2-4 times lower doses than cetirizine.

Response: BZ-5/12/95.

The results from two non-clinical pharmacology studies as well as the pharmacokinetics of the metabolite UCB P026 are discussed in the sponsor's response to this question. Appropriate comments as to the adequacy of this response pertains to the pharmacology and biopharm reviewers.

As the medical reviewer understands this response, it appears that the UCB P026 metabolite is twice as potent for the same route (i.p. or i.v.) as cetirizine, in terms of CNS effects in mice and at least four times as potent in terms of cardiac effects (bradycardia and decrease in blood pressure) in the rat. However, according to expected plasma concentrations of UCB P026 in normal human volunteers (PK study -UCB P026 mean plasma peak concentration is approximately 18% of the cetirizine peak concentration), after multiple oral dosing at recommended doses, the cardiac and CNS effects from UCB P026, would be negligible.

21. For future adverse events where the etiologic factor could be attributed to an immunologic or to an allergic reaction to cetirizine, please document the presence or absence of a positive history of an allergic or immunologic reaction to other piperazine related structures in these patients.

Response: BZ-5/12/95. "Where possible as part of the post marketing surveillance, Pfizer plans to review the data of the immunologic or allergic reactions to cetirizine which are spontaneously reported to Pfizer for a positive medical history of allergic or immunologic reactions to other particular piperazine-related products, specifically those compounds listed in Attachment D. This post-marketing surveillance information will be reported to the FDA."

In Attachment D, the following compounds are listed:

"Buclizine, Chlorcyclizine, Cyclizine, Fluphenazine, Hydroxyzine, Meclizine, Perphenazine, Prochlorperazine, Thiethylperazine, and Trifluoroperazine"

22. Because of the high degree of protein binding of cetirizine, please indicate and submit any in vivo or in vitro data that were generated by examining the displacement by highly bound drugs such as phenytoin, carbamazepin, or warfarin of cetirizine.

Response: BZ-5/12/95. "According to UCB Pharma, no definite audited reports are available describing in vivo or in vitro binding data generated to determine the displacement of cetirizine by phenytoin, carbamazepine, or warfarin."

The sponsor reports an un-audited European in vitro study that was published in the form of an abstract, that reports that cetirizine binding was studied using equilibrium dialysis and radiolabelled cetirizine. The authors report that cetirizine is 88-90% bound mainly to human serum albumin. Inhibition studies indicate that cetirizine could bind to two main binding sites of albumin, to the diazepam site with highest affinity and to the warfarin site with the lowest affinity.

II. Relevant Additional Safety Update Information

- A. The case report forms of all patients discontinued for adverse events (vol 7, 8, 9, and 10), and intercurrent illnesses (vol 11 and 12) as well as the case report of a patient with a serious adverse events (vol 12) were reviewed, no new safety concerns were raised by the review of these case report forms.
- B. In the course of providing us with additional safety information regarding the UCB foreign studies, UCB Pharma identified two additional deaths.

The study UCB 119 was conducted in 1985 to study senile pruritus. Of 9 elderly patients that participated in this study, 2 patients died within 4 days of a clinic visit. All the available information that was provided to us by the sponsor on these two deaths was reviewed [N(BM) 6/14/95 and N(BM) 6/29/95].

The sponsor was then asked: when they had become aware of this trial, why it had not been submitted earlier and what were the standard operating procedures for monitoring reports from UCB studies. Since blood pressure fluctuations had been noted in a group of elderly patients that had also been studied for senile pruritus from which 17 deaths had been previously reported, and there were also blood pressure fluctuations in the two recently reported deaths, the sponsor was asked to provide us with a further analysis of the NDA cumulative data, since this safety update and previous ones did not include information on vital signs. In this analysis we asked the sponsor to provide us with an integrated summary of vital sign data (BP and pulse) for cetirizine versus placebo for placebo controlled US studies of one week duration or longer and to show the data by dose, age (<65 years and 65 years and older), gender and race. The sponsor response to this request was dated 9/12/95.

In summary the 9/12/95 response states that: "UCB was solely responsible for the monitoring, review of source documents, data analysis and preparation of study reports for these studies. In a meeting with the Agency on October 26, 1987, it was agreed that the Pfizer sponsored clinical trials would constitute the pivotal safety and efficacy trial to support the approval of the NDA. The UCB study reports received by Pfizer would be considered "Other Trials" and submitted as individual study reports in order to provide full disclosure. UCB clinical trial are processed in a manner similar to that of literature reports."

In the analysis, "the mean changes and mean percent changes

found in the cetirizine group are small and similar to the placebo group. The mean changes by dose do not suggest a relationship between cetirizine dose and change in vital sign parameter." **Appendix 1**

- B. Hydroxyzine/Meclizine and cardiovascular events (update) in Appendix F volume 35.4 -January 1, 1994 to April 19, 1995. The review identified 14 new hydroxyzine cases, one updated hydroxyzine case, and two new meclizine cases. Of these 16 were spontaneously reported and one was a literature report.

"The updated review of the new cases supports the previous conclusion that there is no indication that serious arrhythmias occur in association with hydroxyzine or meclizine when used in normal therapeutic doses in patients who are otherwise healthy." **Appendix 2.**

- C. Response to a consult request to the Division of Epidemiology and Surveillance, HFD-730 on Ketoconazole and Hydroxyzine drug interaction dated June 23, 1995.

Line-listing corresponding to the Spontaneous Reporting System reports where ketoconazole and Hydroxyzine are listed as concomitant drugs. Between 1982 and the present there have been 20 such reports in the SRS.

Demographics:

Outcome: 2 deaths; 5 hospitalizations; 1 disability

Origin: 18 domestic; 2 foreign

Sex: 6 female; 14 male

Age: range 6-90

Most often reported COSTART terms (2 or more cases each):

Liver function abnorm	5
Bilirubinemim	3
Phosphatase alk inc	3
Pruritus	3
Intracran hyperten	2
Jaundice cholestat	2
Rash	2
Rash mac pap	2

The ketoconazole labeling addresses hepatic adverse events. An interaction with hydroxyzine is not mentioned. In reviewing the report its important to remember the limitations associated with data derived from the Spontaneous Reporting System. **Appendix 3.**

- D. Update on cetirizine literature review in Appendix E, vol 4, SU 4/25/95 with copy of article in correspondence dated 8/8/95.

The photocopy of a case report suggestive of drug induced hepatitis is enclosed in **Appendix 4**.

Appendices

Appendix 1

TABLE 1: SUMMARY OF CHANGES IN VITAL SIGN RESULTS IN PLACEBO-CONTROLLED ADULT STUDIES

		CETIRIZINE					PLACEBO				
		N	MEAN BASELINE	---CHANGE FROM BASELINE ¹ ---			N	MEAN BASELINE	---CHANGE FROM BASELINE ¹ ---		
				MEAN	S.D.	% CHANGE			MEAN	S.D.	% CHANGE
AGE:											
< 65 YRS	SYSTOLIC BP	2100	117.59	-0.552	11.30	0.017	1335	117.43	-0.621	11.11	-0.004
	DIASTOLIC BP	2107	75.23	-0.583	9.35	0.498	1334	75.06	-0.457	9.99	0.222
	HEART RATE	2100	74.34	0.770	10.01	2.051	1330	73.77	0.555	9.90	2.050
≥ 65 YRS	SYSTOLIC BP	132	137.65	-0.174	16.33	0.547	96	139.80	-3.760	15.73	-2.020
	DIASTOLIC BP	132	80.11	0.023	13.29	0.906	96	80.78	-3.083	8.72	-3.190
	HEART RATE	133	74.92	-0.368	7.99	0.206	96	74.47	0.958	8.87	1.910
GENDER:											
MALE	SYSTOLIC BP	1115	120.42	-0.212	12.14	0.303	671	121.64	-1.064	11.51	-0.475
	DIASTOLIC BP	1114	76.30	-0.359	9.34	1.213	670	76.70	-0.558	9.50	-0.133
	HEART RATE	1114	73.31	0.797	10.12	2.151	669	72.04	0.414	10.43	2.421
FEMALE	SYSTOLIC BP	1125	117.13	-0.045	11.15	-0.204	760	116.55	-0.626	11.49	0.016
	DIASTOLIC BP	1125	74.66	-0.733	9.90	-0.162	760	74.33	-0.700	10.30	0.105
	HEART RATE	1127	75.43	0.623	9.70	1.707	757	74.60	0.731	9.27	1.719
RACE:											
WHITE	SYSTOLIC BP	1990	110.01	-0.725	11.77	-0.094	1240	110.95	-0.969	11.52	-0.326
	DIASTOLIC BP	1909	75.50	-0.647	9.79	0.440	1240	75.27	-0.656	10.20	0.002
	HEART RATE	1909	74.14	0.683	9.90	1.924	1236	73.67	0.679	9.87	2.248
BLACK	SYSTOLIC BP	160	121.22	1.331	10.06	1.414	119	120.27	1.412	12.65	1.002
	DIASTOLIC BP	160	77.41	0.131	7.93	0.613	118	77.19	0.153	8.50	0.986
	HEART RATE	162	76.10	1.991	9.45	3.246	118	75.62	0.127	10.06	1.229
OTHER	SYSTOLIC BP	90	113.54	0.478	10.16	0.757	72	116.56	-2.167	8.31	-1.621
	DIASTOLIC BP	90	72.47	0.889	8.57	2.170	72	75.50	-1.542	6.69	-1.774
	HEART RATE	90	76.54	-0.056	8.04	-0.372	72	73.33	-0.333	8.87	-0.029
TOTAL:	SYSTOLIC BP	2240	110.77	-0.530	11.65	0.048	1431	110.94	-0.832	11.49	-0.214
	DIASTOLIC BP	2239	75.51	-0.547	9.63	0.522	1430	75.44	-0.634	9.93	-0.007
	HEART RATE	2241	74.30	0.710	9.90	1.928	1426	73.81	0.582	9.83	2.048

¹ PATIENTS TO BE INCLUDED IN THIS TABLE REQUIRED TO HAVE BASELINE AND ON TREATMENT VITAL SIGN CHANGE OF FINAL VISIT FROM BASELINE AND % CHANGE FROM BASELINE ARE CALCULATED FOR EACH PATIENT AND THEN MEANS OF THESE CHANGES DETERMINED

TABLE 2: SUMMARY OF CHANGES IN VITAL SIGN RESULTS IN PLACEBO-CONTROLLED ADULT STUDIES - BY DOSE AT FINAL DETERMINATION

	N	MEAN BASELINE	---CHANGE FROM BASELINE ¹ ---		
			MEAN	S.D.	% CHANGE
CETIRIZINE 5 MG:					
SYSTOLIC BP	360	116.61	-1.203	12.50	-0.430
DIASTOLIC BP	359	74.23	-0.585	9.89	2.690
HEART RATE	359	74.04	0.994	10.14	2.314
CETIRIZINE 10 MG:					
SYSTOLIC BP	1362	118.90	-0.515	11.28	0.035
DIASTOLIC BP	1362	75.74	-0.659	9.71	-0.071
HEART RATE	1364	74.31	0.490	10.08	1.743
CETIRIZINE 15 MG:					
SYSTOLIC BP	55	120.85	1.309	12.90	1.090
DIASTOLIC BP	55	77.85	0.509	11.92	1.725
HEART RATE	55	76.15	-1.236	8.73	-0.966
CETIRIZINE 20 MG:					
SYSTOLIC BP	463	119.83	-0.268	11.04	0.264
DIASTOLIC BP	463	75.56	-0.313	8.99	0.436
HEART RATE	463	74.65	1.367	9.28	2.515
PLACEBO:					
SYSTOLIC BP	1431	118.94	-0.832	11.49	-0.214
DIASTOLIC BP	1430	75.44	-0.654	9.93	-0.007
HEART RATE	1426	73.81	0.582	9.83	2.040

¹ PATIENTS TO BE INCLUDED IN THIS TABLE REQUIRED TO HAVE A BASELINE AND AT LEAST ONE TREATMENT VALUE WITH A CORRESPONDING CET. DOSE CHANGE OF FINAL VISIT FROM BASELINE AND % CHANGE FROM BASELINE ARE CALCULATED FOR EACH PATIENT AND THEN MEANS OF THESE CHANGES DETERMINED

FILE: CSFXBPB
DATE: 09/06/95 16:14:23

Appendix 2

APPENDIX F

Hydroxyzine/Meclizine and Cardiovascular Events (Update)

4/21/95
Cetir./ Rpt./95Safety.Rpt/

HYDROXYZINE / MECLIZINE AND CARDIOVASCULAR EVENTS: AN UPDATE

Pfizer Inc
Safety Evaluation and Epidemiology
New York, New York
April 21, 1995

Contents:

A Review of Cases

Appendix - Hydroxyzine/Meclizine and Cardiovascular Events. January 14, 1994

A Review of Cases

HYDROXYZINE / MECLIZINE AND CARDIOVASCULAR EVENTS: AN UPDATE

A previous review¹ of Pfizer's early alert safety database for cardiovascular adverse events reported for hydroxyzine and meclizine concluded that heart rate/rhythm events have occurred in association with overdoses of these two compounds, that such events may rarely occur in patients treated with hydroxyzine who appear predisposed to arrhythmias, and that there was no indication that these compounds were associated with serious arrhythmias when used at therapeutic doses in otherwise healthy patients. This review of new hydroxyzine and meclizine cases was conducted to determine if there was any recent evidence to the contrary; none was discovered.

The Pfizer early alert safety database is comprised of cases of adverse events spontaneously reported to Pfizer, cases reported from adverse event registries, reports of adverse events published in the medical literature, and cases of serious adverse events reported from clinical studies regardless of causality. The previous review covered hydroxyzine and meclizine cases entered into the database through December 31, 1993. For this current report the database was reviewed for new hydroxyzine and meclizine cases involving cardiovascular adverse events entered into the database from January 1, 1994 through April 19, 1995, and for any cases entered into the database prior to January 1, 1994 that had been updated based on receipt of new information to include cardiovascular adverse events. This review identified 14 new hydroxyzine cases, one updated hydroxyzine case, and two new meclizine cases. Of these, 16 cases were spontaneously reported and one was a literature case. All are summarized below.

HYDROXYZINE

Of the 15 hydroxyzine patients, six were female, four were males, and gender was unknown in five. Eight patients were adults aged 23 to 84 years (mean $\pm$ SD = 43.25 $\pm$ 21.42 years), one was approximately four years of age, one was approximately one year of age, and for five (one of whom was a nursing home patient) the age was unknown. The route of administration was reported to be orally in seven patients, intramuscularly in four patients, intravenously in three patients, and was unknown in one patient.

The updated case originally entered prior to January 1, 1994 (case # 8900941, originally reported as case # R3P290) involved a 61-year-old female with a history of epilepsy, Alzheimer's disease, and sub-arachnoid hemorrhage receiving therapy with warfarin, phenytoin, lorazepam, and clorazepate. She developed an otitis media, which was treated with erythromycin 500 mg twice daily, and after about ten days of therapy developed urticaria. The erythromycin was discontinued, and hydroxyzine 150 mg/day intramuscularly was started. On the third day of hydroxyzine therapy, she became semi-comatose with right facial paresia, flaccid limbs, hyper-reflexia, absence of the pupilla light reflex, hypotension (supine blood pressure = 90/70 mmHg), and "a decreased heart rate". Hydroxyzine was discontinued, and she recovered within two days.

The treating physician thought that the events were due to the combined effects of hydroxyzine, lorazepam, and clorazepate.

In one case, the events were associated with an intentional hydroxyzine overdose. The patient (case # 9501282) was a 25-year-old male who ingested fifty hydroxyzine 25 mg tablets (1,250 mg). He was hospitalized eight hours later for gastric lavage, at which time physical and laboratory examinations were described as "unremarkable" (blood pressure was 130/80 mmHg and chest x-ray was normal). He was transferred to the intensive care unit because of concern over potential seizures, and a few hours later suffered a cardiac arrest with asystole. Resuscitation for several minutes led to a return of a regular sinus rhythm. The patient was given an external pacemaker set at 50 beats/minute as a prophylactic measure. Four days later, when the pacemaker was removed, his heart rate fell to 45 beats/minute, which was successfully treated with one ampule of intravenous atropine. The patient was discharged in good condition.

In one case the events were associated with an accidental ingestion of hydroxyzine by a young child. The patient (case # 9503721) was a 13-month-old female who ingested between 500 mg and 625 mg of hydroxyzine tablets and developed generalized seizures, sinus tachycardia, mydriasis, intermittent apnea, and mild pyrexia. On admission, she was semi-comatose. Her plasma hydroxyzine concentration 8.5 hours after ingestion was 102.7 $\mu\text{g/mL}$. She received supportive care and seizure control therapy with intravenous physostigmine and diazepam, and lavage with activated charcoal, and completely recovered within 72 hours.

In five cases, the reported events could have been associated with concomitant therapy. The first of these (case # 9408568) involved a female patient of unknown age described as a "nursing home patient" receiving multiple unknown medications, hydroxyzine (indication, dosage, and duration of therapy unknown), and venlafaxine (75 mg/day for depression) who developed hypertonia and trismus. Warfarin (indication, dosage, and duration of therapy unknown) was also listed as a concomitant medication. She reportedly experienced unspecified "problems" in the nursing home, and was transported to an emergency room, where she "arrested". The hydroxyzine and venlafaxine were discontinued, and the hypertonia and trismus improved. She reportedly had a history of atrial fibrillation and was being treated with multiple medications that the reporter was unable to identify. Venlafaxine is reported to be associated with hypertonia and trismus, and, although not reported to be associated with cardiac arrest, it has also been reported to be associated with arrhythmias including extrasystoles, first-degree atrioventricular block, and bundle-branch block².

In two other patients whose events could have involved other medications hydroxyzine was administered as part of a pre-anesthesia regimen for dental surgery. The first of these patients (case # 9390388) was a 23-year-old female who received general anesthesia for extraction of wisdom teeth. She received hydroxyzine 100 mg orally and betamethasone (dose and route of administration unknown) followed by vecuronium bromide, propofol, and fentanyl intravenously. After five minutes, she developed a rash, tachycardia, and hypertension which resolved spontaneously. Skin tests were performed for all drugs administered and were positive

for hydroxyzine and vecuronium bromide. The second of these patients (case # 9501923) involved an approximately four-year-old male with a history of muscle weakness of unknown etiology who received anesthesia prior to a dental procedure. He was given hydroxyzine pamoate 50 mg and diazepam 10 mg mixed with honey, and then inhaled a mixture of 50% nitrous oxide and 50% oxygen. He also received 2.75 Carpules of lidocaine 2% with epinephrine 1:100,000 into the oral mucosa over five minutes. Over the next 50 minutes, the patient appeared twice to have exhibited "early signs of vomiting", but he did not vomit. He then again demonstrated a "rising and falling movement of the chest and stomach", and became apneic. Resuscitation was attempted, and he was found to have no carotid pulse. Paramedics were called, and he was transported to an emergency room. During transport, the paramedics again attempted to resuscitate the patient. He was received at the emergency room in asystole, and was resuscitated and maintained in sinus tachycardia, but his pupils were fixed and dilated. He was transferred to the pediatric intensive care unit, and expired two days later. Hydroxyzine blood concentrations five to six hours after administration were negative. Lidocaine and epinephrine concentrations were not reported. The medical examiner listed the probable cause of death as cardiopulmonary arrest with no precipitating factors. It was reported that he had received diazepam, hydroxyzine, and lidocaine with epinephrine twice before without incident.

The last two cases where the events could have been related to concomitant medication are not very well documented and were difficult to evaluate; however, in both of these the patients appeared to have had pre-existing cardiovascular disease and were receiving other medications which could have contributed to the reported events. In the first of these (case # 9503401) a patient of unknown age and gender with "a deficient heart state" and gastric cancer was treated with hydroxyzine and amiodarone and developed bradycardia which improved following discontinuation of hydroxyzine. In the second (case # 9503402) a patient of unknown age and gender with supraventricular tachycardia and hypertension treated with hydroxyzine 100 mg/day, nordazepam 7.5 mg/day, and nifedipine 20 mg/day experienced sinus tachycardia and "generalized flushing". No additional information is available for these cases, but amiodarone has been reported to be associated with bradycardia³, and nifedipine has been reported to be associated with tachycardia and flushing⁴.

In four patients hydroxyzine was administered as part of a pre-anesthesia regimen prior to general anesthesia. The first of these (case # 9503403) involved a 55-year-old female with no known illnesses receiving no known other medications who received hydroxyzine 150 mg intramuscularly and atropine 0.5 mg intramuscularly prior to surgery to repair a dog bite-induced open fracture of the wrist. Approximately 10 minutes later, she was reported to be "feeling bad", was conscious and "about to vomit". Her blood pressure was reported as "40", and she had an impalpable pulse, severe sweating, and pallor. A plasma expander infusion was started, and another 0.5 mg of atropine was administered intramuscularly. The reaction was reported to be immediate, with blood pressure of "70", and bradycardia (40 beats/minute). Another 0.75 mg of atropine was administered intravenously, and a "complete recovery" occurred within half an hour. The patient underwent surgery the next day without any premedication and without any problems. The second (case # 9503404) involved a 32-year-old male with no known illnesses

receiving no known other medications who received hydroxyzine 150 mg intramuscularly and atropine 0.5 mg intramuscularly prior to an appendectomy. Approximately five minutes later, he wanted to vomit, became very pale, was sweating, had an impalpable blood pressure, and bradycardia (40 beats/minute). A plasma expander infusion was started and his lower limbs were raised. He recovered and underwent the surgery about two hours later.

Two other cases which involved hydroxyzine as part of a pre-anesthesia regimen are not very well documented and difficult to evaluate. The first of these (case # 9503398) involved a 30-year-old male pre-medicated with hydroxyzine 50 mg/day for three days prior to "surgery" who developed "an acute major bronchospasm during surgery", followed by ventricular fibrillation leading to cardiac arrest, phase IV coma, and death. No additional information is available on this case.

The last case (case # 9503399) involving hydroxyzine as pre-anesthesia is also not well documented, but the patient appears to have had pre-existing cardiovascular disease which may have contributed to the reported events. This 84-year-old patient of unknown gender with a history of aortic sclerosis, mitral insufficiency murmur, and left anterior hemibloc received a single intramuscular injection of hydroxyzine 100 mg as premedication for eye cancer surgery, and developed bradycardia which regressed after treatment with atropine. No additional information is available for this case.

There were two cases that were not very well documented. These cases (case #s 9503397 and 9503400) involved two patients of unknown age and gender who experienced bradycardia following intravenous administration of hydroxyzine. No additional information is available for these cases.

The last hydroxyzine case involved a patient who received hydroxyzine and meperidine for pain. This case contained limited information and a possible relationship between the reported events and hydroxyzine and/or meperidine can not be entirely excluded. The patient (case # 9400513) was a 36-year-old female with an unknown medical history admitted to the hospital for a flare-up of previously documented gallstones. She was prescribed meperidine 100 mg and hydroxyzine 100 mg intravenously for pain. During administration, she became nauseated, lightheaded, developed a severe headache, and had temporary hypotension. The medication was stopped immediately. She appeared pale, uncomfortable, and anxious. There were no rashes or wheezing. Electrocardiogram revealed ischemia in leads III, V3, V4, and V5. She was placed on oxygen, put in the Trendelenburg position, and given methylprednisolone, epinephrine, and naloxone. She was transferred to the intensive care unit where she was found to have "an elevation in enzymes associated with a myocardial infarction" (specific details were not provided) and it was reported that "cardiac catheterization and echocardiography revealed a completely normal heart".

MECLIZINE

The first meclizine case (case # 9401063) involved a 47-year-old male with a history of hypertension who experienced a cardiac arrest "manifested as ventricular fibrillation" after being treated with meclizine (dose unknown) for vertigo for "a couple of weeks". He reportedly had been prescribed enalapril for his hypertension, but was not taking it at the time of his cardiac arrest. Cardiac work-up consisting of electrocardiograms before and after this episode were reported as normal. An echocardiogram, cardiac catheterization, and ergonovine provocation were all reported to be normal.

The second meclizine case (case # 9503262) was reported by a consumer, and involved a 45-year-old male with an unknown medical history who took two meclizine 25 mg chewable tablets before an airplane flight. Two to three hours into the flight, upon awakening he "passed out". He felt sick, and the cabin staff administered oxygen to help revive him. It was also reported that meclizine was not effective. No additional information is available for this case.

SUMMARY AND CONCLUSIONS

In summary, this updated review identified two meclizine cases and 14 hydroxyzine cases which involved cardiovascular adverse events entered into Pfizer's early alert safety database from January 1, 1994 to April 19, 1995, and one hydroxyzine case entered prior to January 1, 1994 which had been updated to include cardiovascular events. Sixteen were spontaneously reported cases and one was a literature case.

Among the hydroxyzine cases, two involved non-fatal overdoses. In six cases (the updated case and five new cases) the patients were taking concomitant medications (venlafaxine, vecuronium, propofol, fentanyl, lidocaine with epinephrine, amiodarone, nifedipine, lorazepam, and clorazepate) that have been reported to be associated with the types of events that were reported²⁻¹¹. There were four cases where hydroxyzine was part of a pre-anesthesia regimen prior to general anesthesia, but two of these cases were not very well documented and in one of them the patient may have had pre-existing cardiovascular disease which contributed to the reported event. Another two cases were not very well documented and were difficult to evaluate. In the last hydroxyzine case a patient with an unknown medical history appeared to have experienced a myocardial infarction while receiving hydroxyzine and meperidine, but a subsequent cardiac catheterization and echocardiography were normal.

In one meclizine case the patient had a history of hypertension for which enalapril had been prescribed, but he reportedly had not been taking the enalapril when he started meclizine therapy. Cardiac work-up before and after the event were reported as normal. The other meclizine case was reported by a consumer and is difficult to evaluate since it was not well documented.

The original review, which included cases entered into the database through December 31, 1993, identified 12 hydroxyzine cases and six meclizine cases involving heart rate/rhythm adverse

events or syncope. Among the hydroxyzine cases, two cases were poorly documented, one case involved syncope associated with a seizure, and five cases involved events which could have been due to other causes. In one case a relationship between hydroxyzine and arrhythmia could not be entirely excluded; however, the patient had received terfenadine (which is known to be associated with serious arrhythmias) three days prior to onset of the reported event. In three of the hydroxyzine cases the events were associated with intentional overdoses/suicide attempts, and involved tachycardia following ingestion of 625 mg, cardiac arrest following ingestion of 1,250 mg, and ventricular arrhythmias including torsades de pointes following ingestion of 31,300 mg.

For the meclizine cases discussed in the previous review, limited information was provided in five of the cases, which made evaluation difficult; however, in one of these cases the patient had an underlying illness which may have contributed to the events, and in another case the patient had experienced similar symptoms before. The remaining meclizine case involved an elderly female with a history of heart failure and liver disease who experienced torsades de pointes after she had increased her meclizine dose to about 2,500 mg/day over the preceding four to six weeks.

The previous review concluded that there is no indication that serious arrhythmias occur in association with hydroxyzine or meclizine when used in normal therapeutic doses in patients who are otherwise healthy. This updated review of new cases supports that conclusion.

References

- 1) Hydroxyzine/meclizine and cardiovascular events. Pfizer Inc; Clinical Safety; January 14, 1994.
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- 3) Anon. Amiodarone hydrochloride. *American Hospital Formulary Service - Drug Information 94*. McEvoy GK, Litvak K, and Welsh OH (Eds). American Society of Hospital Pharmacists; Bethesda, Maryland; 1994; pg. 964-973.
- 4) Anon. Calcium channel blocking agents: systemic. *USP-DI: Drug Information for the Health Care Professional (14th Ed)*. United States Pharmacopeial Convention Inc; Rockville, Maryland; 1994; pg. 678-695.
- 5) Anon. DIPRIVAN® 1% (propofol - Stuart). *Physician's Desk Reference (49th Ed)*. Medical Economics; Montvale, New Jersey; 1995; pg. 2436-2441.
- 6) Anon. NORCURON® (vecuronium bromide - Organon). *Physician's Desk Reference (49th Ed)*. Medical Economics; Montvale, New Jersey; 1995; pg. 1751-1753.
- 7) Anon. Vecuronium bromide. *American Hospital Formulary Service - Drug Information 94*. McEvoy GK, Litvak K, and Welsh OH (Eds). American Society of Hospital Pharmacists; Bethesda, Maryland; 1994; pg. 832-838.
- 8) Anon. SUBLIMAZE® (fentanyl citrate - Janssen). *Physician's Desk Reference (49th Ed)*. Medical Economics; Montvale, New Jersey; 1995; pg. 1199-1201.
- 9) Anon. XYLOCAINE® (lidocaine HCl - Astra)/ XYLOCAINE® (lidocaine HCl - Astra) With Epinephrine. *Physician's Desk Reference (49th Ed)*. Medical Economics; Montvale, New Jersey; 1995; pg. 580-582.
- 10) Anon. Local anesthetics, parenteral, general statement. *American Hospital Formulary Service - Drug Information 94*. McEvoy GK, Litvak K, and Welsh OH (Eds). American Society of Hospital Pharmacists; Bethesda, Maryland; 1994; pg. 2112-2115.
- 11) Anon. Benzodiazepines general statement. *American Hospital Formulary Service - Drug Information 94*. McEvoy GK, Litvak K, and Welsh OH (Eds). American Society of Hospital Pharmacists; Bethesda, Maryland; 1994; pg. 1488-1494.

Appendix 3

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

JUN 23 1995

DATE:

FROM: Evelyn Farinas, RPh.
Postmarketing Safety Evaluator
Reports Evaluation Branch, HFD-735

THROUGH: Sandra Kweder, MD, Acting Director *DJG for RW (2/15)*
Division of Epidemiology and Surveillance, HFD-730

TO: Dr. Ana Maria Saavedra
Division of Pulmonary Drugs Products
HFD-155

SUBJECT: Consult Request: Ketoconazole and Hydroxyxine
drug interaction.

INTRODUCTION

Following your telephone request, please find attached the line-listing corresponding to the Spontaneous Reporting System [SRS] reports where Ketoconazole and Hydroxyxine are listed as concomitant drugs. Between 1982 and the present, there have been 20 such reports in the SRS.

DEMOGRAPHICS

Outcome: 2 deaths; 5 hospit.; 1 disability
Origin: 18 domestic; 2 foreign
Sex: 6 female; 14 male
Age: range 6-90
Most often reported COSTART terms (2 or more cases each):

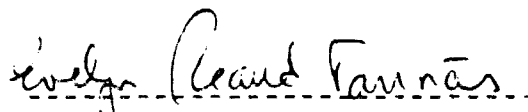
LIVER FUNC ABNORM	5
BILIRUBINEM	3
PHOSPHATASE ALK INC	3
PRURITUS	3
INTRACRAN HYPERTENS	2
JAUNDICE CHOLESTAT	2
RASH	2
RASH MAC FAP	2

DISCUSSION

The Ketoconazole labeling addresses both hepatic adverse events and several drug interactions associated with the use of Ketoconazole. The labeling includes a WARNING box which states: "When used orally, ketoconazole has been associated with hepatic toxicity, including some fatalities." The labeling also indicates that concomitant Ketoconazole use alters the metabolism of the following drugs: terfenadine, astemizole, loratadine, rifampin, coumarin, INH, cyclosporine, phenytoin, methylprednisolone, etc. Hydroxyzine was not mentioned.

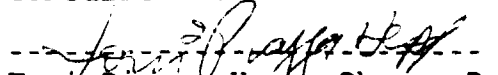
In reviewing this report, it is essential to remember limitations associated with data derived from the Spontaneous Reporting System. In some of these cases, the reported clinical data was incomplete, and there is no certainty that these drugs caused the reported reactions. Furthermore, a given reaction may actually have been due to an underlying disease process or to another coincidental factor. Because this data was generated using computer printouts, some of the numbers may reflect duplicates.

If I may be of further assistance, please call me at 594-5471.

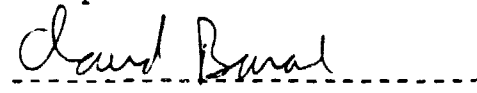


Evelyn R. Farinas, MGA, RPh

Concurrence:



Toni Piazza-Hepp, Pharm. D.
Group Leader



David Barash, RPh.
Chief

CC:
HFD-730/Acting Director
HFD-733/Graham/Acting Chief
HFD-735/Barash/Piazza-Hepp/Farinas/Chron/Consult

NDA 19835

2 OF 3

Drugs Included In FARINASEKETOC

Drugcode	Drug
FARINASEKETOC	KETOCONAZOLE
	NIZORAL
	NIZORAL ZK

Log Area: ALL (DOM + FOB) Costart(code): M/A Drugcode1: FARINASEKETOC Drugcode2: FARINASEKETOC

Drugs Included in FARIMASEDRXZ

Drugcode	Drug
-----	-----
FARIMASEDRXZ	ATIBAX
	EMBAX
	HYDROXYZINE
	HYDROXYZINE HYDROCHLORIDE
	HYDROXYZINE PAMCATE
	PARAX
	VISTARIL

Drugcode2: FARIMASEDRXZ

Drugcode1: FARIMASECTOC

Costart(code): N/A

esg Area: ALL (DOH + FOB)

Number of Cases Per Serious Outcome, By Age Category

Age Category	Total Cases	Total Serious	Total Died	Total Hospit	Total Disabled	Total Congen Anom	Total Life-Thr
0 - 9	2	1	0	1	0	0	0
10 - 19	0	0	0	0	0	0	0
20 - 29	2	2	0	0	0	0	0
30 - 39	3	0	0	2	0	0	0
40 - 49	3	1	0	0	1	0	0
50 - 59	2	0	0	0	0	0	0
60 - 69	3	2	2	1	0	0	0
70 - 79	3	1	0	1	0	0	0
80 - 120	1	1	0	1	0	0	0
UNCL AGE	1	0	0	0	0	0	0
Totals:	20	8	2	6	1	0	0

Drugcode2: FARMASEHBRXZ

Drugcode1: FARMASEKETOC

Costart(code): N/A

COG Area: ALL (DOM + FOR)

Number Of Cases Per Serious Outcome, By Sex and Age Category

Sex	Age Category	Total Cases	Total Serious	Total Died	Total Hospit	Total Disabled	Total Congen Anom	Total Life-Thr
female	0 - 9	0	0	0	0	0	0	0
	10 - 19	0	0	0	0	0	0	0
	20 - 29	0	0	0	0	0	0	0
	30 - 39	1	0	0	0	0	0	0
	40 - 49	2	1	0	0	1	0	0
	50 - 59	1	0	0	0	0	0	0
	60 - 69	1	0	0	0	0	0	0
	70 - 79	1	1	0	1	0	0	0
	80 - 120	0	0	0	0	0	0	0
	MULL AGE	0	0	0	0	0	0	0
Totals:		6	2	0	1	1	0	0
male	0 - 9	2	1	0	1	0	0	0
	10 - 19	0	0	0	0	0	0	0
	20 - 29	2	2	0	2	0	0	0
	30 - 39	2	0	0	0	0	0	0
	40 - 49	1	0	0	0	0	0	0
	50 - 59	1	0	0	0	0	0	0
	60 - 69	2	2	2	1	0	0	0
	70 - 79	2	0	0	0	0	0	0
	80 - 120	1	1	0	1	0	0	0
	MULL AGE	1	0	0	0	0	0	0
Totals:		14	6	2	5	0	0	0
unknown	0 - 9	0	0	0	0	0	0	0
	10 - 19	0	0	0	0	0	0	0
	20 - 29	0	0	0	0	0	0	0
	30 - 39	0	0	0	0	0	0	0
	40 - 49	0	0	0	0	0	0	0
	50 - 59	0	0	0	0	0	0	0
	60 - 69	0	0	0	0	0	0	0
	70 - 79	0	0	0	0	0	0	0
	80 - 120	0	0	0	0	0	0	0
	MULL AGE	0	0	0	0	0	0	0
Totals:		0	0	0	0	0	0	0

Log Area: ALL (DOM + FOR)

CoStart(code): N/A

Drugcode1: FARINASEKETOC

Drugcode2: FARINASEHRKZ

Number of Cases Per Serious Outcome, By Year/Quarter

Year - Qtr	Total Cases	Total Serious	Total Died	Total Hospit	Total Disabled	Total Congen Anom	Total Life-Thr
1982 - 2	1	1	0	1	0	0	0
1983 - 3	1	0	0	0	0	0	0
1983 - 4	1	1	1	1	0	0	0
1985 - 3	1	1	1	0	0	0	0
1988 - 4	1	0	0	0	0	0	0
1989 - 3	1	0	0	0	0	0	0
1990 - 2	2	0	0	0	0	0	0
1990 - 4	1	0	0	0	0	0	0
1991 - 3	2	0	0	0	0	0	0
1991 - 4	1	0	0	0	0	0	0
1992 - 2	1	0	0	0	0	0	0
1992 - 3	2	1	0	0	1	0	0
1993 - 3	1	0	0	0	0	0	0
1993 - 4	1	1	0	1	0	0	0
1994 - 1	1	1	0	1	0	0	0
1994 - 2	1	1	0	1	0	0	0
1995 - 1	1	1	0	1	0	0	0
otals:	20	8	2	6	1	0	0

Log Area: ALL (DOM + FOR)

Costart(code): M/A

Drugcode1: FARIMASEKETOC

Drugcode2: FARIMASEHDXZ

Number Of Dechallenge/Rechallenges Per Serious Outcome

De/Rechall	Total Cases	Total Serious	Total Died	Total Hospit	Total Disabled	Total Congen Anom	Total Life-Thr
DECHALLENGE	6	2	0	2	0	0	0
RECHALLENGE	0	0	0	0	0	0	0
N/A	5	3	2	2	0	0	0
Totals:	11	5	2	4	0	0	0

Log Area: ALL (DOM + FOR)

Costart(code): N/A

Drugcode1: FARINASEKETOC

Drugcode2: FARINASEHDXZ

Number Of Foreign, Study, Consumer and Literature Reports, By General Source

General Source	Total Cases	Total Foreign	Total Study	Total Consumer	Total Literature	Total Exclusions *
DEL	0	0	0	0	0	0
DIAGNOSTIC LABORATORIES	0	0	0	0	0	0
DRUGS	0	0	0	0	0	0
COMMUNITY HEALTH CLINICS	0	0	0	0	0	0
CONSUMERS	0	0	0	0	0	0
DRUGGIST'S OFFICE	0	0	0	0	0	0
DENTIST	0	0	0	0	0	0
DRUG TREATMENT CENTERS	0	0	0	0	0	0
DRUG DISTRICTS	0	0	0	0	0	0
HEALTH CARE STUDENTS	0	0	0	0	0	0
LITERATURE	0	0	0	0	0	0
MANUFACTURER	15	2	0	1	0	3
MILITARY HOSPITAL	0	0	0	0	0	0
MIN-FEDERAL HOSPITAL (MIN)	0	0	0	0	0	0
NURSES	0	0	0	0	0	0
OPTOMETRIST	0	0	0	0	0	0
OSTEOPATHS	0	0	0	0	0	0
OTHER: FOREIGN COUNTRIES	0	0	0	0	0	0
OTHER: HMO'S	0	0	0	0	0	0
OTHER: NURSING HOMES	0	0	0	0	0	0
PHARMACISTS	1	0	0	0	0	0
PHYSICIAN EXTENDERS/ASSISTANTS	0	0	0	0	0	0
PHYSICIANS	1	0	0	0	0	0
PLANNED PARENTHOOD CLINICS	0	0	0	0	0	0
PODIATRISTS	0	0	0	0	0	0
PUBLIC HEALTH SERVICE FACILITIES	0	0	0	0	0	0
SPECIAL PROJECTS	0	0	0	0	0	0
SPECIAL STUDY (IND)	0	0	0	0	0	0
SPECIAL STUDY (NDA)	1	0	1	0	0	1
STATE HEALTH DEPARTMENT	0	0	0	0	0	0
UNKNOWN	0	0	0	0	0	0
VA HOSPITAL	2	0	0	0	0	0
Totals:	20	2	1	1	0	4

Log Area: ALL (DOM + FOR)

Costart(code): N/A

Drugcode1: FARINASEKETOC

Drugcode2: FARINASEHDKZ

For Reports Included In This Analysis, Exclusions = Cases Having At Least One of the Sources FOR, STU, CON, LIT.

Number of Cases Per Serious Outcome, By Report Type

Report Type	Total Cases	Total Serious	Total Died	Total Hospit	Total Disabled	Total Congen Anom	Total Life-Thr
15-DAY	5	4	0	3	1	0	0
PERIODIC	11	2	2	1	0	0	0
DIRECT	4	2	0	2	0	0	0
UNKNOWN	0	0	0	0	0	0	0
otals:	20	8	2	6	1	0	0

Log Area: ALL (DOM + FOR)

Costart(code): N/A

Drugcode1: FARINASEKETOC

Drugcode2: FARINASEHDRXZ

Numbers Of Cases Having 1, 2, 3 Or 4 Or More Drugs

Total Cases	1 Drug	2 Drugs	3 Drugs	4 Or More Drugs
20	0	2	4	14

Drugcode2: FARINASEHDXZ

Drugcode1: FARINASEKETOC

Costart(code): N/A

Log Area: ALL (DOM + FOR)

Number of Cases Per Serious Outcome, By Location Within Geographic Region

Region	Location	Total Cases	Total Serious	Total Died	Total Hospit	Total Disabled	Total Congen Anom	Total Life-Thr
RGN	BELG	1	1	0	1	0	0	0
	FRAN	1	1	0	1	0	0	0
	totals:	2	2	0	2	0	0	0
ATL	PA	1	0	0	0	0	0	0
	totals:	1	0	0	0	0	0	0
E	MA	1	0	0	0	0	0	0
	NJ	1	0	0	0	0	0	0
	totals:	2	0	0	0	0	0	0
AC	CA	4	1	0	1	0	0	0
	totals:	4	1	0	1	0	0	0
E	FL	4	2	1	1	1	0	0
	KY	1	0	0	0	0	0	0
	LA	1	0	0	0	0	0	0
	MS	1	0	0	0	0	0	0
	TN	1	0	0	0	0	0	0
totals:	8	2	1	1	1	0	0	
J	MO	2	2	0	2	0	0	0
	TX	1	1	1	0	0	0	0
totals:	3	3	1	2	0	0	0	

Geog Area: ALL (DOM + FOR)

Costart(code): N/A

Drugcode1: FARINASEKETOC

Drugcode2: FARIMASEHDXZ

NOTE: A location of N/A refers to cases for which no location was entered.

Counts Of COSTARTs In Cases, With Most Frequent COSTART Terms Listed First

COSTART Term	Count
IVER FUNC ABNORM	5
ILIRUBINEM	3
HOSPHATASE ALK INC	3
RURITUS	3
STRACRAM HYPERTENS	2
UNDICE CHOLESTAT	2
SN	2
SN MAC PAP	2
OPECIA	1
RRHYTHMIA	1
ROPHY INJECT SITE	1
RAIN SYND ACUTE	1
URCINOMA LUNG	1
RRHUS	1
TARRHEA	1
RUG INTERACTION	1
RY EYE	1
YPOCALCEM	1
POTENS	1
UNDICE	1
IVER TENDER	1
IN ABDO	1
EACT AGGRAV	1
RSADES DE POINTES	1
ITICAPIA	1
MIT	1

rog Area: ALL (DOM + FOR)

Costart(code): N/A

Drugcode1: FARINASEKETOC

Drugcode2: FARINASEHDXZ

Number Of Cases Per Serious Outcome, By Suspect And Other Drug

us/ th	Generic (Collapsed) Drug	Drug	Total Cases	Total Serious	Total Died	Total Hospit	Total Disabled	Total Congen Anom	Total Life-Thr
usp	AMOXICILLIN	AMOXICILLIN	1	0	0	0	0	0	0
	CIPROFLOXACIN	CIPRO	1	0	0	0	0	0	0
	CIPROFLOXACIN	CIPROFLOXACIN	2	2	0	2	0	0	0
	GANCICLOVIR	CYTOVENE	1	0	0	0	0	0	0
	HYDROXYZINE	HYDROXYZINE HYDROCHLORID	1	0	0	0	0	0	0
	KETOCONAZOLE	KETOCONAZOLE	3	3	1	3	0	0	0
	KETOCONAZOLE	NIZORAL	7	2	1	1	0	0	0
	KETOCONAZOLE	NIZORAL ZX	1	0	0	0	0	0	0
	PENTAMIDINE	NEBUPENT	1	0	0	0	0	0	0
	TERFENADINE	SELDANE	3	2	0	1	1	0	0
	TRIAMCINOLONE	KENALOG	1	0	0	0	0	0	0
		Totals:	22	9	2	7	1	0	0
th	AZIDOTHYIMIDINE	RETROVIR	1	0	0	0	0	0	0
	AZT	RETROVIR	1	0	0	0	0	0	0
	BETAMETHASONE	CELESTONE	1	0	0	0	0	0	0
	BUTOCMAZOLE NITRATE	BUTOCMAZOLE NITRATE	1	1	0	1	0	0	0
	CEFADROXIL	DURICEF	1	0	0	0	0	0	0
	CLINDAMYCIN	CLEOCIN	1	0	0	0	0	0	0
	CLOTRIMAZOLE	MYCELEX	2	0	0	0	0	0	0
	CORTISONE	CORTISONE	1	0	0	0	0	0	0
	DESIPRAMINE	DESIPRAMINE HYDROCHLORID	1	0	0	0	0	0	0
	DEXAMETHASONE	DECADRON	1	1	1	1	0	0	0
	DIPIVEFRIN	PROPINE	1	1	0	1	0	0	0
	DOXEPIN	DOXEPIN	2	0	0	0	0	0	0
	ESTROGENS	PREMARIN	1	0	0	0	0	0	0
	FLURAZEPAM	DALMANE	1	1	0	1	0	0	0
	HEPARIN	HEPARIN	1	0	0	0	0	0	0
	HYDROXYZINE	ATARAK	9	1	0	1	0	0	0
	HYDROXYZINE	HYDROXYZINE	8	5	0	4	1	0	0
	HYDROXYZINE	VISTARIL	2	2	2	1	0	0	0
	IBUPROFEN	IBUPROFEN	2	2	0	2	0	0	0
	KETOCONAZOLE	KETOCONAZOLE	3	2	0	2	0	0	0
	KETOCONAZOLE	NIZORAL	6	1	0	0	1	0	0
	LOPERAMIDE	IMODIUM	1	0	0	0	0	0	0
	MEPERIDINE	DEMEROL	1	1	1	0	0	0	0
	NAPROXEN	NAPROSYN	1	0	0	0	0	0	0
	MYSTATIN	MYSTATIN	1	1	1	1	0	0	0
	PREDNISONE	PREDNISONE	3	1	1	0	0	0	0
	RANITIDINE	ZANTAC	1	1	1	0	0	0	0
	TERFENADINE	SELDANE	1	0	0	0	0	0	0
	THIETNYLPERAZINE	TORCAN	1	0	0	0	0	0	0
	TRIAMCINOLONE	TRIAMCINOLONE	1	0	0	0	0	0	0
	VINCISTINE	VINCISTINE SULFATE	1	1	1	1	0	0	0
	ZALCITABINE	ZALCITABINE	2	2	0	2	0	0	0
	ZIDOVUDINE	RETROVIR	1	0	0	0	0	0	0
	ZONEPIRAC SODIUM	ZONAX	1	1	0	1	0	0	0
		Totals:	63	25	8	19	2	0	0

seg Area: ALL (DOM + FOR)

Costart(code): N/A

Drugcode1: FARINASEKETOC

Drugcode2: FARINASEHDRXZ

Number Of Cases Per Serious Outcome, By Year Of Receipt

Year	Total Cases	Total Serious	Total Died	Total Hospit	Total Disabled	Total Congen Anom	Total Life-Thr
1982	1	1	0	1	0	0	0
1983	2	1	1	1	0	0	0
1985	1	1	1	0	0	0	0
1988	1	0	0	0	0	0	0
1989	1	0	0	0	0	0	0
1990	3	0	0	0	0	0	0
1991	3	0	0	0	0	0	0
1992	3	1	0	0	1	0	0
1993	2	1	0	1	0	0	0
1994	2	2	0	2	0	0	0
1995	1	1	0	1	0	0	0
Totals:	20	8	2	6	1	0	0

Log Area: ALL (DOM + FOR)

Costart(code): N/A

Drugcode1: FARINASEKETOC

Drugcode2: FARINASEHDXZ

Number Of Cases Per Serious Outcome, By Bodysystem

Bodysystem	Total Cases	Total Serious	Total Died	Total Hospit	Total Disabled	Total Congen Anom	Total Life-Thr
BODY	4	3	1	1	1	0	0
CV	2	1	0	1	0	0	0
DIG	7	3	0	2	1	0	0
ENLJO	0	0	0	0	0	0	0
HAL	0	0	0	0	0	0	0
HAN	4	1	0	1	0	0	0
MS	0	0	0	0	0	0	0
MER	4	3	1	3	0	0	0
RES	1	1	1	0	0	0	0
SKIN	8	3	0	2	1	0	0
SS	1	0	0	0	0	0	0
UG	0	0	0	0	0	0	0
Totals:	31	15	3	10	3	0	0

Log Area: ALL (DOM + FOR)

Costart(code): N/A

Drugcode1: FARINASEKETOC

Drugcode2: FARINASEHDRXZ

Number Of Cases Per Serious Outcome, By COSTART Within Bodysystem

Bodysystem	COSTART	Total Cases	Total Serious	Total Died	Total Hospit	Total Disabled	Total Congen Anom	Total Life-Thr
DY	ATROPHY INJECT SITE	1	0	0	0	0	0	0
	DRUG INTERACTION	1	1	0	1	0	0	0
	PAIN ABDO	1	1	0	0	1	0	0
	REACT AGGRAV	1	1	1	0	0	0	0
.tals:		4	3	1	1	1	0	0
F	ARRHYTHMIA	1	1	0	1	0	0	0
	HYPOTENS	1	0	0	0	0	0	0
	TORSADES DE POINTES	1	1	0	1	0	0	0
.tals:		3	2	0	2	0	0	0
G	DIARRHEA	1	1	0	0	1	0	0
	JAUINDICE	1	1	0	1	0	0	0
	JAUINDICE CHOLE	2	0	0	0	0	0	0
	LIVER FUNC ABNM	5	1	0	1	0	0	0
	LIVER TENDER	1	1	0	0	1	0	0
	VOMIT	1	1	0	1	0	0	0
.tals:		11	5	0	3	2	0	0
H	BILIRUBINEM	3	0	0	0	0	0	0
	HYPOCALCEM	1	1	0	1	0	0	0
	PHOSPHATASE ALK INC	3	0	0	0	0	0	0
.tals:		7	1	0	1	0	0	0
R	BRAIN SYND ACUTE	1	1	0	1	0	0	0
	CONVULS	1	1	1	1	0	0	0
	INTRACRAN HYPERTENS	2	1	0	1	0	0	0
.tals:		4	3	1	3	0	0	0
S	CARCINOMA LUNG	1	1	1	0	0	0	0
.tals:		1	1	1	0	0	0	0
IN	ALOPECIA	1	0	0	0	0	0	0
	PRURITUS	3	1	0	0	1	0	0
	RASH	2	0	0	0	0	0	0
	RASH MAC PAP	2	2	0	2	0	0	0
	URTICARIA	1	0	0	0	0	0	0
.tals:		9	3	0	2	1	0	0
	DRY EYE	1	0	0	0	0	0	0
.tals:		1	0	0	0	0	0	0

Log Area: ALL (DON + FOR)

Costart(code): N/A

Drugcode1: FARINASEKETOC

Drugcode2: FARINASENDRXZ

Line Listing Summary Of Cases

Case#	Casenum	Image ID	Rpt Type	Age	Sex	Loc	Mfg Control No.	S/O	Dose	Unit	Route	Durat (Days)	DC	BC
		Serious Outcome	COSTART				Drug							
482	C131771 (NOSP	N131771	NFR 15-DAY (JAUNDICE (LIVER FUNC ABNORM (BRAIN SYND ACUTE	090	M	CA		S	200.00	MG	PO	21057	Y	NA
							(NIZORAL (DALMANE (ZOMAX (ATARAX (PROPINE	0 0 0 0 0	.00 .00 .00 .00					
483	C166154	N166154	NFR 15-DAY (INTRACRAN HYPERTENS		M	MS	N432	S	.00		PO			
							(NIZORAL (TRIAMCINOLONE (ATARAX	0 0 0	.00 .00 .00		TOP PO			
483	C177396 (NOSP (DIED	N177396	PERIODIC (CONVULS	062	M	FL	41400302	S	200.00	MG	PO	12		
							(KETOCANAZOLE (MYSTATIN (DECADRON (VISTARIL (VINCRIStINE SULFATE	0 0 0 0 0	20.00 6.00 200.00 1.50	ML MG MG GM	PO PO PO IV	9 27 37		
485	C364338 (DIED	N364338	PERIODIC (CARCINOMA LUNG (REACT AGGRAV	064	M	TX	N644	S	200.00	MG	PO	2		NA
							(NIZORAL (PREDNISONE (ZANTAC (DENEROL (VISTARIL	0 0 0 0 0	20.00 .00 225.00 150.00	MG MG MG MG	PO PO PO PO	159 16 16 16		
488	C559684	N559684	DIRECT (RASH	057	F	FL		S	1.50	GM	PO	1		
							(CIPRO (HEPARIN (NIZORAL (HYDROXYZINE (CLEOCIN	0 0 0 0 0	.00 .00 .00 .00					
489	C600699	N600699	PERIODIC (JAUNDICE CHOLESTAT (PHOSPHATASE ALK INC (BILIRUBINEM (LIVER FUNC ABNORM	070	M	MA	N944	S	200.00	MG	PO	28	Y	NA
							(NIZORAL (SELDAME (ATARAX (DOKEPIN (PREDNISONE	0 0 0 0 0	.00 .00 .00 .00					
490	C657697	N657697	PERIODIC (DRY EYE	040	M	CA	00013139	S	600.00	MG	IV			NA NA
							(CYTOVENE (NYCELEX (KETOCANAZOLE (DESIPRAMINE HYDROCHLORIDE (HYDROXYZINE	0 0 0 0 0	.00 .00 .00 .00					
490	C661002	N661002	DIRECT (URTICARIA (PRURITUS	040	F	KY		S	.00		PO			NA
							(AMOXICILLIN (ATARAX (NIZORAL	0 0 0	.00 .00 .00					

Log Area: ALL (DOM + FOR)

Costart(code): N/A

Drugcode1: FARIMASEKETOC

Drugcode2: FARIMASENDRXZ

Line Listing Summary Of Cases

ear	Casenum	Image ID	Rpt Type	Age	Sex	Loc	Mfg Control No.									
	Serious Outcome		COSTART		Drug			S/O	Dose	Unit	Route	Durat	(Days)	DC	RC	
790	C707343	N707343	PERIODIC (ATROPHY INJECT SITE	036	F	LA	0290041	S	60.00	MG	IM	8		NA	NA	
			(KEMALOG					0	.00							
			(ATARAX					0	.00							
			(NIZORAL					0	.00							
			(CELESTONE					0	.00							
791	C759135	N759135	PERIODIC (PRURITUS (LIVER FUNC ABNORM (PHOSPHATASE ALK INC (BILIRUBINEM	070	M	NJ	US9001061	S	.00		PO	28		NA	NA	
			(SELDAME					S	.00		PO	28		NA	NA	
			(NIZORAL					S	200.00	MG	PO	28		NA	NA	
			(ATARAX					0	.00							
			(DONEPIN					0	.00							
			(PREDNISONE					0	.00							
791	C767201	N767201	PERIODIC (LIVER FUNC ABNORM	039	M	CA	N1311	S	200.00	MG	PO	37		Y	NA	
			(NIZORAL					0	.00							
			(IMODIUM					0	.00							
			(NAPROSYN					0	.00							
			(TORECAM					0	.00							
			(ATARAX					0	.00							
791	C785575	N785575	PERIODIC (RASH	050	M	PA	AR161	S	100.00	MG	PO	1		NA	NA	
			(HYDROXYZINE HYDROCHLORIDE					0	.00							
			(NIZORAL													
792	C852627	N852627	PERIODIC (ALOPECIA	006	M	FL	NS240	S	.00		TOP	22		Y	NA	
			(NIZORAL ZX					0	.00							
			(ATARAX					0	.00							
			(CORTISONE					0	.00							
792	C863064	N863064	PERIODIC (HYPOTENS	035	M	TN	US1921091NB	S	300.00	MG	INN	1		Y	NA	
			(NEBUPENT					0	.00							
			(RETROVIR					0	.00							
			(NIZORAL					0	.00							
			(HYDROXYZINE					0	.00							
			(NYCELEX					0	.00							
792	C870140	N870140	REFR 15-DAY (DISABLED (PAIN ABDO (PRURITUS (LIVER TENDER (DIARRHEA	042	F	FL	9207657	S	.00		PO	1065		N	NA	
			(SELDAME					0	.00							
			(NIZORAL					0	.00							
			(HYDROXYZINE					0	.00							
793	C1364372	N1360128	PERIODIC (JAUNDICE CHOLESTAT (PHOSPHATASE ALK INC (BILIRUBINEM (LIVER FUNC ABNORM	060	F	CA	N1606	S	200.00	MG	PO	15		Y	NA	
			(NIZORAL					0	.00							
			(DURICEF					0	.00							
			(PREMARIN					0	.00							
			(ATARAX					0	.00							

30g Area: ALL (DCM + FOR)

Costart(code): N/A

Drugcode1: FARIMASEKETOC

Drugcode2: FARIMASEHDRXZ

Line Listing Summary Of Cases

ear	Casenum	Image ID	Rpt Type	Age	Sex	Loc	Mfg Control No.									
		Serious Outcome	COSTART	Drug			S/O	Dose	Unit	Route	Durat (Days)	DC	RC			
793	C1399838 (HOSP	N1403748	DIRECT (RASH MAC PAP	028	M	MO	(CIPROFLOXACIN (HYDROXYZINE (IBUPROFEN (KETOCONAZOLE (ZALCITABINE	S 0 0 0 0	500.00 .00 .00 .00 .00	MG	PO	95		Y	NA	
794	C1433747 (HOSP	N1439071	DIRECT (RASH MAC PAP	028	M	MO	(CIPROFLOXACIN (HYDROXYZINE (IBUPROFEN (KETOCONAZOLE (ZALCITABINE	S 0 0 0 0	500.00 .00 .00 .00 .00	MG	PO	86		Y	NA	
794	C1451429 (HOSP	N1462815	MFR 15-DAY (INTRACRAN HYPERTENS (VOMIT	007	M	BELG	REF3712JAFRA3712 (KETOCONAZOLE (HYDROXYZINE	S 0	20.00 .00	MG	PO	7		NA	NA	
795	C1542491 (HOSP	N1554908	MFR 15-DAY (HYPOCALCEM (ARRHYTHMIA (DRUG INTERACTION (TORSADES DE POINTES	073	F	FRAN	94007559 (SELDANE (KETOCONAZOLE (BUTOCONAZOLE NITRATE (HYDROXYZINE	S S 0 0	120.00 400.00 .00 .00	MG	PO	15 14		Y Y	NA NA	

Total Cases: 20

Log Area: ALL (DOM + FOR)

Costart(code): N/A

Drugcode1: FARINASEKETOC

Drugcode2: FARINASEHDRXZ

Comments for Cases

.serum: C131771 Image ID: M131771
BILL 4.7, SGPT 695, SGOT 230, ALK PHOS 523; ONYCHOMYCOSIS RESISTENT TO GRISEOFULVIN.

.serum: C166154 Image ID: M166154
BULGING FONTANELLE.

Log Area: ALL (DOM + FOR)

Costart(code): N/A

Drugcode1: FARINASEKETOC

Drugcode2: FARINASEHDXZ

Listing Of Case Numbers and Initial and Followup Image ID Numbers

Initial Case Image ID	Followup Image ID	Followup Entry Date	Followup Release Date	Casenum
.1771	M332974			C131771
.1154				C166154
.7396	M364293			C177396
.4338				C364338
.9684				C559684
.0699				C600699
.7697				C657697
.1002				C661002
.17343				C707343
.9135				C759135
.7201				C767201
.5575				C785575
.2627	M882610			C852627
.3064				C863064
.0140				C870140
.60128				C1364372
.03748				C1399838
.39071				C1433747
.62815				C1451429
.54908	M0			C1542491
.54908	M1573588	03-APR-1995	05-APR-1995	C1542491

al Cases: 20

g Area: ALL (DOM + FOR)

Costart(code): N/A

Drugcode1: FARINASEKETOC

Drugcode2: FARINASEHDXZ

NOTE: SUBMIT CASENUM/IMAGE ID PAIRS ON DATA REQUESTS, IN ASCENDING IMAGE ID ORDER. INCLUDE C AND M PREFIXES ***

Appendix 4

Cytolytic hepatic injury after cetirizine (Zyrtec®) administration

Several cases of hepatitis attributed to terfenadine (Teldane®) have been reported [1, 2]. However, no cases of hepatitis during treatment with cetirizine (Zyrtec®), a new non-anti-cholinergic type H1 antihistamine [3] have been reported apart from a moderate elevation in alanine aminotransferase (ALT) [1]. We are reporting a case of hepatitis during treatment with cetirizine.

A 46-year-old man with no history of alcohol intoxication, drug addiction, transfusion, or recent trip abroad, whose serum hepatic enzymes had been normal before introduction of the drug, was treated with 10 mg/day cetirizine (Zyrtec®), and no other drugs, for rhinorrhea and allergic tearing. A few months after the cetirizine was started he presented with jaundice, without fever or skin rash, itching, or abdominal pain. The results of the blood tests were: total bilirubin: 93 µmol/L; serum aspartate aminotransferase activity (AST): 553 IU/L (N < 25), ALT: 217 IU/L (N < 30), alkaline phosphatase (AP): 481 IU/L (N < 220), and gammaglutamyl transpeptidase (GGT): 445 IU/L (N < 38); leukocytes: 6200/mm³ of which 4% were eosinophilic polymorphonuclears and 2% monocytes. The results of the hepatitis A (anti-HAV IgM), B (HBs and anti-HBs antibody), and C (anti-HCV) virus serologies were negative. Serologies for cytomegalovirus and infectious mononucleosis, biliary tract ultrasound, and anti-tissue antibody study were not done. Administration of cetirizine was stopped 3 days after the jaundice started. Four days after cetirizine withdrawal, the rise in aminotransferases increased: ALT: 1040 IU/L, AST: 240 IU/L. One month after withdrawal, the hepatic enzyme values were normal (ALT: 23 IU/L, AST: 9 IU/L, AP: 201 IU/L).

Two months after recovery and 10 days after the accidental reintroduction of cetirizine there was further asymptomatic liver disease characterized by abnormal lab values: ALT 244 IU/L and AST: 74 IU/L. HCV serology and differential blood count were not done. Withdrawal of the drug was once again followed by complete normalization of the liver tests in 2 months.

This liver disorder was of the cytolytic type, occurred after several months of treatment with cetirizine, regressed when it was withdrawn, and reappearing when the drug was introduced once again. Even though all other diagnostic hypotheses (biliary lithiasis, autoimmune hepatitis, infectious mononucleosis) were not completely ruled out, post-reintroduction of cetirizine makes it appear likely that the liver was involved. Despite the absence of an abdominal ultrasound, the diagnosis of lithiasis migration is unlikely in view of the absence of biliary history, fever, and biliary-pain in both episodes. Also, there were differential blood count anomalies suggesting infectious mononucleosis. Other non-anti-cholinergic H1 type antihistamines, terfenadine [1] and oxatomide [4] may be responsible for hepatitis. On the other hand, no cases of hepatitis following ingestion of loratadine (Clarityne®) or astemizole (Hismanal®) have been published. Our case report is the first of hepatitis attributed to cetirizine. The action mechanism of H1 type antihistamine hepatotoxicity is unknown. Despite the absence of hyper eosinophilia and skin rash, an allergic mechanism may be deduced from the short time to onset following reintroduction. This agrees with one case of terfenadine hepatitis [2]. The occurrence of unaccountable liver disorder in a patient taking H1 antihistamines should suggest a drug origin.

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sence de manifestations extra-hépatiques (fièvre, érythrodermie) sont en faveur d'une origine immuno-allergique. Cette observation permet d'attirer l'attention sur la possibilité d'une atteinte hépatique précoce secondaire à la prise d'acitretine.

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Atteinte hépatique cytolytique après administration de cétirizine (Zyrtec®). #10 "Hepatic injury after cetirizine administration"

Plusieurs cas d'hépatites attribuées à la terféndine (Tel-dane®) ont été rapportés (1, 2). En revanche, aucune hépatite n'a été publiée au cours d'un traitement par la cétirizine (Zyrtec®), un nouvel anti-histaminique de type H1 non anti-cholinergique (3), en dehors d'une augmentation modérée de l'alanine aminotransférase (ALAT) (1). Nous rapportons un cas d'hépatite survenue au cours d'un traitement par cétirizine.

Un homme de 46 ans, sans antécédent d'intoxication alcoolique, de toxicomanie, de transfusion ou de voyage récent à l'étranger, dont l'activité sérique des enzymes hépatiques était normale avant l'introduction du médicament, était traité par 10 mg/j de cétirizine (Zyrtec®), sans autre médicament, pour une rhinorrhée et un larmolement allergique. Quelques mois après l'introduction de la cétirizine, survint un ictère, sans fièvre ni éruption cutanée, prurit ou douleur abdominale. Les résultats biologiques sanguins étaient les suivants : bilirubinémie totale : 93 µmol/L; activité sérique de l'aspartate aminotransférase (ASAT) : 553 UI/L (N < 25), de l'ALAT : 217 UI/L (N < 30), des phosphatases alcalines (PAL) : 481 UI/L (N < 220) et de la gamma-glutamyl transpeptidase (GGT) : 445 UI/L (N < 38); leucocytes : 6 200/mm³ dont 4 % de polynucléaires éosinophiles et 2 % de monocytes. Les résultats des sérologies des virus des hépatites A (IgM anti-VHA), B (antigène HBs et anticorps anti-HBc) et C (anti-VHC) étaient négatifs. Les examens sérologiques du cytomegalovirus et de la mononucléose infectieuse, l'échographie des voies biliaires et la recherche d'anticorps anti-tissus ne furent pas effectués. L'administration de cétirizine fut arrêtée 3 jours après le début de l'ictère. Quatre jours après l'arrêt de la cétirizine l'augmentation des aminotransférases était accrue : ALAT : 1 040 UI/L, ASAT : 240 UI/L. Un mois après l'arrêt, les tests enzymatiques hépatiques étaient normaux (ALAT : 23 UI/L, ASAT : 9 UI/L, PAL : 201 UI/L).

Deux mois après la guérison et 10 jours après la réintroduction accidentelle de cétirizine apparut une nouvelle atteinte hépatique, asymptomatique, et caractérisée par une atteinte biologique : ALAT : 244 UI/L et ASAT : 74 UI/L. La sérologie du VHC et la numération formule sanguine ne furent pas effectuées. L'arrêt de l'administration du médicament fut à nouveau suivi d'une normalisation complète des tests hépatiques en 2 mois.

Il s'agit d'une atteinte hépatique de type cytolytique, survenant après plusieurs mois d'un traitement par cétirizine, régressant à son arrêt et réapparaissant au décours de la réintroduction du médicament. Même si toutes les autres hypothèses diagnostiques n'ont pas été totalement éliminées (lithiase biliaire, hépatite auto-immune, mononucléose infectieuse), la réintroduction positive de la cétirizine rend vraisemblable le rôle du médicament. Malgré l'absence d'échographie abdominale, le diagnostic d'une migration lithiasique est peu probable devant l'absence d'antécédent biliaire, de fièvre et de douleur de type biliaire lors des 2 épisodes. Par ailleurs, il n'y avait pas d'anomalie à la numération formule sanguine orientant vers une mononucléose infectieuse. Parmi les anti-histaminiques de type H1 non anti-cholinergiques, la terféndine (1, 2) et l'oxatémide (4), peuvent être responsable d'hépatites. En revanche, aucune hépatite survenant après la prise de loratadine (Clarityne®) ou d'astémizole (Hismanal®) n'a été publiée. Notre observation constitue le premier cas d'hépatite attribuée à la cétirizine. Le mécanisme d'action de l'hépatotoxicité des anti-histaminiques de type H1 n'est pas connu. Malgré l'absence d'hyperéosinophilie et d'éruption cutanée, un mécanisme allergique peut être évoqué dans notre observation d'après le délai de survenue plus court lors de la réintroduction. Ceci est en accord avec un cas d'hépatite à la terféndine (2). La survenue de perturbations hépatiques inexplicables chez un patient prenant des anti-histaminiques de type H1 devrait faire penser à une origine médicamenteuse.

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Curiothérapie à haut débit de dose dans le traitement du cancer œsophagien.

Le traitement par radiothérapie externe (RE), chimiothérapie concomitante avec, dans certains cas, irradiation laser associée semble efficace dans le traitement non chirurgical à visée curative du cancer œsophagien (KCO) (1). La curiothérapie à haut débit de dose (CHDD) permet, comme la curiothérapie à faible débit, d'augmenter la dose délivrée à la tumeur sans majorer les complications relatives aux tissus sains, mais, en raison d'un temps court d'irradiation, avec un confort très supérieur à celui du « faible débit » (2). Nous rapportons les résultats préliminaires obtenus chez 9 patients atteints d'un carcinome épidermoïde œsophagien.

De 1990 à 1992, les patients ont été traités à visée curative et, en raison d'une contre-indication opératoire d'ordre général, par RE, chimiothérapie et CHDD complémentaire. Il s'agissait de 8 hommes et 1 femme, d'âge moyen 62 ans (extrêmes : 52-74 ans) atteints d'un carcinome épidermoïde œsophagien du tiers supérieur dans 2 cas, du tiers moyen dans 3 cas, du tiers inférieur dans 2 cas, à double localisation dans 1 cas. La lésion initiale était classée T1 N0 M0 dans 2 cas, T1 N1 M0 dans 1 cas, T3 N0 M0 dans 1 cas, T3 N1 M0 dans 1 cas, T3 N1 M0 dans 4 cas (classification de l'UICC 1987, complétée par les données endosonographiques dans 6 cas). Le traitement a consisté, dans tous les cas, en une RE délivrant 64 Gy en 32 fractions (4 faisceaux plus cyclothérapie), 2 cures de chimiothérapie à la 1^{re} et 3^e semaines de la RE (5 fluoro-uracile : 1 g/m² de J1 à J4 et cisplatyl : 35 mg/m² de J2 à J5) et, 3 semaines après la fin de la RE, une séance de CHDD réalisée, sous simple analgésie, avec le projecteur de source Curietron 192 HDR jusqu'en juin 1991 et IR 192, Nucletron par la suite, délivrant 7 Gy/surface au moyen d'un applicateur œsophagien de type Savary-Gilliard-Bonvoisin de 12,8 mm de diamètre (2). Les patients ont tous bénéficié d'un contrôle endoscopique avec biopsies 1 mois après la CHDD et, par la suite, d'un suivi trimestriel : clinique, endoscopique, tomodynamométrique avec, dans certains cas, une endosonographie.

La tolérance du traitement par CHDD a été parfaite, sans aucun effet secondaire chez les 9 patients. La réponse locale en fin de traitement a été complète dans 8 cas sur 9 avec histologie œsophagienne normale, et partielle dans 1 cas avec persistance en fin de traitement d'une ulcération creusante avec tissu néoplasique résiduel (lésion classée initialement T3 N0 M0). Un seul malade a eu une complication iatrogène sous forme de tassements vertébraux multiples en regard des champs de RE sur rachis ostéoporotique. Les 9 patients sont en vie, avec une alimentation orale normale, sans dilatation œsophagienne et sans rechute dans 8 cas, avec un recul de 7 à 33 mois, supérieur à 24 mois dans 5 cas.

Ce travail confirme la facilité d'utilisation du projecteur de source de CHDD et la bonne tolérance immédiate du traitement (2), sans dysphagie ni douleurs au décours de la séance de CHDD (3). Aucun patient n'a eu de complication à type d'ulcère, sténose ou fistule œsophagiennes imputables à la CHDD, contrairement à ce qui a déjà été

rapporté (4). Si, pour Hishikawa et al., l'adjonction de la CHDD à la RE permet d'augmenter la survie des patients (5), cette étude, en raison d'un recul insuffisant et d'un nombre encore limité de patients traités, ne permet pas de préjuger du résultat carcinologique, des effets secondaires à long terme et du bénéfice en matière de survie de l'utilisation de la CHDD.

Si l'exérèse chirurgicale est considérée comme le traitement de choix pour les tumeurs œsophagiennes classées T1 et T2, les résultats très prometteurs de cette étude confirment que les cancers œsophagiens évolués (T3) bénéficient des associations thérapeutiques non chirurgicales et soulignent la nécessité d'une prise en charge pluridisciplinaire du cancer œsophagien. Des travaux prospectifs multicentriques sont nécessaires pour l'évaluation précise du bénéfice de la curiothérapie à haut débit de dose, d'application simple et bien tolérée, notamment en matière de réponse carcinologique et œsophagienne, d'effets secondaires à long terme et de survie.

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Section 2

I. ANNOTATED PACKAGE INSERT

The reviewer's comments in this section were presented as a draft to Dr. Himmel as Group Leader and at the September 21, 1995 "in-house" meeting. Some clarifications were made to the text as suggested by Dr. Himmel. The text used in the submitted proposed labeling has been typed in a CG Times Scalable font and the reviewer's comments in a Courier 10 Cpi font.

ZYRTEC
cetirizine hydrochloride
Tablets
For Oral Use

DESCRIPTION

Cetirizine hydrochloride, the active component of ZYRTEC tablets, is an orally active and selective H₁-receptor antagonist. The chemical name is (±)-[2-[4-(p-chloro-α-phenylbenzyl)-1-piperazinyl]ethoxy] acetic acid, dihydrochloride. Cetirizine is a racemic compound with an empirical formula of C₂₁H₂₅ClN₂O₃·2HCl. The molecular weight is 461.8 and the chemical structure is shown below:

Cetirizine hydrochloride is a white, crystalline powder and is water soluble. ZYRTEC is formulated as a white (dye-free), film-coated, rounded-off rectangular shaped tablet for oral administration and is available in 5 and 10 mg strengths. Inert ingredients are: lactose; magnesium stearate; povidone; titanium dioxide; hydroxypropyl methylcellulose; polyethylene glycol; and corn starch.

CLINICAL PHARMACOLOGY

Mechanism of Actions: Cetirizine, a human metabolite of hydroxyzine is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H₁ receptors (1,2). The antihistaminic activity of cetirizine has been clearly documented in a variety of animal and human models (3-24). In vivo and ex vivo animal models have shown negligible anticholinergic and antiserotonergic activity (5,8,10,13,14,17). In clinical studies, however, dry mouth was more common with cetirizine than with placebo (89). In vitro receptor binding studies have shown no measurable affinity for other than H₁ receptors (16). Autoradiographic studies with radiolabeled cetirizine in the rat have shown negligible penetration of the brain (25). Ex vivo experiments in the mouse have shown that systemically administered cetirizine does not significantly occupy cerebral H₁ receptors (16).

Pharmacokinetics: Cetirizine is rapidly absorbed after oral administration of a tablet, which had bioavailability similar to an oral solution (26). Food had no effect on the extent of cetirizine absorption, but T_{max} was delayed by 1.7 hours and C_{max} was decreased by 23% in the presence of food (27). A mass balance study in 6 healthy male volunteers indicated that 70% of the administered radioactive dose was recovered in the urine and 10% in the feces, for a combined total recovery of

about 80% (28). Approximately 50% of the administered radioactive dose was excreted in urine as unchanged drug (28). Most of the rapid increase in peak plasma radioactivity is associated with parent drug indicating low first pass metabolism (28). Cetirizine is metabolized to a very limited extent by oxidative o-dealkylation to a metabolite (28,29) with negligible antihistaminic activity (30).

Cetirizine exhibits linear kinetics over the dosage range of 5 to 60 mg (31,32). In pharmacokinetic studies in 146 healthy volunteers, the mean $\pm$ SD terminal half-life was 8.3 ± 1.8 hours, oral clearance was 54 ± 13 mL/min, and the apparent volume of distribution was 0.50 ± 0.08 L/kg (33). No accumulation was observed for cetirizine following daily doses of 10 mg, for 10 days (34). The steady-state maximum plasma concentration was 311 ± 40 ng/mL and was achieved within 1.0 ± 0.5 hour (34). Individual histograms of cetirizine C_{max} and AUC showed unimodal distributions with a two- to four-fold variability in healthy subjects (100). Plasma protein binding of cetirizine is 93 ± 0.3 % and was independent of concentration in the range of 0.025 to 1.0 mcg/mL (29); this concentration range covers the therapeutic plasma levels.

Reviewer's comments:

In this section, a limited description of the human PK of cetirizine's enantiomers based on foreign study results may be appropriate. It would be up to Biopharm's recommendations.

SPECIAL POPULATIONS

Effect of Age: Following a single 10 mg oral dose, half-life increased by about 50% and clearance decreased by 40% in 16 elderly subjects as compared to the 14 normal subjects (35). The decrease in cetirizine clearance in these elderly volunteers was directly correlated to their decreased renal function.

Effect of Gender: No gender-related differences were observed in the kinetics of cetirizine between 86 white adult males and 3 white adult females (36).

Effect of Race: No race-related differences were observed in the kinetics of cetirizine between 86 white adult males and 11 black adult males (36).

Renally Impaired Patients: The kinetics of cetirizine were studied following multiple oral daily doses of 10 mg for 7 days in 7 normal volunteers (creatinine clearance 89-128 mL/min), 8 patients with mild renal function impairment (creatinine clearance 42-77 mL/min) and 7 patients with moderate renal function impairment (creatinine clearance 11-31 mL/min) (37). The pharmacokinetics of the drug were similar in patients with mild impairment and normal volunteers. Moderately renally impaired patients had a 3-fold increase in half-life and 70% decrease in clearance compared to normal volunteers (37). Accumulation of cetirizine was also more pronounced in patients with moderate impairment (37).

Following a single oral 10 mg dose of cetirizine, 5 patients on hemodialysis (creatinine clearance less than 7 mL/min) had a 3 fold increase in half-life accompanied by a 70% decrease in clearance. Cetirizine was not completely cleared by hemodialysis as less than 10% of the administered dose was removed during the dialysis session (37).

Dosing adjustment is necessary in patients with moderate or severe renal impairment and patients on dialysis. (See also DOSAGE AND ADMINISTRATION).

Hepatically Impaired Patients: Following single oral doses of 10 mg and 20 mg cetirizine administered to 6 and 10 patients, respectively, with chronic liver diseases (hepatocellular, cholestatic, and biliary cirrhosis), resulted in a 50% increase in half-life along with a 40% decrease in clearance compared to 16 healthy subjects (37,38,39).

Dosing adjustment may be necessary in hepatically impaired patients. (See also DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Theophylline: A multiple dose study in 24 healthy male volunteers showed that the pharmacokinetics of cetirizine (20 mg QD for 3 days) and theophylline (400 mg QD for 3 days) were not altered when they were given in combination (40).

Pseudoephedrine: A multiple dose study showed no significant differences in any pharmacokinetic parameters for either cetirizine (20 mg QD) or pseudoephedrine (120 mg Q12h) when they were concomitantly administered to 24 healthy male subjects for 6 days (41).

Antipyrine: Cetirizine 10 mg QD was administered for 9 days to 10 healthy male volunteers. Following coadministration on the ninth day with 250 mg antipyrine, no changes were observed in plasma clearance or elimination half-life of antipyrine. Therefore, cetirizine does not alter the oxidative metabolizing enzyme activity in the liver (42).

Ketoconazole: In a multiple-dose study involving 16 healthy male volunteers, the pharmacokinetics of cetirizine (20 mg QD) and ketoconazole (400 mg QD) were not altered when they were given in combination (43).

Erythromycin: In a multiple-dose study involving 16 healthy male volunteers, the pharmacokinetics of cetirizine (20 mg QD) and erythromycin (500 mg Q8h) were not altered when they were given in combination (44).

Cimetidine: In a double-blind, randomized, single-dose, crossover study, cetirizine 20 mg was administered to 6 healthy volunteers concomitantly with placebo or 400 mg cimetidine. Neither cetirizine plasma concentrations nor wheal and flare measurements at 2 and 4 hours post dose were significantly different after cimetidine and placebo treatment (45).

Pharmacodynamics: Studies in normal volunteers show that ZYRTEC at doses of 5 and 10 mg strongly inhibits the skin wheal and flare caused by the intradermal injection of histamine (17-20,22,23,46-48). The onset of activity after a single 10 mg dose occurs within 20 minutes in 50% of subjects and in 95% of subjects within one hour (49,50), and this activity persists for at least 24 hours (17,22,46,49). In a 35 day study in children ages 5 to 12, no tolerance to the antihistaminic effects of ZYRTEC was found (51).

Reviewer's comments:

The labeling should somehow clarify that the antihistaminic effect that this article supports is the ability of the drug to continue to suppress the formation of wheal and flare reaction after a histamine cutaneous injection after 35 days of cetirizine treatment in the same way than after a single dose. The study design and endpoints measured are not adequate to support no tolerance to the antihistaminic effects as a clinical endpoint.

The following change is proposed:

In a 35 day study in children ages 5 to 12, no tolerance to Zyrtec's ability to suppress histamine induced wheal and flare reaction was found (51).

The referenced underlined article was submitted in Appendix G, pages 9 648-655, volume 35.4. Watson et al: Cetirizine: A pharmacokinetic and pharmacodynamic evaluation in children with seasonal allergic rhinitis. Journal of Allergy and Clinical Immunology 84:457-464, 1989.

In this study, a population of 19 children (5-12), received cetirizine 5 mg (10 patients) or 10 mg (9 patients) over a period of 35 days, after a 7 day wash out period with placebo. Pseudoephedrine was used as a rescue medication.

Pharmacodynamic endpoints: cutaneous wheal and flare inhibition of histamine skin tests after a single dose and at the end of treatment and change in weekly investigator assessed symptom scores from baseline.

Due to the fact that the study was designed primarily as a PK PD study, a small number of children were enrolled. It did not have a concurrent placebo arm. The 5 and 10 mg cetirizine capsules were administered in a randomized, double blind manner. The investigators knew that during the wash-out period patients were receiving placebo and that during the study period they were receiving active medication.

The initial improvement in investigator assessed total symptom scores following a single dose compared to baseline, was not lost over the following weekly evaluations. The authors state that "the 10 mg dose appeared to have more rapid onset of action in controlling rhinitis symptoms than did the 5 mg dose, but both doses provided excellent relief of symptoms through out the 35 days of dosing."

At the end of the article the authors state that "the

efficacy of cetirizine in the treatment of allergic rhinitis needs to be confirmed in a larger, placebo-controlled, noninvasive study in children."

The effects of intradermal injection of various other mediators or histamine releasers are also inhibited by cetirizine (17,23,47,48,52), as is cold-induced urticaria (53).

Reviewer's comments:

The title for the article that is referenced in the above underlined statement is: "Skin reactivity to cold in patients suffering from cold urticaria before and after a single oral administration of cetirizine 2HCL." This study was submitted as part of the NDA vol 52, 8 276. It was not part of the material reviewed by this reviewer. The proposed labeling statement emphasizes cetirizine's inhibition of the clinical condition of cold induced urticaria. Even though a single dose of cetirizine is reported as inhibiting cold induced reactivity or in other words wheal and flare formation, in patients with cold urticaria, this single dose study by itself should not be considered enough evidence to support this clinical claim.

The following change is proposed:

The effects of intradermal injection of various other mediators or histamine releasers are also inhibited by cetirizine (17,23,47,48,52), as is skin reactivity to cold in patients with cold-induced urticaria (53).

Reviewer's comments:

It would seem appropriate from the clinical research standpoint that a description of the observed differences in antihistaminic effects by cetirizine's enantiomers in humans should be part of this section.

The following sentence is recommended:

The ability of cetirizine's enantiomers to inhibit wheal and flare reactions in humans differs; no activity has been demonstrated for the L (-) enantiomer.

Refer to the results of UCB study 101, vol 35.17 pages 11 1314-1736.

In mildly asthmatic subjects, ZYRTEC at 5 to 20 mg blocked bronchoconstriction due to nebulized histamine, with virtually total blockade after a 20 mg dose (24). In addition, the late phase recruitment of eosinophils, neutrophils and basophils, components of the allergic inflammatory

response, are inhibited by ZYRTEC following cutaneous antigen challenge (54-58).

Four randomized double-blind, placebo-controlled trials were conducted in healthy subjects to assess the psychomotor/psychophysical effects (as measured by the multiple sleep latency test, simulated assembly line task, Stroop word test, and the critical flicker frequency test) of ZYRTEC versus hydroxyzine or diphenhydramine. These studies showed that ZYRTEC was generally not significantly different from placebo but was different from hydroxyzine and diphenhydramine which produced significantly decreased test performance (59-62, 103).

Reviewer's comments:

The above underlined paragraph should be deleted.

The overview and analysis submitted in the safety update of 4/25/95 does not adequately support the above underlined paragraph. The fact that the conclusions for the above paragraph are derived from the single dose phase of 3 studies included in the pooled analysis presented in reference 103 is not stated. In addition, it is not stated that the conclusions based on the pooled cognitive test performance results may not predict what would be expected after multiple dosing in clinical practice.

Although the labeling refers to the results from 4 studies in the above paragraph only the data from 3 of them is pooled in the analysis that is presented in the 4/25/95 submission as reference 103 to support these statements. An additional study is referenced but not used in the analysis. In the other two studies that are referenced in the 4/25/95 submission as reference 103 that also measure performance, no statistically significant differences between cetirizine and diphenhydramine or hydroxyzine are reported. A summary of the overview and analysis that supports the above underlined paragraph as included in reference 103 in the 4/25/95 safety update follows.

Reference 103, the overview and analysis of cetirizine performance studies was submitted in the safety update of 4/25/95 in vol 35.4, Appendix G, pages 9 759-769. In it, the data from 3 studies was pooled and analyzed (Gengo-cognitive function, Walsh-SALT I and SALT II). These were cross over, placebo controlled trials. The single dose phase of these studies was chosen for the analysis. A correlation was made between the perception of drowsiness while on drug (using VAS -visual analog for sedation) compared to placebo and the scores of the cognitive tests while on drug compared to placebo. The pooled analysis presented in this safety update does not report a statistical value for this comparison. A series of tables (scatter plots) are included and portray the individual

patient values. Although in the majority of cetirizine treated patients the perceived alertness and performance results compare favorably to the results obtained during placebo treatment, there are individual patients that report to feel less alert and have cognitive scores that are lower on cetirizine than when they were on placebo, particularly in the 3.5 -4 hr time, post study drug.

In reference to the results of the individual study reports listed in reference 103, Table 1, in only 2 out of 3 studies there was a significant difference between cetirizine and hydroxyzine (Walsh (SALT I) study, for the simulated assembly line task and between cetirizine and diphenhydramine (Walsh (SALT II) study, for the simulated assembly line task. The study on cognitive function by Gengo does not report a significant difference between cetirizine and hydroxyzine, using the flash-fusion frequency and the stroop word score.

There are two other studies that are also included in Table 1 but are not included in the analysis presented in this section. These are the Dement (Sleep Latency) and the Gengo (Driving Performance). In the first one no statistically significant differences were reported between treatments (hydroxyzine, placebo and cetirizine) for the Stanford Sleepiness test and the visual analog for sedation (VAS). There were no statistical differences reported between hydroxyzine and cetirizine for the vigilance performance test. In the Gengo (Driving Performance), there were significantly less number of correct answers given by patients on 20 mg of cetirizine than those on placebo for DSS (digit symbol substitution), No significant differences are reported between treatments (which include diphenhydramine) for the trails B tracking (TBT); no significant differences are reported between diphenhydramine and cetirizine for the simulated accident avoidance (SAA) or the driving reaction time (DRT).

In four clinical studies in healthy volunteers, no clinically significant mean increases in QTc were observed in ZYRTEC treated subjects (32,43,44,63).

Reviewer's comments:

Proposed change:

In three clinical studies in healthy male adult volunteers, no clinically significant mean increases in QTc were observed in ZYRTEC treated subjects (32, 44, 63).

The proposed changes imply that the reviewer recommends that the results of the cetirizine-ketoconazole interaction

Report # 92CK 16-0603 be discussed separately. The discussion to support this proposed change will follow.

Reference is made to the MOR dated February 27, 1994 for the review of the studies: Report # 90CK16-0497 (ref. 39) and #92CK16-0604 (ref.44).

A separate summary MOR review of the study Report #93CK16-0624 reference 63, is included in **Appendix 1**. The study report was submitted in the 4/25/95 safety update submission in Section K.1.

In view of the limited characterization of PK in women in this NDA and that women have a higher incidence of reported torsades de pointes, it would be relevant to note that the following studies were conducted in male volunteers.

Since additional retrospective analysis was requested and conducted on the Pediatric studies conducted so far, these should also be part of a separate discussion in the labeling. This paragraph should clarify that the following data refers to studies conducted in adults.

In the first study, a placebo-controlled crossover trial, ZYRTEC was given at doses up to 60 mg per day, 6 times the maximum clinical dose for 1 week, and no significant QTc prolongation occurred (32). In the second study (43), a crossover trial, ZYRTEC and erythromycin were given alone and in combination. The effect of ZYRTEC 20 mg alone on QTc (Hodges corrections) was statistically estimated as a small decrease from baseline of 5.1 msec (-1.3%) after 5 days of therapy.

Reviewer's comments:

It is recommended that the QTc changes included in the labeling be expressed using the Bazzet correction which is more familiar to most physicians. If the Hodges correction is going to be used, the inclusion of a description of the Hodges correction and a reference (published article, not an abstract) that supports the superiority of Hodges method over the Bazzet in the heart rate range studied would be acceptable.

The adjective small should be deleted and the change reported as found.

There was no significant drug interaction effect on QTc with the combination of ZYRTEC 20 mg and erythromycin (43).

Reviewer's comments:

It is this reviewer's understanding that reference #43 refers as is listed in the annotations to the cetirizine-ketoconazole interaction study, or study report # 92CK-0603. Therefore, the annotated reference should be #44 instead of

#43.

In the third trial (44), also a crossover study, ZYRTEC and ketoconazole were given alone and/or in combination. The effect of ZYRTEC 20 mg alone on QTc was statistically estimated as a small increase from baseline of 8.2 msec (1.8%) after 10 days of therapy. The estimated effect of the combination on QTc change from baseline (16.1 msec) was equal to the sum of the individual component effects. Thus, there was no significant drug interaction effect on QTc with the combination of ZYRTEC and ketoconazole. In the fourth study (63), a placebo-controlled parallel trial, ZYRTEC was given alone or in combination with azithromycin. Results of this trial showed no significant increase in QTc associated with ZYRTEC 20 mg alone or in combination with azithromycin.

Reviewer's comments:

The underlined sentences should form part of a separate paragraph.

In the fourth study (63), a placebo-controlled parallel trial, ZYRTEC was given alone or in combination with azithromycin. Results of this trial showed no significant increase in QTc associated with ZYRTEC 20 mg alone or in combination with azithromycin.

Reviewer's comments:

The proposed label should describe the third study.

A separate summary MOR review of the study Report #93CK16-0624 reference 63, is included in Appendix 1. The study report was submitted in the 4/25/95 safety update submission in Section K.1.

In the third trial (44), also a crossover study, ZYRTEC and ketoconazole were given alone and/or in combination.

Reviewer's comments:

As noted above, this reviewer proposes to describe separately the results of this trial. Reference is made to the MOR dated 2/27/94 for this study Report # 92CK16-0603. As noted earlier the appropriate annotated reference for this study should be #43 instead of #44.

The following change is proposed for this sentence:

In a clinical study in healthy male volunteers (43), also a

crossover study, ZYRTEC and ketoconazole were given alone and/or in combination.

The effect of ZYRTEC 20 mg alone on QTc was statistically estimated as a small increase from baseline of 8.2 msec (1.8%) after 10 days of therapy. The estimated effect of the combination on QTc change from baseline (16.1 msec) was equal to the sum of the individual component effects.

Reviewer's comments:

The following changes are recommended:

The effect of ZYRTEC 20 mg alone on the mean increase in QTc from baseline was statistically estimated to be 8.2 msec (1.8%) after 10 days of therapy. The estimated effect of the combination on mean QTc change from baseline (16.1 msec) was equal to the sum of the individual component effects.

The adjective small should be deleted and the change reported as found. The reported change refers to the mean increase in QTc from baseline. This was mentioned at the beginning of the original paragraph, but since a separate paragraph is proposed, the reference to the mean increase in QTc from baseline should be added for clarity.

As noted earlier, it is recommended that the QTc changes included in the labeling be expressed using the Bazzet correction which is more familiar to most physicians. If the Hodges correction is going to be used, the inclusion of a description of the Hodges correction and a reference (published article, not an abstract) that supports the superiority of Hodges method over the Bazzet in the heart rate range studied would be acceptable.

Thus, there was no significant drug interaction effect on QTc with the combination of ZYRTEC and ketoconazole.

Reviewer's comments:

It is proposed that the above sentence should read:

There was no significant **pharmacokinetic** drug interaction effect on QTc with the combination of ZYRTEC and ketoconazole.

It is not clear to the reviewer if the drug interaction effect refers to the PK parameters on QTc. It was clear from the referenced MOR review of 2/27/94, that for change in QTc AUC and QTcmax, the estimated overall cetirizine, ketaconazole and combination effects were significantly

different to placebo. From the PK stand point the only positive significant correlation in this study was between cetirizine and QTcmax versus drug clearance. Since no significant effects were obtained with the drug combination on changes in QTc, it was considered that it would imply a lack of interaction of cetirizine metabolites with ketoconazole.

Reviewer's comments:

The addition of the following paragraph is recommended:

In the retrospective analysis of ECGs obtained from 202 children ages 6-11, that were treated with Zyrtec for four weeks in a placebo controlled clinical study, the mean change in QTc adjusted for baseline differences was 9.94 msec (Bazett) for Zyrtec 10 mg, - 2.52 msec for Zyrtec 5 mg and 1.77 msec for placebo when the ECGs recorded within 11-17 days of first dose were compared to baseline. The statistical analyses did not demonstrate significant differences between treatment groups, or treatment related effects in QTc by dose corrected by weight, gender or race. Reference is made to original MOR of NDA 20346 and to the summary review of the requests related to the ECG analysis that were submitted to NDA 19835 in the safety update dated 4/25/95. These are summarized and discussed in Appendix 2.

Clinical Studies: Eleven multicenter, randomized, double-blind, placebo-controlled clinical trials were conducted in the United States. Five studies in seasonal allergic rhinitis were conducted for up to 4 weeks in duration (64); four studies in perennial allergic rhinitis for up to 8 weeks in duration (65,66); and two studies in chronic idiopathic urticaria each for 4 weeks in duration (67). Doses of 5-20 mg per day were studied. In general, most patients were controlled on a 10 mg dose. Five (5) mg was the minimally effective dose and 20 mg did not give added effectiveness compared with 10 mg.

Reviewer's comments:

The following recommended highlighted paragraph takes into consideration the Sponsor's suggestions in terms of dosing but describes the studies that support efficacy. This is important because it gives a fair sense to the prescribing physician of this issue.

Eleven multicenter, randomized, double-blind, placebo-controlled clinical trials were conducted in the United States; 7 of these support effectiveness, 3 in seasonal allergic rhinitis (1 to 4 weeks in duration), 2 in perennial allergic rhinitis for up to 8 weeks in duration, and 2 in chronic idiopathic urticaria of 4 weeks in duration. Doses of 5-20 mg per day were studied. In general, most patients were controlled on a 10 mg dose.

Five (5) mg was the minimally effective dose and 20 mg did not give added effectiveness compared with 10 mg.

A less desirable alternative that may be more agreeable to the Sponsor and that conveys the information would be to only describe the 7 trials that supported efficacy. The paragraph would then read: Seven multicenter, randomized, double-blind, placebo-controlled clinical trials conducted in the United States support effectiveness, 3 in seasonal allergic rhinitis (1 to 4 weeks in duration), 2 in perennial allergic rhinitis for up to 8 weeks in duration, and 2 in chronic idiopathic urticaria of 4 weeks in duration. Doses of 5-20 mg per day were studied. In general, most patients were controlled on a 10 mg dose. Five (5) mg was the minimally effective dose and 20 mg did not give added effectiveness compared with 10 mg.

INDICATIONS AND USAGE

Seasonal Allergic Rhinitis: ZYRTEC is indicated for the relief of symptoms associated with seasonal allergic rhinitis due to allergens such as ragweed, grass and tree pollens. Symptoms treated effectively include sneezing, rhinorrhea, nasal pruritus, ocular pruritus, tearing and redness of the eyes (68).

Perennial Allergic Rhinitis: ZYRTEC is indicated for the relief of symptoms associated with perennial allergic rhinitis due to allergens such as dust mites, animal dander and molds. Symptoms treated effectively include sneezing, rhinorrhea, post-nasal discharge, nasal pruritus, ocular pruritus and tearing (69).

Chronic Urticaria: ZYRTEC is indicated for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria. It significantly reduces the occurrence, severity and duration of hives and significantly reduces pruritus (70).

CONTRAINDICATIONS

ZYRTEC is contraindicated in those patients with a known hypersensitivity to it or any of its ingredients, or to its parent compound, hydroxyzine.

PRECAUTIONS

Activities Requiring Mental Alertness: In clinical trials, the occurrence of somnolence has been reported in some patients taking ZYRTEC; due caution should therefore be exercised when driving a car or operating potentially dangerous machinery. Concurrent use of ZYRTEC with alcohol or other CNS depressants should be avoided because additional reductions in alertness and additional impairment of CNS performance may occur.

Drug-drug interactions: No clinically significant drug interactions have been found with theophylline, pseudoephedrine,

ketoconazole, erythromycin and cimetidine (40,41,43-45). In clinical trials, there did not appear to be an increased incidence of adverse experiences in patients administered ZYRTEC and beta-agonists, non-steroidal anti-inflammatory drugs, oral contraceptives, corticosteroids, H₂-antagonists, cephalosporins, penicillins, thyroid hormones and thiazide diuretics (71).

Reviewer's comments:

Comments to the following statement if any should be made by Biopharm:

No clinically significant drug interactions have been found with theophylline, pseudoephedrine, ketoconazole, erythromycin and cimetidine (40,41,43-45)

However, it should be noted that in clinical trials, for theophylline users both placebo and cetirizine treated patients the incidence of study discontinuation (6.45% and 5.0% respectively due to adverse experiences was higher than for non users (2.73% and 2.39%). However, the total number patients exposed was small, there were 124 cetirizine and 80 placebo patients. The reasons for study discontinuation for these patients is not readily available in the submission. In the individual listing in the submission for discontinued patients, concomitant drugs were not included.

The following changes are recommended for the following statement:

In clinical trials, there did not appear to be an increased incidence of adverse experiences in patients administered ZYRTEC and beta-agonists, oral contraceptives, corticosteroids, and thiazide diuretics (71).

Supportive data regarding the following statement: In clinical trials, there did not appear to be an increased incidence of adverse experiences in patients administered ZYRTEC and beta-agonists, non-steroidal anti-inflammatory drugs, oral contraceptives, corticosteroids, H₂-antagonists, cephalosporins, penicillins, thyroid hormones and thiazide diuretics (71) is included in the safety update 4/25/95, Vol 35.4, pages 9 656-735. The tables of incidence and median exposure of medication categories are included in **Appendix 3**.

In the supportive data set, the incidence of exposure to thyroid, H₂ inhibitors, cephalosporin and penicillin is less than 2% for cetirizine treated patients (2,676) in placebo controlled studies, or less than 100 patients for each drug. In this reviewer opinion this is a very small data set from

which to derive meaningful conclusions unless a proper statistical analysis is made and found to be otherwise. Even though the total incidence of adverse events may be similar for patients concurrently receiving these drugs, the incidence of specific adverse events may be more or less than expected and it is difficult to ascertain the true clinical meaning. As an example: in thyroid treated patients the incidence of cetirizine treated patients reporting fatigue was 9.09% (4/44) and 3.92% (2/51) for placebo treated patients. Dry mouth was also reported twice as frequently on cetirizine treated patients.

For NSAID users (cetirizine and placebo) the reported incidence of adverse events is higher than for non users. Refer to table in **Appendix 3**. NSAID users that received cetirizine report a higher incidence of somnolence, fatigue and dry mouth than placebo treated patients also using NSAID and cetirizine-non NSAID user, treated patients. The reported rates for these adverse events in placebo treated patients, NSAID users and non users, were very similar. With an incidence of exposure of 14% for NSAID use in cetirizine treated patients and 16.9% in placebo treated patients, the increased incidence of somnolence, mouth dry and fatigue in cetirizine treated patients that were also treated with NSAID should be part of the labeling.

Carcinogenesis, mutagenesis and impairment of fertility: No evidence of carcinogenicity was observed in a 2-year carcinogenicity study in rats (72) at dietary doses up to 20 mg/kg/day (15 times the recommended human dose on a mg/m²/day basis). An increased incidence of benign liver tumors was found in a 2-year carcinogenicity study in male mice (73) at a dietary dose of 16 mg/kg/day (6 times the recommended human dose on a mg/m²/day basis). The clinical significance of these findings during long-term use of ZYRTEC is not known. Cetirizine was not mutagenic in Ames test, and not clastogenic in human lymphocyte assay, mouse lymphoma assay, and in vivo micronucleus test in rats (74-77). No impairment of fertility was found in a fertility and general reproductive performance study in mice (78,79) at a dose of 64 mg/kg/day (26 times the recommended human dose on a mg/m²/day basis).

Pregnancy Category B: Cetirizine has not been shown to be teratogenic in mice, rats and rabbits at doses up to 96, 225, and 135 mg/kg/day (or 40, 180, and 216 times the recommended human dose on a mg/m²/day basis), respectively (80-82). There are no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, ZYRTEC should be used in pregnancy only if clearly needed.

Nursing Mothers: Retarded pup weight gain was found in mice during lactation (79) when dams were given cetirizine at 96 mg/kg/day (40 times the recommended human dose on a mg/m²/day basis). Studies in beagle dogs indicate that approximately 3% of the dose is excreted in milk (83). Cetirizine has been reported to be excreted in human breast milk (102). Because many drugs are excreted in human milk, use of ZYRTEC in nursing mothers is not recommended.

Geriatric Use: The safety and efficacy of ZYRTEC has been demonstrated in patients 65 years and older (84). As with the general population, clearance of ZYRTEC is reduced in proportion to creatinine clearance (35).

Pediatric Use: In more than 588 children aged 6 to 11 years, ZYRTEC was administered in doses from 1.25 to 10 mg. In these studies ZYRTEC was well-tolerated at doses up to 10 mg (85,86). The safety of ZYRTEC in children under the age of 6 years has not yet been established. ZYRTEC is not indicated for the treatment of children under the age of 12 years.

Reviewer's comments:

Although the statement that more than 588 have received Zyrtec is probably correct, the data received in the safety update of 4/25/95, 588 patients form this dataset. These patients received 1.5 to 10 mg of cetirizine for up to 5 weeks. Reference is made to safety update section D.3, vol 35.2, page 9 32-33. Unless the chosen one it is the customary way for labeling the number of patients that were studied, the following changes to the above underlined statement are recommended:

In clinical trials where 588 children aged 6-11 years participated, ZYRTEC was administered in doses from 1.25 to 10 mg up to 5 weeks. These patients had a mean body weight of 75 lbs (range 34-232).

Reviewer's comments:

Following the Division's recommendations based on the Pediatric Rule the following statement should be deleted:

ZYRTEC is not indicated for the treatment of children under the age of 12 years.

ADVERSE REACTIONS

Controlled and uncontrolled clinical trials included more than 6000 patients, with more than 3900 receiving ZYRTEC at doses of 5 to 20 mg per day; the duration of treatment ranged from 1 week to 6 months (87). In addition, there were more than 1400 ZYRTEC treated patients in foreign clinical trials.

Reviewer's comments:

The following change is recommended:

Controlled and uncontrolled clinical trials included more than 6000 patients, with more than 3900 receiving ZYRTEC at doses of 5 to 20 mg per day; **in adults** the duration of treatment ranged from 1 week to 6 months, **with a mean duration of exposure of 30 days.**

Reviewer's comments:

There were 3982 adult patients in the cumulative database that were exposed to cetirizine for up to 6 months. The mean duration of exposure to cetirizine in the cumulative database was 30.1 days. The total number of adult patients exposed to cetirizine for more than 12 week and up to 6 months was 237. Refer to Table F1.C, vol 35.3, included in **Appendix 4.**

Reviewer's comments:

This reviewer could not find the reference to the number of patients listed as having received cetirizine as part of foreign clinical trials. The reference for the total number of adult patients treated with cetirizine is not part of the 4/25/95 safety update. In the 6/7/95 N (BM), the number of patients that received cetirizine in the 17 UCB trials that were submitted in the 4/25/95 safety update was recorded as 385. The following statement should have an annotated reference or it should be deleted:

there were more than 1400 ZYRTEC treated patients in foreign clinical trials.

Most adverse reactions reported during therapy with ZYRTEC were mild or moderate (88). In placebo-controlled trials, the incidence of discontinuations due to adverse reactions in patients receiving ZYRTEC 5 mg or 10 mg was not significantly different from placebo (2.9% vs 2.4%, respectively) (89).

Reviewer's comments:

The following change is recommended:

In placebo-controlled trials, the incidence of discontinuations due to adverse reactions in patients

receiving ZYRTEC 5 mg or 10 mg was not significantly different from placebo (2.6% (11/430) and 3.0% (44/1489) for 5 and 10 mg of cetirizine respectively versus 2.4% (37/1521) for placebo treated patients).

In reference 89, the recorded number of discontinued patients in placebo-controlled, fixed-dose studies that received cetirizine 5 or 10 mg is listed as 2.9% (59/2034). In the following section (D.5.c, vol 35.2 page 9 37) the recorded number of discontinued patients in placebo-controlled, fixed-dose studies is listed as 2.6% (11/430) for 5 mg of cetirizine, 3.0% (44/1489) for 10 mg cetirizine and 2.4% (37/1521) for placebo treated patients.

The most common adverse reactions at the recommended doses were headache and somnolence (89). The incidence of headache associated with ZYRTEC was not different from placebo (89). The incidence of somnolence associated with ZYRTEC was dose related (90) and, predominantly, mild to moderate (88). The incidence of somnolence in fixed dose studies was 6% in placebo, 11% at 5 mg and 14% at 10 mg (90).

Reviewer's comments:

The following changes are recommended:

The incidence of somnolence in fixed dose studies was 6% in placebo, 11% at 5 mg and 14% at 10 mg. **These were significantly different from placebo (90).**

The reference for this change is also the annotated reference #90 (SU 4/25/95, vol 35.2 page 9 38).

Discontinuations due to somnolence for ZYRTEC (91) were not significantly different from placebo (1.0% vs 0.6%, respectively). In addition, fatigue and dry mouth were also considered treatment-related adverse reactions. There was no difference by age, race, gender or by body weight with regard to the incidence of adverse reactions (92-94).

Table 1 lists adverse experiences which were reported for ZYRTEC 5 and 10 mg in controlled clinical trials in the United States (89).

Table 1. Adverse Reactions Reported in Placebo-Controlled United States ZYRTEC Trials (Maximum Dose of 10mg) at Rates of 1% or Greater

(Percent Incidence)

Adverse Experience	ZYRTEC (N=2034)	Placebo (N=1612)
Headache	17.6%	17.9%
Somnolence	13.7	6.3
Fatigue	5.9	2.6
Dry Mouth	5.0	2.3
Nausea	2.5	2.9
Pharyngitis	2.0	1.9
Dizziness	2.0	1.2
Insomnia	1.4	1.2
Epistaxis	1.2	0.6
Coughing	1.0	0.6
Abdominal Pain	1.0	0.9
*Dyspepsia	0.8	1.6
Pruritus	0.3	1.2

Reviewer's comments:

The following change to the above table is recommended:

Delete the rows for dyspepsia and pruritus.

Note: dyspepsia is misspelled in the table. The incidence rates of dyspepsia and pruritus do not need to be included in the above table, since the intent was to include only those adverse events that had an incidence of 1% or greater in the cetirizine treated group.

The following events were observed infrequently (equal to or less than 1%), in 3982 patients who received ZYRTEC in U.S. trials, including an open study of six months duration (88); a causal relationship with ZYRTEC administration has not been established.

Application Site: application site reaction, injection site inflammation

Autonomic Nervous System: anorexia, urinary retention, flushing, saliva increased

Cardiovascular: palpitation, tachycardia, hypertension, arrhythmia, cardiac failure

Central and Peripheral Nervous Systems: paresthesia, confusion, hyperkinesia, hypertonia, migraine, tremor, vertigo, cramps legs, ataxia, dysphonia, coordination abnormal, hyperesthesia, hypoesthesia, myelitis, paralysis, ptosis, speech disorder, twitching, visual field defect

Endocrine: thyroid disorder

Gastrointestinal: appetite increased, dyspepsia, abdominal pain, diarrhea, flatulence, constipation, vomiting, stomatitis ulcerative, tongue disorder, tooth caries aggravated, stomatitis, tongue discoloration, tongue edema, gastritis, hemorrhage rectum, hemorrhoids, melena, hepatic function abnormal

Genitourinary: polyuria, urinary tract infection, cystitis, dysuria, hematuria, urine abnormal

Hearing and vestibular: earache, tinnitus, deafness, ototoxicity

Metabolic/Nutritional: thirst, edema, dehydration, diabetes mellitus

Note: thirst is misspelled in this listing.

Musculoskeletal: myalgia, arthralgia, bone disorder, arthrosis, tendon disorder, arthritis, muscle weakness

Psychiatric: insomnia, nervousness, depression, emotional lability, concentration impaired, anxiety,

depersonalization, paroniria, thinking abnormal, agitation, amnesia, libido decreased, euphoria

Resistance Mechanism: healing impaired, herpes simplex, infection, infection fungal, infection viral

Respiratory System: epistaxis, rhinitis, coughing, respiratory disorder, bronchospasm, dyspnea, upper respiratory tract infection, hyperventilation, sinusitis, sputum increased, bronchitis, pneumonia

Reproductive: dysmenorrhea, menstrual disorder, breast pain female, intermenstrual bleeding, leukorrhea, menorrhagia, pregnancy unintended, vaginitis, testes disorder

Reticuloendothelial: lymphadenopathy

Skin: pruritus, rash, skin disorder, skin dry, urticaria, acne, dermatitis, rash erythematous, sweating increased, alopecia, angioedema, furunculosis, bullous eruption, eczema, hyperkeratosis, hypertrichosis, photosensitivity reaction, photosensitivity toxic reaction, rash maculo-papular, seborrhea, purpura

Special Senses: taste perversion, taste loss, parosmia

Vision: eye abnormality, vision abnormal, eye pain, conjunctivitis, xerophthalmia, glaucoma, ocular hemorrhage

Body as a Whole: weight increase, back pain, malaise, pain, chest pain, fever, asthenia, edema generalized, edema periorbital, edema peripheral, rigors, edema legs, face edema, hot flushes, abdomen enlarged, allergic reaction, nasal polyp

Occasional instances of transient, reversible hepatic transaminase elevations have occurred during cetirizine therapy (95).

Reviewer's comment:

The following changes to the above underlined statement are recommended:

Occasional instances of transient, reversible hepatic transaminase elevations have occurred during cetirizine therapy. The incidence of abnormal hepatic transaminases in all cetirizine treated patients that were considered to be clinically significant and possibly related to study medication was: SGOT 27/ 2979 (1%) and SGPT 52/2926 (2%); for placebo treated patients it was: SGOT 6/1525 (0%) and for SGPT 12/1480 (1%). Regardless of attributable cause, the incidence of abnormal SGOT, more than twice the upper limit of normal, appears to be similar in cetirizine and placebo treated patients (0.4%); for SGPT the incidence is (0.3%) for cetirizine versus (0.1%) in placebo treated patients.

The incidence of abnormal hepatic transaminases in all cetirizine treated patients that were considered to be clinically significant and possibly related to study medication was: SGOT 27/ 2979 (1%) and SGPT 52/2926 (2%) -SU 4/25/92, vol 35.2, page 9 58. For placebo treated these incidences were: SGOT 6/1525 (0%) and for SGPT 12/1480 (1%), Table F 23.B in SU 4/25/95, vol 35.3, page 9 322.

The majority of the SGOT and SGPT abnormalities regardless of attributable causality are generally less than twice the upper limit of normal. Regardless of attributable cause, the incidence of abnormal SGOT more than twice the upper limit of normal appear to be similar in cetirizine and placebo treated patients (0.4%), for SGPT the incidence is (0.3%) versus (0.1%) -SU 4/25/95, vol 35.2 page 9 60.

In foreign marketing experience the following additional rare, but potential severe adverse events have been reported: hemolytic anemia, thrombocytopenia, orofacial dyskinesia, severe hypotension, anaphylaxis, hepatitis, glomerulonephritis, stillbirth, and cholestasis (96).

In a six-week, placebo-controlled study of 186 patients with allergic rhinitis and mild to moderate asthma, ZYRTEC 10 mg QD improved rhinitis symptoms and did not alter pulmonary function. This study

supports the safety of administering ZYRTEC to allergic rhinitis patients with mild to moderate asthma (101).

DRUG ABUSE AND DEPENDENCE

There is no information to indicate that abuse or dependency occurs with ZYRTEC.

OVERDOSAGE

Overdosage has been reported with ZYRTEC. In one patient who took 150 mg of ZYRTEC,

the patient was somnolent but did not display any other signs or abnormal blood chemistry or hematology results (97). Should overdose occur, treatment should be symptomatic or supportive, taking into account any concomitantly ingested medications. There is no known specific antidote to ZYRTEC. ZYRTEC is not effectively removed by dialysis, and dialysis will be ineffective unless a dialyzable agent has been concomitantly ingested (37). The minimal lethal oral dose in rodents is approximately 100 times the maximum recommended clinical dose on a mg/m² basis and the liver was the target organ of toxicity (98).

DOSAGE AND ADMINISTRATION

The recommended initial dose of ZYRTEC is 5 or 10 mg, depending on symptom severity. Most patients in clinical trials started at 10 mg (99). ZYRTEC is given as a single daily dose, with or without food. The time of administration may be varied to suit individual patient needs.

In patients with decreased renal function (creatinine clearance 11-31 ml/min), patients on hemodialysis (creatinine clearance less than 7 mL/min), and in hepatically impaired patients, a dose of 5 mg QD is recommended.

HOW SUPPLIED:

ZYRTEC tablets are white (dye free), film coated, rounded-off rectangular shaped containing 5 mg or 10 mg cetirizine hydrochloride.

5 mg tablets are engraved with "PFIZER" on one side and with "550" on the other. Bottles of 100: (NDC 0069-5500-66)

10 mg tablets are engraved with "PFIZER" on one side and with "551" on the other. Bottles of 100: (NDC 0069-5510-66)

Cetirizine is licensed from UCB, Pharma Inc.

STORAGE: Store at room temperature 59° to 86°F (15° - 30°C).

Appendix 1

Protocol No.: 93CK16-0624

Study No.: 93-N-0096

Title: A multiple dose study to evaluate the pharmacokinetics and/or ECG effects on concomitant administration of a course of azithromycin therapy with cetirizine

Study design: Randomized, multiple dose, open (except that the cardiologist reading the ECGs was blinded), parallel group study. Subjects were randomized to one of three treatment groups, which received the following regimes during an 11-day period of drug administration:

Group A	Day 1:	placebo QD
	Days 2-6:	20 mg cetirizine QD
	Day 7:	500 mg azithromycin QD/20 mg cetirizine QD
	Days 8-11:	250 mg azithromycin QD/20 mg cetirizine QD
Group B	Day 1:	placebo QD
	Days 2-6:	20 mg cetirizine QD
	Day 7:	20 mg cetirizine QD
	Days 8-11:	20 mg of cetirizine QD
Group C	Day 1:	placebo QD
	Days 2-6:	placebo QD
	Day 7:	placebo QD
	Days 8-11:	placebo QD

ECGs were recorded on Days 1, 6, and 11 immediately prior to dosing and 1, 2, 3, 4, 6, 8, 10, 12 and 16 hours post-dose. ECGs were also recorded prior to dosing, 1 and 24 hrs post-dose on days 2 and 7, and 24 hours after the Day 11 dose (morning of Day 12).

Blood samples for the determination of plasma cetirizine and azithromycin levels were obtained immediately prior to dosing and 1, 2, 3, 4, 6, 8, 10, 12 and 16 hours post-dose on Days 6 and 11. Blood samples were obtained pre-dose and 1 hr post-dose on days 1, 2 and 7, and additionally 24 hours post-dose on Days 2 and 7. A final blood sample was obtained 24 hours after the Day 11 dose (morning of Day 12).

Analysis: ECGs. For study Days 6 and 11 separately, the following variables were computed for changes from baseline in the electrocardiographic QT interval,

using Hodges correction. AVGCHG (the mean of the 11 changes over hour 0-24), AUCCHG (the area under the change curve from hour 0 to 24 calculated by the trapezoidal rule), MAXCHG (the maximum of the 11 changes (sign included) over hour 0-24, HR2CHG (change at hour 2 only). These ECG parameters were analyzed comparatively among treatments using analysis of variance procedures appropriate to a repeated measures model. For each on-drug ECG recording in each subject (including Days 2, 6, 7 and 11) the percent change from baseline in Hodges QTc was determined, and the number of occurrences of prolongations of 10% or greater over baseline was computed for each treatment group.

PK. The following pharmacokinetic parameters were determined for cetirizine on Day 6 and 11, for subjects in Group A and B: AUC (24), Cmax, Tmax and T1/2. These parameters, excluding T1/2, were also calculated for azithromycin on Day 11, for subjects on Group B. **Statistical analyses were performed only for the cetirizine data.** An analysis of variance was performed on log transformed cetirizine PK parameters in subjects in Group B, for Day 11 vs Day 6. Geometric mean ratios of the parameters for Day 11 versus Day 6 and 90% confidence intervals for these ratios were obtained by reexponentiation of the results of the analysis. The same analysis was used to make the following additional comparisons of cetirizine parameters: 1) Day 6 values for Group A versus Day 6 values for Group B and 2) Day 11 values for Group A versus Day 11 values for Group B.

Results: Forty two healthy male subjects entered and completed the study. There were 14 subjects in each of the three treatment groups. **All three treatment groups showed small mean increases from baseline after 5 and 10 doses of study drug with respect to each of the four derived QTc variables (with the exception of HR2CHG for the cetirizine only group, which was a small decrease from baseline), but differences among groups were not statistically significant for any analysis.**

Mean AVGCHG at Study Day 6 was an increase of 0.27 msec in the combination treatment group (which represents cetirizine alone given for 5 days) and an increase of 0.69 msec in the cetirizine only group. Combining these two mean changes yields a mean increase from baseline in Hodges QTc after 5 doses of cetirizine of 0.48 msec compared to a 1.62 msec in the placebo group. At Study Day 11, the mean AVGCHG of 2.41 msec for combination treatment, 2.01 msec for cetirizine and 1.33 msec for placebo were not significantly different among groups. The treatment day interaction in the repeated analysis of variance, which measures the difference among treatment groups with respect to the changes in QTc from Day 6 to Day 11, was not statistically significant. The results for AUCCHG,

MAXCHG, and HR2CHG parallel the results described above for AVGCHG.

The incidence of prolongation of 10% or greater over baseline Hodges QTc in the three treatment groups did not suggest any effect of cetirizine or the combination on QT intervals. Up to Study Day 6, only one subject in the placebo group experienced a prolongation of 10% or greater over baseline. For the period after Study Day 6, three subjects in the cetirizine only group and a subject in the placebo group had a single occurrence each of a Hodges QTc prolongation of 10% or greater than baseline. The maximum prolongation over baseline recorded for individuals while taking placebo and cetirizine and placebo were 16% and 14%, respectively. In the cetirizine/azithromycin combination group, no subject had a prolongation in Hodges QTc that was 10% or greater.

Three subjects (21%) in Group A (cetirizine/azithromycin) reported dizziness, and one subject (7%) in Group B (cetirizine alone); none of the subjects in the placebo group reported dizziness. Tachycardia was reported by two subjects (14%) in Group B and one subject (7%) in Group C (placebo).

Four subjects (two in Group A and two in Group B) had elevated SGOTs and SGPTs that were clinically significant and possibly related to study medication (Category 9). In the investigator's opinion, these elevations (maximum recorded SGOT and SGPT values were 67 mu/mL, and 107 mu/ml, respectively) were not clinically significant. In three of the four subjects these values declined to within the normal range at a follow up determination.

There were no significant differences in mean cetirizine AUC (24), C max or Tmax on Day 11 compared to Day 6, among subjects in Group B, indicating that steady state had been reached by Day 6 or before. No differences were found in cetirizine pharmacokinetic parameter between Group A and Group B for Day 6. It is assumed that steady state was reached by Day 6 or before in these two groups. There were no significant differences in Day 11 values of cetirizine AUC (24), Cmax or Tmax in group a compared with Group B, indicating that the addition of azithromycin does not affect steady state plasma concentration of cetirizine.

The results from the combination azithromycin-cetirizine cannot be compared to the results using azithromycin alone. However, according to the sponsor

the results using the combination are comparable with single dose administration data (azithromycin) from other studies.

Sponsor's conclusion:

The results indicate that cetirizine 20 mg QD administered for ten 10 does not affect the QT interval. There is no indication that concomitant administration of azithromycin and cetirizine produces any significant changes in QT interval. No pharmacokinetic interaction occurs when subjects who are taking cetirizine and have attained steady state levels of the drug are additionally administered the five-day recommended dosage regimen of azithromycin. Cetirizine alone and in combination with azithromycin was well tolerated in this study.

Reviewer's comments:

After reviewing the study the following questions were faxed to the Sponsor August 4, 1995. For clarity the questions are bolded and a summary of the response that was submitted and the amendment to the NDA dated, 8/11/95, follows.

1. **Please provide the corresponding ECG values in the format of Appendix F.2 in vol 14, for the following ECGs with QTc prolongations that are listed in Table 1.5, vol 1:**

Cetirizine pt. # 25 Treatment Day 9 (Study Day 10) Hour 0
Day 10 : QTc 410 (Bazzet), 12.02% increase QTc Bazzet

Cetirizine pt. #38 Treatment Day 3 (Study Day 4) Hour 6
Day 4: QTc 436 (Bazzet), 10.66% increase QTc Bazzet

Cet/Azi pt. #35 Treatment Day 9 (Study Day 10) Hour 0
Day 10: QTc 427 (Bazzet), 17.96% increase QTc Bazzet

Cet/ Azi pt. #39 Treatment Day 9 (Study Day 10) Hour 0
Day 10: QTc 431 (Bazzet), 12.53% increase QTc Bazzet

Placebo pt. #12 Treatment Day 9 (Study Day 10) Hour 0
Day 10: QTc 435 (Bazzet), 12.40% increase QTc Bazzet

Placebo pt. # 33 Treatment Day 9 (Study Day 10) Hour 0
Day 10: QTc 433 (Bazzet), 13.05% increase QTc Bazzet

Please explain why the corresponding ECG values for the above patients were not included in the Appendix F.2 listing and what was the reason for obtaining these ECGs out of the regular protocol schedule. Please submit the listings for any other ECGs obtained out of the regular protocol

schedule. Please explain why they were obtained and why they were not included in the Appendix F.2 listing.

The investigator made 104 additional ECG's that were not required by the protocol schedule; the protocol allowed it to ensure the safety of the subjects. Prior to the study the investigator informed Pfizer that they would obtain ECGs at 0 hrs on days 9 and 10 for all 42 subjects. This accounts for 83 of the 104 unscheduled ECGs (subject #9 did not have day 9 hour 0 ECG). Additionally, 12 ECGs were obtained on unscheduled days. A specific safety reason was described for only one of these subjects (Subject #38, Day 4, Hour 4) and the reason given was because of an increase QTC from baseline. Of the remaining 9 ECGs, all were repeat ECGs made back to back with a scheduled ECG. No specific safety reason was given for 7 of these ECGs and 2 ECGs were obtained because the investigator noted a greater than 20% increase change from baseline (Subject #6, Day 11, Hour 6 on placebo; and Subject #13, Day 11, Hour 0, on combination). In both instances the repeat ECG was normal and the cardiologist's blinded reading did not indicate greater than 20% increase in QTC.

All the analyses presented as well as that of the derived variables were based on the scheduled ECGs. The analysis of QTC prolongations over 10% predicted included days other than 6 and 11, but only included the scheduled ECGs. The Appendix F.2 data listing was intended to provide the actual data used in the data analysis and therefore did not include "unscheduled" ECGs.

The inclusion of "unscheduled" QTC readings in the analysis would only have affected the account of 10% prolongations over baseline Hodges presented in Tables 3 and 4 of the summary. This analysis was rerun including the 103 on treatment extra QTC's and no additional 10% prolongations (based on the Hodges QTC's) were found.

In regard to Table 1.5 in volume 1 of the safety update 4/25/95, all QTC readings, including the unscheduled reading were included. Although this deviation from the analysis should have been noted in the response, the results do not impact the conclusions of the study.

2. Please provide us with an analysis for Max QTC change (MAXCHG) using the Bazett formula as was provided in Table E.1.3 using the Hodges formula.

Attached see Table E.2.2

The largest values for MAXCHG for Day 6 and 11 were observed in the placebo treated group. The significant statistical change is observed between the cetirizine group and the combination, result from the lower change in the cetirizine group for Day 6 and an apparent larger change from Day 6 to Day 11 compared to the other groups. This results do not indicate any effect of cetirizine alone or in combination with azithromycin on the maximum change from baseline Bazzet QTc.

Reviewer's comments:

After reviewing the data submitted (8/11/95) as response to our fax the following are noted.

1. From the group of unscheduled ECGs, those that had a Bazzet QTc prolongation of 10% or greater were included in the response to Question 1 of our approvable letter.
2. The sponsor should have noted the existence of the 104 unscheduled ECGs in the study report and in their initial response.

The following Tables list the # of patients with QTc prolongations of 10% or greater along with those patient that in addition had a QTc of 440 msec or longer by treatment days.

Placebo treatment:

Days	# patients with QTc prolongation 10% or greater	# ECGs, QTc 10% or greater	# ECGs, QTc > 440
1-5	6	14	5
6-9	3	3	0
10	7	11	4

After reviewing the individual patient data, for Days 1-5 in placebo treated patients there is one subject #36 that accounts for 4/5 of the ECGs with QTc of 440msec or longer, and of 5 ECGs that have a QTc with a 10% prolongation ore greater (range from 10.9% to 16.7% over baseline).

Cetirizine treated patients:

Days	# of patients with QTc prolongation 10% or greater	# ECGs, QTc 10% or greater	# ECGs, QTc>440
1-5	4	4	1
6-9	3	3	0
10	7	12	5

Combination treatment:

Days	# of patients with QTc prolongation 10% or greater	# ECGs, QTc 10% or greater	# ECGs, QTc>440
5*	5	6	3
6-9	5	5	1
10	4	7	2

* Please note that from days 1-5 inclusive patients were receiving only cetirizine

In the attached Table E.2.2., the statistical difference between cetirizine and the combination is $p=0.02$ for the treatment effect from Day 6 to Day 11. We would have expected the patients for both cetirizine and combination to have approximate equal Day 6 change, since the two groups were receiving the same drug for those 5 days of treatment. However, the cetirizine only group had a lower increase in QTc, than the combination, in this reviewer agrees with the Sponsor's interpretation for Day 6, since in addition the baseline QTc for cetirizine was 425 msec and for the combination it was 429 msec.

However, when the treatment effect from Day 6 to Day 11 is calculated, (Day 11-Day 6) cetirizine group it is 13.41 msec, versus the -1.43 in the combination and 3.14 in the placebo treated group. Using the Hodges correction as depicted in Table E.1.3. p11 550 vol 35.14, the maxchange (Day 11-Day6) for cetirizine treated patients was 6.79, versus 0.43msec for the combination and 1.79 for placebo. The mean increase for cetirizine treated patients in the cetirizine -ketaconazole study (Hodges) at 10 days of treatment was 8.2 msec. The results of this study suggest that the combination of cetirizine/azithromycin is favorable in decreasing the expected increase in QTc that has been observed in cetirizine treated

PROTOCOL 93CK16-0624: A MULTIPLE DOSE STUDY TO DETERMINE THE INTERACTION OF CETIRIZINE WITH AZITHROMYCIN IN YOUNG HEALTHY MALES

TABLE E.2.2
STATISTICAL ANALYSIS OF MAXCHG: MAXIMUM QTc CHANGE FROM BASELINE FROM HOUR 0 TO 24.
QT CORRECTED BY BAZETT FORMULA

OBSERVED MEAN CHANGE FROM BASELINE ± STD DEVIATION BY TREATMENT (MSEC)

TREATMENT PERIOD	PLACEBO	CETIRIZINE	CETIRIZINE/ COMBINATION ¹	P-VALUE OVERALL ²	ESTIMATED CETIRIZINE EFFECTS ³	ESTIMATED COMBINATION EFFECT
(NO. SUBJ)	(14)	(14)	(14)			
BASELINE	425.71 ± 19.66	425.43 ± 14.16	429.43 ± 14.70			
DAY 6 CHANGE	40.14 ± 17.35	20.79 ± 14.94	36.07 ± 13.79	.156	-7.71 (P=.135)	
DAY 11 CHANGE	45.29 ± 16.22	42.50 ± 19.45	34.64 ± 16.85	.364	-0.79 (P=.906)	-8.64 (P=.201)

TREATMENT EFFECTS FROM DAY 6 TO DAY 11 (DAY 11 - DAY 6)	3.14 ± 20.72	13.71 ± 13.53	-1.43 ± 13.49			

ANALYSIS OF VARIANCE(SAS TYPE III MS)

EFFECT	DF	MEAN SQUARE	F-RATIO	P-VALUE	P-VALUES FOR DIRECT PAIRWISE COMPARISONS OF TREATMENT EFFECTS FROM DAY 6 TO DAY 11	
					CETIRIZINE	COMBINATION
TREATMENT	2	361.00	0.87	.4262		
SUBJ(TREAT)	39	414.14	3.13	.0003		
DAY	1	555.43	4.19	.0473		
TREAT*DAY ⁴	2	422.29	3.19	.0522	PLACEBO	0.0936
ERROR	39	132.44			CETIRIZINE	0.4618
						0.0184

¹SUBJECTS RECEIVED CETIRIZINE ALONE UP TO STUDY DAY 6 AND THEN RECEIVED CETIRIZINE + AZITHROMYCIN STARTING ON DAY 7.

²FROM ONE-WAY ANOVA F-TEST.

³FOR DAY 6 THE ESTIMATED CETIRIZINE EFFECT IS (.5 X CETIRIZINE MEAN + .5 X COMBINATION MEAN) MINUS PLACEBO MEAN. FOR DAY 11 THE ESTIMATED EFFECTS ARE THE RESPECTIVE PAIRWISE DIFFERENCES FROM PLACEBO.

⁴CORRESPONDS TO THE OVERALL DIFFERENCE IN TREATMENT EFFECTS FROM DAY 6 TO DAY 11.

PROGRAM: C62404A SAS ON CLAL DATE: 08AUG95, TIME: 13:41

patients after 10 days of treatment.

This study lacked a treatment arm that started patients on azithromycin and then added the cetirizine. In addition it was not a cross over study. The results in terms of changes on QTc can only be stated as suggestive. The possibility of an interaction of azithromycin with the enantiomer of cetirizine that according to animal studies is more extensively metabolized by the liver, could be considered. However, the data in this study does not support at this time, a definite QTc change with the azithromycin interaction that should be included in the labeling.

3. Please provide us with follow up values for SGOT and SGPT for patient # 17. The last reported values were SGOT=61 and SGPT=107 mu/mL. If these are not available, please explain. Please contact the investigator to obtain a follow up in this patient.

No additional information was obtained after contacting the investigator.

Reviewer's comments:

It had been noted in the cetirizine database the 1-2% increases in liver transaminases. In the cetirizine/erythromycin study 4 cases were noted out of 16 subjects. In this study, 1/14 subjects develop the increase in enzymes by Day 5 of treatment on cetirizine alone before receiving the combination, 2/14 on cetirizine alone by Day 11 and one on the combination by Day 11. No patient treated with placebo has an elevation in liver transaminases that is considered to be of category 9. In three of the 4 subjects we have values returning to normal after the drug is discontinued at the end of the study.

As noted elsewhere in the reviewer's comments to the labeling, the statement regarding elevation of liver transaminases needs to be more specific than the one proposed by the Sponsor.

4. Please provide us with the individual patient listing for concomitant medications in this study.

The only additional concomitant medication in this study was Keri Lotion by two subjects.

Appendix 2

Refer to Sponsor's response to item 2 of the cetirizine approvable letter dated 2/21/95 in the SU 4/25/95, vol 35.1 and to the MOR for NDA 20346 March 18, 1994.

PEDS-4: Multicenter [(12), Albany, N.Y.; Minneapolis, MN; Dallas, TX; Aurora, CO; San Diego, CA; Atlanta, GA; Overland Park, KS; Sylvania, OH; East Meadow, NY; Bend, OR; Oregon, CA; Gainesville, FL], randomized, double-blind, multicenter, parallel study. Patients (6-11 yrs old) were treated for 4 weeks, during the ragweed pollen season. The randomization was stratified by entry weight to ensure patients 25 kg (55 lbs) or greater and patients less than 25 kg will be equally distributed, across all 3 treatment groups: cetirizine 5 mg Q.A.M., cetirizine 10 mg Q.A M , or placebo.

"The protocol required that ECGs be recorded at the week 2 visit, but many were recorded at the end of week 3 or week 4. In many cases recordings were made at week 2 and repeated at the end of treatment. Accordingly, an endpoint analysis was conducted on the change from baseline to the last ECG recorded.

All cases were included in this analysis regardless of time on treatment to last ECG, including discontinued patients, providing both a baseline and endpoint value were available. Five patients (2 placebo cases, 1 cetirizine 5 mg case and 2 cetirizine 10 mg cases) had their full ECG recorded more than two days after the last dose of medication and one patient's baseline ECG was obtained during treatment. A subset analysis was also conducted which excluded these cases to account for any possible biases related to the withdrawal of study drug. Also, in order to conform to the protocol, a subset analysis was conducted which included only those ECGs recorded 11 to 17 days after the first dose (i.e., within ± 3 days of the end of week 2 visit on day 14). If more than one ECG was recorded, the recording made closest to day 14 of treatment was included. Since some study sites consistently, recorded ECGs at the end of treatment only, all their follow-up ECG data did not conform to the 11 to 17 day window. Therefore, these sites (92NO042, 92NO043 AND 92NO044) were completely excluded from the 11 to 17 day window analysis."

"The mean change from baseline and percent change from baseline for Peds-4 included in the report filed on September 2, 1993 using the Bazzet's correction. At that time it included ECGs within 48 hrs after the last dose. In this submission the analyses were revised to exclude any

ECGs recorded more than 24 hrs after the last dose."

"The patient groupings used in the original report to NDA 20346 (9/2/93) were also used in this report:

1. Includes patients with QT recorded in the 11 to 17 day window after the first dose of study drug
2. Includes all patients for the endpoint change (i.e. the last recorded).
3. Includes all patients for the maximum change.

Analysis 3 was added to this response as a supplement. Analysis 1 and 2 differed from the original in that 2 or 3 patients were reduced from the original analysis and in several instances where a patient had multiple ECGs, a different endpoint may have been selected."

Change from baseline for ECGs recorded within days 11-17 of first dose from Table 2.1:

Number of patients	Placebo 40	Cet 5 mg 35	Cet 10 mg 44	p-value
QTc (Bazett)				
Baseline	425.05 +/- 25.47	417.36 +/- 25.33	420.54 +/- 22.34	
Change	-0.79 +/- 24.25	-0.08 +/- 35.67	10.32 +/- 25.18	
(p-value within)	0.833	0.970	0.015	0.061
Adjusted change	1.77	-2.52	9.94	

Change from baseline for ECGs recorded last or maximum ECG recorded on treatment (11-17 Days ECGs), from Table 2.2:

Number of patients	Placebo 64	Cet 5 mg 64	Cet 10 mg 65	p-value
QTc (Bazett)				
Baseline	418.93 +/- 24.88	421.02 +/- 25.98	421.15 +/- 21.31	
Change	-5.89 +/- 27.21	-2.84 +/- 31.52	10.22 +/- 24.84	
(p-value within)	0.107	0.887	0.002	0.006
Adjusted change	4.92	-2.40	10.73	

Distribution of percent change from baseline for ECGs recorded within days 11-17 of first dose, from Table 2.4:

	under 5%	5- <10%	10- <20%
Placebo-# of pts.	32	6	2
Row %	80%	15%	5%
5 mg cet	27	4	4
Row %	77.14%	11.43%	11.43%
10 mg cet	31	7	6
Row %	70.45%	15.91%	13.64%

Reviewer's comments:

There is a persistent increase in QTc change from baseline observed in the 10 mg treated cetirizine patients of approximately 10 msec for the group of patients that had their ECGs within 11 to 17 post dose, Table 2.1. This prolongation in QTc is also observed for the maximum QTc prolongation in ECGs for cetirizine treated patients when all patients were considered, Table 2.2.

The above noted differences in cetirizine treated patients are not statistically significant against placebo, but it is consistent in both analyses. It is important to consider that this study was not originally designed to detect such differences.

Appendix 3

Table: Incidence and median exposure of medication categories during placebo controlled studies; SU 4/25/95, vol 35.4, Appendix G, page 9 657

POOLED CETIRIZINE PROTOCOLS

TABLE : INCIDENCE AND MEDIAN EXPOSURE OF MEDICATION CATEGORIES DURING PLACEBO-CONTROLLED STUDIES.

MEDICATION CATEGORIES	--- CETIRIZINE --- (N=2679)		----- PLACEBO ----- (N=1671)	
	INCIDENCE	EXPOSURE (DAYS)	INCIDENCE	EXPOSURE (DAYS)
NSAID	376 (14.0%)	4.0	282 (16.9%)	4.0
CORTICOSTEROIDS	196 (7.1%)	7.0	123 (7.4%)	7.0
BIRTH CONTROL	185 (6.9%)	29.0	142 (8.5%)	26.0
BETA AGONIST	179 (6.7%)	27.0	97 (5.8%)	22.0
THIAZIDE & RELATED AGENTS	93 (3.5%)	22.0	67 (4.0%)	21.0
THYROID	44 (1.6%)	15.5	51 (3.1%)	20.0
PENICILLINS	44 (1.6%)	8.0	33 (2.0%)	8.0
H2 INHIBITOR	20 (0.7%)	16.0	14 (0.8%)	15.0
CEPHALOSPORIN	11 (0.4%)	8.0	7 (0.4%)	7.0

PATIENTS MAY BE INCLUDED IN MORE THAN ONE CATEGORY.

* EACH PATIENT IS COUNTED ONLY ONCE ON THIS LINE.

PROGRAM: CSFICMVC SAS IN C.MN
DATE : 11APR95 TIME: 9:16

9 657

Table: Incidence and median exposure of medication categories during all studies; SU 4/25/95, vol 35.4, Appendix G, page 9 658

POOLED CETIRIZINE PROTOCOLS

TABLE : INCIDENCE AND MEDIAN EXPOSURE OF MEDICATION CATEGORIES DURING ALL STUDIES.

MEDICATION CATEGORIES	--- CETIRIZINE ---	
	(N=8982) INCIDENCE	EXPOSURE (DAYS)
NSAID	603 (15.1%)	5.0
BIRTH CONTROL	345 (8.7%)	15.0
BETA AGONIST	245 (6.2%)	24.0
CORTICOSTEROIDS	222 (5.6%)	7.0
THIAZIDE & RELATED AGENTS	125 (3.1%)	10.0
PENICILLINS	92 (2.3%)	10.0
THYROID	68 (1.7%)	15.0
H2 INHIBITOR	26 (0.7%)	14.5
CEPHALOSPORIN	25 (0.6%)	11.0

PATIENTS MAY BE INCLUDED IN MORE THAN ONE CATEGORY.

* EACH PATIENT IS COUNTED ONLY ONCE ON THIS LINE.

PROGRAM: CSFICMC SAS IN C.ML
DATE : 11APR95 TIME: 9:16

9
628

Table: Incidence of adverse experiences in patients treated with cetirizine or placebo in placebo-controlled studies; SU 4/25/95, vol 35.4, Appendix G, page 9 667

TABLE : INCIDENCE OF ADVERSE EXPERIENCES IN PATIENTS TREATED WITH CETIRIZINE OR PLACEBO
IN PLACEBO-CONTROLLED STUDIES

ADVERSE EXPERIENCES	INCIDENCE IN SAFETY EVALUABLE PATIENTS			
	NSAID USER		NON-NSAID USER	
	CETIRIZINE NO. PTS. (%)	PLACEBO NO. PTS. (%)	CETIRIZINE NO. PTS. (%)	PLACEBO NO. PTS. (%)
TOTAL NO. OF PATIENTS	376	282	2303	1389
NO. OF PTS. WITH ADVERSE EXPERIENCES	251 (66.76%)	178 (63.12%)	987 (39.38%)	452 (31.10%)
HEADACHE	179 (47.61%)	122 (43.26%)	273 (11.85%)	188 (12.96%)
SOMNOLENCE	71 (18.88%)	18 (6.38%)	334 (14.50%)	87 (6.26%)
FATIGUE	27 (7.18%)	7 (2.48%)	128 (5.56%)	56 (4.02%)
MOUTH DRY	23 (6.12%)	8 (2.84%)	112 (4.86%)	31 (2.23%)
NAUSEA	10 (2.66%)	8 (2.84%)	56 (2.43%)	46 (3.31%)
DIZZINESS	6 (1.60%)	5 (1.77%)	41 (1.78%)	18 (1.30%)
PHARYNGITIS	12 (3.19%)	11 (3.90%)	35 (1.52%)	20 (1.44%)
INSOMNIA	5 (1.33%)	4 (1.42%)	29 (1.26%)	18 (1.30%)
EPISTAXIS	6 (1.60%)	3 (1.06%)	21 (0.91%)	8 (0.58%)
COUGHING	3 (0.80%)	4 (1.42%)	23 (1.00%)	7 (0.50%)
NERVOUSNESS	5 (1.33%)	2 (0.71%)	21 (0.91%)	12 (0.86%)
ABDOMINAL PAIN	6 (1.60%)	5 (1.77%)	18 (0.78%)	10 (0.72%)
DYSPEPSIA	3 (0.80%)	4 (1.42%)	21 (0.91%)	21 (1.51%)
RESPIRATORY DISORDER	7 (1.86%)	4 (1.42%)	17 (0.74%)	11 (0.79%)
RHINITIS	3 (0.80%)	1 (0.35%)	16 (0.69%)	9 (0.65%)
EARACHE	4 (1.06%)	2 (0.71%)	14 (0.61%)	8 (0.58%)
DIARRHEA	3 (0.80%)	2 (0.71%)	14 (0.61%)	15 (1.08%)
EYE ABNORMALITY	4 (1.06%)	0 (0.00%)	13 (0.56%)	6 (0.43%)
BACK PAIN	7 (1.86%)	7 (2.48%)	9 (0.39%)	4 (0.29%)
MALAISE	4 (1.06%)	2 (0.71%)	12 (0.52%)	4 (0.29%)
APPETITE INCREASED	1 (0.27%)	1 (0.35%)	14 (0.61%)	4 (0.29%)
WEIGHT INCREASE	2 (0.53%)	1 (0.35%)	11 (0.48%)	5 (0.36%)
PAIN	4 (1.06%)	5 (1.77%)	7 (0.30%)	1 (0.07%)
PALPITATION	1 (0.27%)	1 (0.35%)	10 (0.43%)	4 (0.29%)
PARESTHESIA	3 (0.80%)	1 (0.35%)	8 (0.35%)	2 (0.14%)
PRURITUS	0 (0.00%)	2 (0.71%)	11 (0.48%)	20 (1.44%)
DYSMENORRHEA	7 (1.86%)	5 (1.77%)	3 (0.13%)	1 (0.07%)
RASH	3 (0.80%)	2 (0.71%)	7 (0.30%)	6 (0.43%)

-- (CONTINUED) --

Appendix 4

Tables F1C and F1D in SU 4/25/95, vol 35.3

TABLE F1.C: NUMBER OF PATIENTS EXPOSED TO DRUG BY DURATION OF EXPOSURE, BY FINAL DOSE - ADULT STUDIES

DURATION OF EXPOSURE	NDA (NUMBER OF PATIENTS)					CUMULATIVE (NUMBER OF PATIENTS)					
	TOTAL	5 MG	10 MG	15 MG	20 MG	TOTAL	5 MG	10 MG	15 MG	20 MG	N/A
UP TO 2 WEEKS	407	127	162	4	114	1540	192	736	4	268	340
3 - 4 WEEKS	551	87	367	6	91	1141	124	697	6	112	202
5 - 12 WEEKS	371	83	143	49	96	980	239	461	49	206	25
13 WKS-6 MONTHS	236	38	74	0	124	237	39	74	0	124	0
NOT AVAILABLE	3	0	1	0	2	84 ¹	8	79	0	2	3
TOTAL NUMBER OF PATIENTS	1568	335	747	59	427	3982	594	2047	59	712	570 ²
MEAN DURATION OF EXPOSURE (DAYS)	41.2	31.3	31.3	39.0	66.7	30.1	34.8	25.7	39.6	49.8	15.2

¹ FOR 84 PATIENTS (84N0055 PATIENT 71, 85N0051 PATIENT 8 AND 86N0199, PATIENT 8, PROTOCOL C-89001: 78 PATIENTS AND PROTOCOL L-0103: 3 PATIENTS) THE DURATION OF EXPOSURE COULD NOT BE DETERMINED.

² 526 PATIENTS (L-0103) HAD FINAL DOSE UNKNOWN WITH A PROTOCOL SPECIFIED MAXIMUM POSSIBLE TITRATED DOSE OF 20 MG.
44 PATIENTS (L-0192) HAD FINAL DOSE UNKNOWN WITH A PROTOCOL SPECIFIED MAXIMUM POSSIBLE TITRATED DOSE OF 10 MG.

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DATE: 04/10/95 10:34:56

Appendix 5

Proposed Amendment to the revised labeling for NDA 19835 drafted
in the 9/21/95 "in house meeting

Memo

From: Ana M. Saavedra-Delgado, M.D.
To: Marty Himmel, M.D.
Subject: Proposed amendment to the revised labeling for NDA
19835 drafted in the 9/21/95 "in-house" meeting
Date: September 27, 1995

"Following cutaneous antigen challenge, the late phase recruitment of eosinophils, neutrophils and basophils, components of the allergic inflammatory response, is inhibited by Zyrtec."

The following change is proposed:

"In studies conducted for up to twelve hours following cutaneous antigen challenge, the late phase recruitment of eosinophils, neutrophils and basophils, is inhibited by Zyrtec."

The references for the sponsor's statement are attached. Only the summary for studies CP-18, CP19 and CP20 were readily available. Copies of the two referenced literature articles, #57 and #58 are attached. In addition, the reviewer references UCB study 104, that was submitted in the 4/25/95 submission in vol 18.

The summary report of study CP-18 appears to be the same study described in reference #57: J Allergy Clin Immunol:83(5):905-912, 1989.

The two published articles by the Baltimore group use the same skin chamber technique. In both studies 20 mg of cetirizine was used; in #57 for 2 days and in #58 for 3 days and they both had placebo controls. In #57 the cell infiltration was studied for up to 8 hrs and in study #58 for up to 12 hours. Statistical significant reduction of eosinophil and neutrophil infiltration was achieved for the pooled results of hours 6-8 in study #57. At 8 hours there was significant reduction in neutrophil and eosinophil infiltration. The results in basophils followed the same trend but perhaps due to small numbers they were not statistically significant.

In study #58 the group extends the observation for up to 12 hours and other two antihistamines are studied. In this study the statistical significant changes on cell infiltration are observed at 10-12 hrs for eosinophils and basophils and 8-12 hours for neutrophils.

In study #58, wheal and flare were measured at hourly intervals for up to 12 hours and cetirizine significantly inhibited the immediate reaction to cutaneous antigen challenge (up to 3 hours) but did not alter the late phase cutaneous reactivity as measured by wheal and flare (4-12 hours).

Study UCB 104 studied cetirizine 15 mg bid for 4.5 days in a cross-over design comparing it to prednisolone 20 mg for 4.5 days and placebo. The investigators attempted to use the skin window technique but was not effective. Skin biopsy at 6 and 24 hours were obtained. Biopsies were read blindly. No statistical significant effect was noted with cetirizine in terms of the number of eosinophils or neutrophils at 6 or 24 hours compared to placebo. Prednisolone significantly inhibited the number of eosinophils compared to placebo in the skin biopsies. Neutrophils were also reduced but the difference was not statistically significant.

In summary, the above results do support Zyrtec's inhibition of cellular infiltration at the skin following cutaneous antigen challenges of eosinophils, neutrophils and basophils in studies conducted up to 12 hours post antigen challenge. However, even though the cellular infiltration is inhibited, the cutaneous manifestation of late phase reactivity, i.e. wheal and flare, does not appear to be inhibited.

The elimination of the phrase "component of allergic inflammatory response" is proposed because even though these cell types indeed are component of the inflammatory response, for the reader, the statement could imply that cetirizine inhibits this response.

Section 3.

- I. Revised Labeling for NDA 19835 dated September 29, 1995

OCT 2 1995

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 29, 1995
FROM: Koung Lee
SUBJECT: NDA 19-835 Revised Cetirizine Tablet Labeling
TO: NDA 19-835 Zyrtec (cetirizine 5 and 10 mg) tablet

A labeling meeting was held on September 21, 1995 to revise Pfizer's April 25, 1995 proposed labeling for Zyrtec Tablet. Present at the meeting were Drs. Robert Temple, John Jenkins, Martin Himmel, Mehul Mehta, Joseph Sun, Mark Vogel, Bradley Gillespie, Anamaria Saavedra-Delgado, Mr. Bob Barron, Mr. Koung Lee, and Ms. Cathie Schumaker. Ms. Schumaker made the labeling revisions during the meeting using the PROXIMA to allow the team to see the changes as they were being made.

The Red Strike Out and Strike Out functions on WordPerfect 6.0 were used to identify the revisions. The Red Strike Out function changes the color of the letters to red on the monitor but the letters come out highlighted (eg., ZYRTEC) when printed on the laser jet printer. The Strike Out function prints the way it appears on the monitor (eg., ~~ZYRTEC~~). After the revisions were made, the labeling was printed and circulated for concurrence from the team. The revised labeling was then faxed to Pfizer on September 29, 1995 with the request to submit to the NDA revised labeling with the recommended changes.

 10.2.95
Koung Lee, CSO

ATTACHMENT - REVISED LABELING

cc: Orig. NDA 19-835

HFD-155/Div. Files

HFD-155/C. Schumaker (9-29-95)

HFD-155/M. Himmel

HFD-426/M. Mehta

HFD-155/J. Sun

HFD-155/A. Saavedra-Delgado

HFD-426/B. Gillespie

HFD-155/M. Vogel

HFD-150/B. Barron

HFD-155/K. Lee

ANNOTATED PACKAGE INSERT

ZYRTEC

cetirizine hydrochloride

Tablets

For Oral Use

DESCRIPTION

Cetirizine hydrochloride, the active component of ZYRTEC tablets, is an orally active and selective H₁-receptor antagonist. The chemical name is (±)-[2-[4-(p-chloro-α-phenylbenzyl)-1-piperazinyl]ethoxy] acetic acid, dihydrochloride. Cetirizine hydrochloride is a racemic compound with an empirical formula of C₂₁H₂₃ClN₂O₃·2HCl. The molecular weight is 461.82 and the chemical structure is shown below:

Cetirizine hydrochloride is a white, crystalline powder and is water soluble. ZYRTEC is formulated as a white (dye-free), film-coated, rounded-off rectangular shaped tablet for oral administration and is available in 5 and 10 mg strengths. Inert ingredients are: lactose; magnesium stearate; povidone; titanium dioxide; hydroxypropyl methylcellulose; polyethylene glycol; and corn starch.

CLINICAL PHARMACOLOGY

Mechanism of Actions: Cetirizine, a human metabolite of hydroxyzine is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H₁ receptors (1,2). The antihistaminic activity of cetirizine has been clearly documented in a variety of animal and human models (3-24). *In vivo* and *ex vivo* animal models have shown negligible anticholinergic and antiserotonergic activity (5,8,10,13,14,17). In clinical studies, however, dry mouth was more common with cetirizine than with placebo (89). *In vitro* receptor binding studies have shown no measurable affinity for other than H₁ receptors (16). Autoradiographic studies with radiolabeled cetirizine in the rat have shown negligible penetration of the brain (25). *Ex vivo* experiments in the mouse have shown that systemically administered cetirizine does not significantly occupy cerebral H₁ receptors (16).

Pharmacokinetics: Cetirizine is rapidly absorbed after oral administration of a tablet, which had bioavailability similar to an oral solution (26). Food had no effect on the extent of cetirizine absorption, but T_{max} was delayed by 1.7 hours and C_{max} was decreased by 23% in the presence of food (27). A mass balance study in 6 healthy male volunteers indicated that 70% of the administered radioactive dose was recovered in the urine and 10% in the feces, for a combined

total recovery of about 80% (28). Approximately 50% of the administered radioactive dose was excreted in urine as unchanged drug (28). Most of the rapid increase in peak plasma radioactivity is associated with parent drug indicating low first pass metabolism (28). Cetirizine is metabolized to a very limited extent by oxidative o-dealkylation to a metabolite (28,29) with negligible antihistaminic activity (30).

Cetirizine exhibits linear kinetics over the dosage range of 5 to 60 mg (31,32). In pharmacokinetic studies in 146 healthy volunteers, the mean $\pm$ SD terminal half-life was 8.3 ± 1.8 hours, oral clearance was 54 ± 13 mL/min, and the apparent volume of distribution was 0.50 ± 0.08 L/kg (33). No accumulation was observed for cetirizine following daily doses of 10 mg τ for 10 days (34). The steady-state maximum plasma concentration was 311 ± 40 ng/mL and was achieved within 1.0 ± 0.5 hour (34). Individual histograms of cetirizine C_{max} and AUC showed unimodal distributions with a two- to four-fold variability in healthy subjects (100). Plasma protein binding of cetirizine is 93 ± 0.3 % and was independent of concentration in the range of 0.025 to 1.0 mcg/mL (29); this concentration range covers the therapeutic plasma levels.

SPECIAL POPULATIONS

Effect of Age: Following a single 10 mg oral dose, half-life increased by about 50% and clearance decreased by 40% in 16 elderly subjects as compared to the 14 normal subjects (35). The decrease in cetirizine clearance in these elderly volunteers appeared to be related and was directly correlated to their decreased renal function.

Effect of Gender: ~~No gender-related differences were observed in the kinetics of cetirizine between 86 white adult males and 3 white adult females (36). The effect of gender on cetirizine pharmacokinetics has not been adequately studied.~~

Effect of Race: No race-related differences were observed in the kinetics of cetirizine between 86 white adult males and 11 black adult males (36).

Renally Impaired Patients: The kinetics of cetirizine were studied following multiple oral daily doses of 10 mg for 7 days in 7 normal volunteers (creatinine clearance 89-128 mL/min), 8 patients with mild renal function impairment (creatinine clearance 42-77 mL/min) and 7 patients with moderate renal function impairment (creatinine clearance 11-31 mL/min) (37). The pharmacokinetics of the drug were similar in patients with mild impairment and normal volunteers. Moderately renally impaired patients had a 3-fold increase in half-life and 70% decrease in clearance compared to normal volunteers (37). ~~Accumulation of cetirizine was also more pronounced in patients with moderate impairment (37).~~

~~Patients (N=5) on hemodialysis (creatinine clearance less than 7 mL/min) given a~~
Following a single oral 10 mg dose of cetirizine, 5 patients on hemodialysis had a 3 fold increase in half-life ~~accompanied by~~ and a 70% decrease in clearance ~~compared to normals~~. Cetirizine was not completely cleared by hemodialysis as less than 10% of the administered dose was removed during the dialysis session (37).

Dosing adjustment is necessary in patients with moderate or severe renal impairment and patients on dialysis. (See also DOSAGE AND ADMINISTRATION).

Hepatically Impaired Patients: ~~Following single oral doses of 10 mg and 20 mg~~
cetirizine administered to 6 and 10 patients, respectively; ~~Severely impaired~~ with chronic liver diseases (hepatocellular, cholestatic, and biliary cirrhosis) - ~~given 10 or 20 mg of~~
cetirizine as a single oral dose ~~resulted in~~ had a 50% increase in half-life along with a

40% decrease in clearance compared to 16 healthy subjects (37,38,39).

Dosing adjustment may be necessary in hepatically impaired patients. (See also DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Formal pharmacokinetic interaction studies were conducted with cetirizine and pseudoephedrine, antipyrine, ketoconazole, erythromycin, and azithromycin. No pharmacokinetic interactions were observed. In a multiple dose study of theophylline (400 mg once daily) and cetirizine, there was a small (16%) decrease in clearance of cetirizine.

~~Theophylline: A multiple dose study in 24 healthy male volunteers showed that the pharmacokinetics of cetirizine (20 mg QD for 3 days) and theophylline (400 mg QD for 3 days) were not altered when they were given in combination (40).~~

~~Pseudoephedrine: A multiple dose study showed no significant differences in any pharmacokinetic parameters for either cetirizine (20 mg QD) or pseudoephedrine (120 mg Q12h) when they were concomitantly administered to 24 healthy male subjects for 6 days (41).~~

~~Antipyrine: Cetirizine 10 mg QD was administered for 9 days to 10 healthy male volunteers. Following coadministration on the ninth day with 250 mg antipyrine, no changes were observed in plasma clearance or elimination half-life of antipyrine. Therefore, cetirizine does not alter the oxidative metabolizing enzyme activity in the liver (42).~~

~~Ketoconazole: In a multiple dose study involving 16 healthy male volunteers, the~~

pharmacokinetics of cetirizine (20 mg QD) and ketoconazole (400 mg QD) were not altered when they were given in combination (43).

~~Erythromycin:~~ In a multiple-dose study involving 16 healthy male volunteers, the pharmacokinetics of cetirizine (20 mg QD) and erythromycin (500 mg Q8h) were not altered when they were given in combination (44).

~~Cimetidine:~~ In a double-blind, randomized, single-dose, crossover study, cetirizine 20 mg was administered to 6 healthy volunteers concomitantly with placebo or 400 mg cimetidine. Neither cetirizine plasma concentrations nor wheal and flare measurements at 2 and 4 hours post-dose were significantly different after cimetidine and placebo treatment (45).

Pharmacodynamics: Studies in normal volunteers show that ZYRTEC at doses of 5 and 10 mg strongly inhibits the skin wheal and flare caused by the intradermal injection of histamine (17-20,22,23,46-48). The onset of this activity after a single 10 mg dose occurs within 20 minutes in 50% of subjects and in 95% of subjects within one hour (49,50), and this activity persists for at least 24 hours (17,22,46,49). In a 35 day study in children ages 5 to 12, no tolerance to the antihistaminic (suppression of wheal and flare response) effects of ZYRTEC was found (51). The effects of intradermal injection of various other mediators or histamine releasers are also inhibited by cetirizine (17,23,47,48,52), as is response to a cold challenge in patients with cold-induced urticaria (53). In mildly asthmatic subjects, ZYRTEC at 5 to 20 mg blocked bronchoconstriction due to nebulized histamine, with virtually total blockade after a 20 mg dose (24). In addition, in studies conducted for up to 3 hours following cutaneous antigen challenge, the late phase recruitment of eosinophils, neutrophils and basophils, components of the allergic inflammatory response, is inhibited by ZYRTEC at a dose of 20 mg following

cutaneous antigen challenge (54-58)

Four randomized double-blind, placebo-controlled trials were conducted in healthy subjects to assess the psychomotor/psychophysical effects (as measured by the multiple sleep latency test, simulated assembly line task, Stroop word test, and the critical flicker frequency test) of ZYRTEC versus hydroxyzine or diphenhydramine. These studies showed that ZYRTEC was generally not significantly different from placebo but was different from hydroxyzine and diphenhydramine which produced significantly decreased test performance (59-62, 103).

In four clinical studies in healthy adult males volunteers, no clinically significant mean increases in QTc were observed in ZYRTEC treated subjects (32,43,44,63). In the first study, a placebo-controlled crossover trial, ZYRTEC was given at doses up to 60 mg per day, 6 times the maximum clinical dose for 1 week, and no significant mean QTc prolongation occurred (32). In the second study (43), a crossover trial, ZYRTEC 20 mg and erythromycin (500 mg every 8 hours) were given alone and in combination. The effect of ZYRTEC 20 mg alone on QTc (Hodges corrections) was statistically estimated as a small decrease from baseline of 5.1 msec (-1.3%) after 5 days of therapy. There was no significant drug interaction effect on QTc seen with the combination of ZYRTEC 20 mg and erythromycin or with ZYRTEC alone (43). In the third trial (44), also a crossover study, ZYRTEC 20 mg and ketoconazole (400 mg per day) were given alone and/or in combination. The effect of ZYRTEC 20 mg ~~caused~~ alone on QTc was statistically estimated as a small mean increase in QTc from baseline of 8.2 msec (1.8%) (replace with Baseline value) after 10 days of therapy. Ketoconazole also increased QTc by about (8.2 msec value). The combination caused an increase of (the Baseline value) about equal to the sum of the individual effects. The estimated effect of the combination on QTc change from baseline (16.1 msec) was equal to the sum of the individual component effects. Thus, there was no significant drug interaction effect on QTc with the combination of

ZYRTEC and ketoconazole. In the fourth study (63), a placebo-controlled parallel trial, ZYRTEC 20 mg was given alone or in combination with azithromycin (500 mg as a single dose on the first day followed by 250 mg once daily). Results of this trial showed There was no significant increase in QTc associated with ZYRTEC 20 mg alone or in combination with azithromycin.

In a six-week, placebo-controlled study of 186 patients with allergic rhinitis and mild to moderate asthma, ZYRTEC 10 mg QD improved rhinitis symptoms and did not alter pulmonary function. This study supports the safety of administering ZYRTEC to allergic rhinitis patients with mild to moderate asthma (107).

Clinical Studies: Eleven multicenter, randomized, double-blind, placebo-controlled clinical trials were conducted in the United States. Five studies in seasonal allergic rhinitis were conducted for up to 4 weeks in duration (64); four studies in perennial allergic rhinitis for up to 8 weeks in duration (65,66); and two studies in chronic idiopathic urticaria each for 4 weeks in duration (67). Doses of 5-20 mg per day were studied. In general, most patients were controlled on a 10 mg dose. Five (5) mg was the minimally effective dose and 20 mg did not give added effectiveness compared with 10 mg.

Nine multicenter, randomized, double-blind, clinical trials comparing cetirizine 5 (o) 20 mg to placebo in patients with seasonal or perennial allergic rhinitis were conducted in the United States. Five of these showed significant reductions in symptoms of allergic rhinitis. In seasonal allergic rhinitis (one to 4 weeks in duration) and in perennial allergic rhinitis for up to 8 weeks in duration. Two 4-week multicenter, randomized, double-blind, clinical trials comparing cetirizine 5 (o) 20 mg to placebo in patients with chronic idiopathic urticaria were also conducted and showed significant improvement in symptoms of chronic idiopathic urticaria. In general, the 10 mg dose was more effective than the 5 mg dose and the 20 mg dose gave no added effect.

INDICATIONS AND USAGE

Seasonal Allergic Rhinitis: ZYRTEC is indicated for the relief of symptoms associated with seasonal allergic rhinitis due to allergens such as ragweed, grass and tree pollens. Symptoms treated effectively include sneezing, rhinorrhea, nasal pruritus, ocular pruritus, tearing and redness of the eyes ~~(68)~~.

Perennial Allergic Rhinitis: ZYRTEC is indicated for the relief of symptoms associated with perennial allergic rhinitis due to allergens such as dust mites, animal dander and molds. Symptoms treated effectively include sneezing, rhinorrhea, post-nasal discharge, nasal pruritus, ocular pruritus and tearing ~~(69)~~.

Chronic Urticaria: ZYRTEC is indicated for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria. It significantly reduces the occurrence, severity and duration of hives and significantly reduces pruritus ~~(70)~~.

CONTRAINDICATIONS

ZYRTEC is contraindicated in those patients with a known hypersensitivity to it or any of its ingredients, or ~~to its parent compound~~ hydroxyzine.

PRECAUTIONS

Activities Requiring Mental Alertness: In clinical trials, the occurrence of somnolence has been reported in some patients taking ZYRTEC; due caution should therefore be exercised when driving a car or operating potentially dangerous machinery. Concurrent use of ZYRTEC with alcohol or other CNS depressants should be avoided because additional reductions in alertness and additional

impairment of CNS performance may occur.

Drug-drug interactions: No clinically significant drug interactions have been found with theophylline at a low dose, ~~clarithromycin~~, pseudoephedrine, ketoconazole, or erythromycin and cimetidine (40,41,43-45). ~~There was a small decrease in the clearance of cetirizine caused by a 400 mg dose of theophylline. It is possible that larger doses could have a larger effect.~~ In clinical trials, there did not appear to be an increased incidence of adverse experiences in patients administered ~~ZYRTEC and beta-agonists, non-steroidal anti-inflammatory drugs, oral contraceptives, corticosteroids, H₂-antagonists, cephalosporins, penicillins, thyroid hormones and thiazide diuretics~~ (71).

Carcinogenesis, mutagenesis and impairment of fertility: No evidence of carcinogenicity was observed in a 2-year carcinogenicity study in rats (72) at dietary doses up to 20 mg/kg/day (15 times the recommended human dose on a mg/m²/day basis). An increased incidence of benign liver tumors was found in a 2-year carcinogenicity study in male mice (73) at a dietary dose of 16 mg/kg/day (6 times the recommended human dose on a mg/m²/day basis). The clinical significance of these findings during long-term use of ZYRTEC is not known. Cetirizine was not mutagenic in Ames test, and not clastogenic in human lymphocyte assay, mouse lymphoma assay, and in vivo micronucleus test in rats (74-77). No impairment of fertility was found in a fertility and general reproductive performance study in mice (78,79) at a dose of 64 mg/kg/day (26 times the recommended human dose on a mg/m²/day basis).

Pregnancy Category B: Cetirizine ~~has not been shown to be~~ ~~was~~ ~~not~~ teratogenic in mice, rats and rabbits at doses up to 96, 225, and 135 mg/kg/day (or 40, 180, and 216 times the recommended human dose on a mg/m²/day basis), respectively (80-82). There are no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, ZYRTEC should be used in pregnancy only if clearly needed.

Nursing Mothers: Retarded pup weight gain was found in mice during lactation⁽⁷⁹⁾ when dams were given cetirizine at 96 mg/kg/day (40 times the recommended human dose on a mg/m²/day basis). Studies in beagle dogs indicate that approximately 3% of the dose is excreted in milk⁽⁸³⁾. Cetirizine has been reported to be excreted in human breast milk⁽¹⁰²⁾; ~~Because many drugs are excreted in human milk,~~ use of ZYRTEC in nursing mothers is not recommended.

Geriatric Use: The safety and efficacy of ZYRTEC has been demonstrated in patients 65 years and older⁽⁸⁴⁾. ~~As with the general population, clearance of ZYRTEC is reduced in proportion to creatinine clearance⁽³⁵⁾.~~ (See CLINICAL PHARMACOLOGY section)

Pediatric Use: Safety and effectiveness in the pediatric population has not been established. In more than 588 children aged 6 to 11 years, ZYRTEC was administered in doses from 1.25 to 10 mg. In these studies ZYRTEC was well tolerated at doses up to 10 mg^(85,86). ~~The safety of ZYRTEC in children under the age of 6 years has not yet been established. ZYRTEC is not indicated for the treatment of children under the age of 12 years.~~

ADVERSE REACTIONS

Controlled and uncontrolled clinical trials included more than 6000 patients, with more than 3900 receiving ZYRTEC at doses of 5 to 20 mg per day; the duration of treatment ranged from 1 week to 6 months, ~~with a mean of exposure of 30 days⁽⁸⁷⁾.~~ In addition, there were more than 1400 ZYRTEC-treated patients in foreign clinical trials.

Most adverse reactions reported during therapy with ZYRTEC were mild or moderate⁽⁸⁸⁾. In placebo-controlled trials, the incidence of discontinuations due to adverse reactions in patients receiving ZYRTEC 5 mg or 10 mg was not significantly different from placebo (2.9% vs 2.4%, respectively)⁽⁸⁹⁾.

The most common adverse reactions that occurred more frequently on cetirizine than placebo was somnolence. ~~the recommended doses were headache and somnolence (89). The incidence of headache associated with ZYRTEC was not different from placebo (89).~~ The incidence of somnolence associated with ZYRTEC was dose related, (90) and, ~~predominantly, mild to moderate (88). The incidence of somnolence in fixed dose studies was 6% in placebo, 11% at 5 mg and 14% at 10 mg (90).~~ Discontinuations due to somnolence for ZYRTEC (91) were uncommon, ~~not significantly different from placebo (1.0% on Zyrtec vs 0.6% on placebo, respectively).~~ In addition, Fatigue and dry mouth were also appeared to be considered treatment-related adverse reactions. There was no difference by age, race, gender or by body weight with regard to the incidence of adverse reactions (92-94).

Table 1 lists adverse experiences which were reported for ZYRTEC 5 and 10 mg in controlled clinical trials in the United States ~~(89)~~ and that were more common on ZYRTEC than placebo.

Table 1. Adverse Reactions Reported in Placebo-Controlled United States ZYRTEC Trials (Maximum Dose of 10mg) at Rates of $\pm$ 2% or Greater

(Percent Incidence)

Adverse Experience	ZYRTEC (N=2034)	Placebo (N=1612)
Headache	17.6%	17.9%
Somnolence	13.7	6.3
Fatigue	5.9	2.6
Dry Mouth	5.0	2.3
Nausea	2.5	2.9
Pharyngitis	2.0	1.9
Dizziness	2.0	1.2
Insomnia	1.4	1.2
Epistaxis	1.2	0.6
Coughing	1.0	0.6
Abdominal Pain	1.0	0.9
Dyspepsia	0.8	1.6
Pruritus	0.3	1.2

In addition, headache and nausea occurred in more than 2% of the patients, but were more common on placebo.

The following events were observed infrequently (equal to or less than $\pm$ 2%), in 3982 patients who received ZYRTEC in U.S. trials, including an open study of six months duration (88); a causal relationship with ZYRTEC administration has not been established.

~~Application Site: application site reaction, injection site inflammation~~

Autonomic Nervous System: anorexia, urinary retention, flushing, saliva increased
salivation

Cardiovascular: palpitation, tachycardia, hypertension, ~~arrhythmia~~ cardiac failure

Central and Peripheral Nervous Systems: insomnia, paresthesia, confusion, hyperkinesia, hypertonia, migraine, tremor, vertigo, cramps legs, ataxia, dysphonia, ~~abnormal~~ coordination ~~abnormal~~, hyperesthesia, hypoesthesia, myelitis, paralysis, ptosis, ~~speech disorder~~, twitching, visual field defect

Endocrine: ~~thyroid disorder~~

Gastrointestinal: ~~increased~~ appetite ~~increased~~, dyspepsia, abdominal pain, diarrhea, flatulence, constipation, vomiting, ~~ulcerative~~ stomatitis ~~ulcerative~~, ~~tongue disorder~~, ~~aggravated~~ tooth caries ~~aggravated~~, stomatitis, tongue discoloration, tongue edema, gastritis, ~~rectum~~ hemorrhage ~~rectum~~, hemorrhoids, melena, abnormal hepatic function
abnormal

Genitourinary: polyuria, urinary tract infection, cystitis, dysuria, hematuria, ~~urine~~
abnormal

Hearing and vestibular: earache, tinnitus, deafness, ototoxicity

Metabolic/Nutritional: thirst, ~~edema~~, ~~dehydration~~, diabetes mellitus

Musculoskeletal: myalgia, arthralgia, ~~bone disorder~~, arthrosis, ~~tendon disorder~~, arthritis,

muscle weakness

Psychiatric: insomnia, nervousness, depression, emotional lability, impaired concentration ~~impaired~~, anxiety, depersonalization, paroniria, abnormal thinking ~~abnormal~~, agitation, amnesia, ~~decreased libido decreased~~, euphoria

~~Resistance Mechanism:~~ ~~healing impaired, herpes simplex, infection, infection fungal, infection viral~~

Respiratory System: epistaxis, rhinitis, coughing, ~~respiratory disorder~~, bronchospasm, dyspnea, upper respiratory tract infection, hyperventilation, sinusitis, increased sputum ~~increased~~, bronchitis, pneumonia

Reproductive: dysmenorrhea, ~~menstrual disorder, female~~ breast pain ~~female~~, intermenstrual bleeding, leukorrhea, menorrhagia, ~~pregnancy unintended~~, vaginitis, ~~testes disorder~~

Reticuloendothelial: lymphadenopathy

Skin: pruritus, rash, ~~skin disorder, dry~~ skin dry, urticaria, acne, dermatitis, rash erythematous, ~~increased~~ sweating ~~increased~~, alopecia, angioedema, furunculosis, bullous eruption, eczema, hyperkeratosis, hypertrichosis, photosensitivity reaction, photosensitivity toxic reaction, ~~maculo-papular rash maculo-papular~~, seborrhea, purpura

Special Senses: taste perversion, taste loss, parosmia

Vision: ~~eye abnormality, vision abnormal~~, blindness, loss of accommodation, eye pain, conjunctivitis, xerophthalmia, glaucoma, ocular hemorrhage

Body as a Whole: increase weight increase, back pain, malaise, ~~pain, chest pain~~, fever, asthenia, ~~generalized edema~~ ~~generalized~~, periorbital edema ~~periorbital~~, peripheral edema ~~peripheral~~, rigors, legs edema legs, face edema, hot flushes, enlarged abdomen ~~enlarged~~, ~~allergic reaction~~, nasal polyp

Occasional instances of transient, reversible hepatic transaminase elevations have occurred during cetirizine therapy (95). There was a single report of possible drug-induced hepatitis with significant transaminase elevation (600 to 1000 IU/L) and elevated bilirubin.

In foreign marketing experience the following additional rare, but potential severe adverse events have been reported: hemolytic anemia, thrombocytopenia, orofacial dyskinesia, severe hypotension, anaphylaxis, hepatitis, glomerulonephritis, stillbirth, and cholestasis (96).

In a six-week, placebo-controlled study of 186 patients with allergic rhinitis and mild to moderate asthma, ZYRTEC 10 mg QD improved rhinitis symptoms and did not alter pulmonary function. This study supports the safety of administering ZYRTEC to allergic rhinitis patients with mild to moderate asthma (101).

DRUG ABUSE AND DEPENDENCE

There is no information to indicate that abuse or dependency occurs with ZYRTEC.

OVERDOSAGE

Overdosage has been reported with ZYRTEC. In one patient who took 150 mg of ZYRTEC, the patient was somnolent but did not display any other signs or abnormal blood chemistry or hematology results⁽⁹⁷⁾. Should overdose occur, treatment should be symptomatic or supportive, taking into account any concomitantly ingested medications. There is no known specific antidote to ZYRTEC. ZYRTEC is not effectively removed by dialysis, and dialysis will be ineffective unless a dialyzable agent has been concomitantly ingested⁽⁹⁷⁾. The minimal lethal oral dose in rodents is approximately 100 times the maximum recommended clinical dose on a mg/m² basis and the liver was the target organ of toxicity⁽⁹⁸⁾.

DOSAGE AND ADMINISTRATION

The recommended initial dose of ZYRTEC is 5 or 10 mg, depending on symptom severity. Most patients in clinical trials started at 10 mg⁽⁹⁹⁾. ZYRTEC is given as a single daily dose, with or without food. The time of administration may be varied to suit individual patient needs.

In patients with decreased renal function (creatinine clearance 11-31 mL/min), patients on hemodialysis (creatinine clearance less than 7 mL/min), and in hepatically impaired patients, a dose of 5 mg QD is recommended.

HOW SUPPLIED:

ZYRTEC tablets are white (dye free), film coated, rounded-off rectangular shaped containing 5 mg or 10 mg cetirizine hydrochloride.

5 mg tablets are engraved with "PFIZER" on one side and with "550" on the other. Bottles of 100: (NDC 0069-5500-66)

10 mg tablets are engraved with "PFIZER" on one side and with "551" on the other. Bottles of 100: (NDC 0069-5510-66)

Cetirizine is licensed from UCB, Pharma Inc.

STORAGE: Store at room temperature 59° to 86°F (15° - 30°C).

II. Reviewer's comments and regulatory recommendations

The medical reviewer has views and concerns that differ from those reflected in the revised labeling dated September 29, 1995. The MO draft review of the labeling dated September 12, 1995 may not have portrayed these issues adequately. The following comments are included to clarify these issues.

1. Electrocardiographic effect.

Reference is made to the MOR dated 2/27/1994 that reviewed cetirizine's electrocardiographic effect on QTc. In the review of this safety update submission that includes the results of the analysis of the PEDS-4 electrocardiographic data and the cetirizine -azithromycin study, a consistent statistical significant change in mean QTc over baseline is not demonstrated. However, there are a number of other indicators that support that cetirizine can prolong the QTc alone and in combination with ketoconazole. These are: individual patient data in SAR-8, SARA/LORA, 90CK16-0497, and 92CK16-0603; PEDS-4 (11-17 day group analysis); increase in frequency of >10% prolongation in patients receiving the combination in the cetirizine-ketoconazole study, and to a lesser extent in the cetirizine-erythromycin study.

In the other side of the spectrum, we have a case reported spontaneously of a patient that developed torsades de pointes, received on 4/22/93. A 73 y/o female that had a history of supraventricular tachycardia was placed on dysopyramide. She had a documented history of QT interval prolongation post-dysopyramide. For allergic symptoms, the patient was placed on 10 mg cetirizine daily for 13 days. For symptoms of fever and viral illness she was placed on lysinesprin, paracetamol and josamycin, 2 days prior to the event. The case was evaluated by Dr. Woosley and we concurred with him that torsades was most likely due to dysopyramide, perhaps precipitated by hypokalemia. However, it is not clear what is potential role that the addition of 10 mg cetirizine may have to produce torsades when it is added to a multidrug regimen in a patient treated with antiarrhythmics that produce slow repolarization, in a situation where electrolyte control is not closely monitored.

Cetirizine is indicated for the treatment of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria. It would be marketed to a very wide section of the population, by for the most part primary care physicians that will not consider the current revised labeling of the

drug to indicate that there could be any problems for this "allergy" drug, that they may need to be concerned about. However, there are indications, that there could be, given the common use of multidrug therapy for whom physicians may consider that this drug would be a safe, very low risk choice.

Unless the drug labeling provides a distinct and clear warning of the drug's potential to prolong the QTc in susceptible patients at recommended doses, i.e. black box, the medical reviewer recommends the non approval of the drug based on the drug's electrocardiographic effects.

2. Liver transaminase elevations

Reference is made to the sponsor's response to question 6.c. of the NDA approvable letter, in Section 1 of this review and to the individual patient data provided in that section:

"Mean changes in laboratory results for patients treated with cetirizine and placebo in placebo controlled studies were analyzed and are shown in Table 22.A. There were statistically significant differences between treatment groups for change from baseline in SGOT, SGPT, and creatinine. The mean change for SGOT was 0.84 U/L for the cetirizine group compared to -0.05 U/L for placebo ($p < 0.02$). The mean change for the SGPT from baseline for the cetirizine treatment group was 1.35 U/L compared to -0.19 U/L for placebo ($p < 0.001$). The creatinine mean change from baseline was 0 for creatinine treated patients and 0.13 mg/dl for placebo treated patients."

According to the sponsor's Table 22.A (cumulative database), these mean changes from baseline represent the following mean percent changes from baseline:

N	Cetirizine	N	Placebo
2488	SGOT=11.64%	1511	SGOT=5.96%
2421	SGPT=15.6%	1451	SGPT=6.85%
2500	T.bili=6.9%	1527	T.bili=6.8%
2497	creatinine=1.84%	1523	creatinine=2.85%
2423	BUN=3.80%	1448	BUN=4.53%

Table 22.B summarizes the changes in laboratory results by dose as found in the NDA versus the cumulative database. When the cumulative database is compared to the NDA database, in the cumulative database the mean percent changes from baseline decreased for SGOT and SGPT for the 5 and 10 mg dose but not for the dose where the mean percent change from baseline increased or stayed the same.

Table 22.E summarizes the changes in laboratory results by race as found in the NDA versus the cumulative database. Although the numbers for non-white patients are small compared to the white patient population in the cumulative database, for SGPT, the mean percent change from baseline in the cumulative database is larger for blacks, 17% (N=228) and "others", 17.5% (N=109) versus 14.8% in the white population (N=2546). In addition, the mean percent change from baseline in SGPT in black patients increased from 12.7% to 17% from the NDA to the cumulative database, which was opposite to the decrease in the other two groups; twice the number of patients were studied in the cumulative database

versus the NDA database.

"Evaluation of the incidence of abnormal liver function tests in patients with normal baseline tests in placebo-controlled studies show that cetirizine is associated with elevations in SGOT and SGPT but not total bilirubin or alkaline phosphatase. Abnormalities are generally less than twice the upper limit of normal. The incidence of abnormal SGOT and SGPT more than twice the upper limit of normal appear to be similar in cetirizine and placebo-treated patients." (SU 4/25/95, vol 32, 9 60).

The above data needs to be interpreted in terms of the mean duration of exposure (30.1 days-cumulative database) and the populations studied. If the decision is made to approve this drug, the revised labeling should reflect the fact that no placebo controlled studies have been conducted beyond eight weeks and that there may be individuals that may be more susceptible to these effects (if not populations). In addition, the incidence of these elevations should be included. A Phase IV commitment from the sponsor should be obtained to study these effects particularly in the non-white populations on a long term basis, i.e. 3-6 months.

3. Comparison of human PK of cetirizine's enantiomers following treatment with hydroxyzine to human PK data following treatment with cetirizine tablet.

We refer to our request to the sponsor in item 16 of cetirizine's approvable letter dated 2/21/95. In that request we asked which enantiomer form of cetirizine is formed when hydroxyzine is given to humans. In their response (BZ 5/15/95) the sponsor reported that this data was not available.

Hydroxyzine is reported to be a racemic mixture (USP-23, 1995). According to its chemical structure it would be assumed that its chiral center would be maintained, and that most likely a mixture of the two enantiomers of cetirizine would be formed in humans (no data is available). However, even if the two enantiomers are formed, we have no data as to whether there would be the same or a different ratio of exposure to the enantiomers in patients following treatment with hydroxyzine than when cetirizine is given.

The data from two clinical UCB sponsored studies (4/25/95 SU-UCB 101 and UCB 102) suggest that for the same route and dose there are statistical and clinical significant differences between the two enantiomers in the inhibition of the cutaneous histamine challenge as well as the in the response to nasal histamine challenge in normal volunteers.

Reference is made to the Pharm-Tox Amendment Review dated

10/11/95. In rats the liver is the primary target of treatment effects. The systemic exposure to the (-) enantiomer, UCB 28557 is considerably less than to the (+) enantiomer, UCB 28556. In the four week studies, the toxic effects were similar for the two enantiomers but the degree of toxicity was greater for UCB 28556 than for UCB 28557. Effects were more marked in males than in females. Systemic exposure was similar in males and females but renal excretion was substantially greater in females. In dogs there is no liver toxicity.

The sponsor has maintained that adequate data has been submitted to support the use of cetirizine at the recommended doses and that its safety profile should stand by itself without making a reference to hydroxyzine. However, particularly in terms of evaluation of safety after long term exposure (>12 weeks-33 weeks) to cetirizine the available data is minimal (around 200 patients). There are no placebo controlled studies of more than 8 weeks in duration in the cumulative database.

The fact that we do not know if the PK profile of the cetirizine enantiomers in patients receiving hydroxyzine is the same as in the patients receiving cetirizine, puts in question the rationale for using the long term safety profile of hydroxyzine to base safety decisions for cetirizine.

With the limited long term safety data available on cetirizine, if the long term safety data for hydroxyzine is going to be use in its place, this reviewer recommends that the sponsor should provide a comparison of the data of human PK on cetirizine's enantiomers after oral dosing with hydroxyzine and cetirizine prior to making a decision in favor of the drug's approval.

4. Incidence of reported adverse events.

The medical reviewer recommended that for the adverse event table in the revised labeling events at the 1% level would be reported. The following were the main reasons for this recommendation: Reference is made to MO review dated 2/23/94. In the majority of placebo controlled studies conducted in the US, the record of adverse experiences that was reported to the sponsor came from the report of the patients to the investigators and not from the daily records in diary cards. This method could have underestimated the frequency of these events. In addition, and to a lesser extend the fact that intercurrent illnesses were tabulated and kept as a separate database and they are not reported in the labeling, could also make the adverse event data in the table look better than it would be. If the decision is made

to approve the drug, then it would be appropriate to include in the labeling how the adverse event data was derived for the majority of patients in the database as well as a description of the most common intercurrent illnesses and their reported incidence in placebo controlled studies.

CC: Original NDA-19835

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Medical Officer Review

ORIGINAL

NDA 19835

Drug : Cetirizine tablets

Correspondence: 1) N(BL)10/4/95

Sponsor's response to the Agency's telephone facsimile dated September 29, 1995 regarding the revised labeling for this product.

2) CSO Preliminary Labeling Review dated October 20, 1995

Date: October 24, 1995

Medical Officer Reviewer: Ana M. Saavedra-Delgado, M.D.

A. Saavedra-Delgado MD

The Sponsor's labeling dated 10/4/95 was reviewed against the Agency's labeling dated September 29, 1995. *10/24/95*

The changes made by the Sponsor to the Agency's revised labeling dated September 29, 1995 have been captured in the CSO preliminary review dated October 20, 1995. *Noted. See comments on package insert in my memo on 11/9/95*

Changes were also made to the labeling by the Sponsor in response to the Agency's request to provide QTc measurements in the labeling using the Bazett correction. These changes were checked by the medical reviewer and they appear to be correct.

1. The numerical figures for the estimated ketoconazole and cetirizine effect using the Bazett correction in this labeling revision (10/04/95) correspond to those listed in Table E.1.2, September 30, 1993 (attached).

2. The numerical figure for the estimated effect of the combination using the Hodges correction is not given in Table E.1.2. In the 9/30/93 submission, the section Statistical Methods for Change from Baseline pages 15 and 16 and the section in Results-Mean QT Interval pages 18 and 19, describe how the effect of the combination was estimated using the Hodges correction. A copy of Table E.1.1. from the 9/30/93 submission using the Hodges correction, as well as copies of pages 15, 16, 18, and 19 are provided for the comparison. The same method would be used to estimate the effect of the combination using the Bazett correction.

Reference is made to the comments and recommendations made in the Medical Officer Review (10/17/95) of the sponsor's response to the approvable letter of 2/21/95 and to the proposed labeling. No further changes to the labeling are recommended at this time.

NDA 19835

3 OF 3

PROTOCOL 92CK16-0603: A MULTIPLE DOSE STUDY TO DETERMINE THE INTERACTION OF CETIRIZINE WITH KETOCONAZOLE IN YOUNG HEALTHY MALES

TABLE E.1.2
STATISTICAL ANALYSIS OF CHANGE FROM BASELINE BAZETT QTC (AVERAGED OVER HOUR OF DAY)

OBSERVED MEAN ± STD DEVIATION BY TREATMENT AND ESTIMATED DRUG EFFECTS

TREATMENT PERIOD	PLACEBO/ CETIRIZINE ¹ ³	KETOCONAZOLE/ COMBINATION ² ³	ESTIMATED KETOCONAZOLE EFFECTS	ESTIMATED OVERALL KETO EFFECTS
BASELINE	390.36± 13.52	388.09± 18.16		
CHANGE				
DAY 6 W/O CETIRIZINE	1.07± 6.69	7.22± 10.10	6.14	
DAY 16 WITH CETIRIZINE	7.90± 10.35	10.43± 15.07	10.46	8.30 (P=.051)

ESTIMATED CETIRIZINE EFFECTS BY REGIMEN 6.90 11.22

ESTIMATED OVERALL CETIRIZINE EFFECT 9.06 (P=.001)

ANALYSIS OF VARIANCE(SAS TYPE III MS)

EFFECT	DF	MEAN SQUARE	F-RATIO ⁴	P-VALUE	P-VALUES FOR DIRECT PAIRWISE COMPARISONS OF COMPONENTS AND COMBINATION		
					CETIRIZINE	KETOCONAZOLE	COMBINATION
SUBJECT	14	106.29	2.62	.041			
KETOCONAZOLE	1	1033.70	5.70	.031			
SUBJ=KETO	14	170.09	2.51	.048			
CETIRIZINE	1	1230.96	27.63	.001			
SUBJ=CETIR	14	44.55	0.63	.004	PLACEBO	.042	.066
KETO=CETIR	1	69.04	0.98	.339	CETIRIZINE	.009	.004
SUBJ=KETO=CETIR	14	71.16			KETOCONAZOLE		.003

¹SUBJECTS RECEIVED PLACEBO FOR THE FIRST FIVE DAYS AND THEN RECEIVED CETIRIZINE FOR AN ADDITIONAL TEN DAYS

²SUBJECTS RECEIVED KETOCONAZOLE FOR THE FIRST FIVE DAYS AND THEN RECEIVED COMBINATION FOR AN ADDITIONAL TEN DAYS

³SUBJECTS RECEIVED BOTH REGIMENS WITH INTERVENING WASHOUT IN CROSSOVER FASHION

⁴EFFECTS ARE TESTED AGAINST CORRESPONDING MS FOR INTERACTION WITH SUBJECT.

PROTOCOL 92CK16-0603: A MULTIPLE DOSE STUDY TO DETERMINE THE INTERACTION OF CETIRIZINE WITH KETOCONAZOLE IN YOUNG HEALTHY MALES

TABLE E.1.1
STATISTICAL ANALYSIS OF CHANGE FROM BASELINE HODGES QTC (AVERAGED OVER HOUR OF DAY)

OBSERVED MEAN ± STD DEVIATION BY TREATMENT AND ESTIMATED DRUG EFFECTS

TREATMENT PERIOD	PLACEBO/ CETIRIZINE ¹ 3	KETOCONAZOLE/ COMBINATION ² 3	ESTIMATED KETOCONAZOLE EFFECTS	ESTIMATED OVERALL KETO EFFECTS
BASELINE	306.16± 14.73	305.15± 15.69		
CHANGE				
DAY 6 W/O CETIRIZINE	-2.32± 5.21	4.91± 9.69	7.23	
DAY 16 WITH CETIRIZINE	4.75± 9.73	14.15± 12.17	9.41	8.30 (P=.028)

ESTIMATED CETIRIZINE EFFECTS BY REGIMEN 7.07 9.24

ESTIMATED OVERALL CETIRIZINE EFFECT 0.15 (P=.001)

ANALYSIS OF VARIANCE(SAS TYPE III MS)

EFFECT	DF	MEAN SQUARE	F-RATIO ⁴	P-VALUE	P-VALUES FOR DIRECT PAIRWISE COMPARISONS OF COMPONENTS AND COMBINATION			
					CETIRIZINE	KETOCONAZOLE	COMBINATION	
SUBJECT	14	115.14	2.40	.051				
KETOCONAZOLE	1	1037.90	5.90	.028				
SUBJ=KETO	14	173.50	3.73	.010				
CETIRIZINE	1	997.31	34.92	.001	PLACEBO	.013	.012	.000
SUBJ=CETIR	14	20.54	0.61	.014	CETIRIZINE		.948	.002
KETO=CETIR	1	17.77	0.30	.546	KETOCONAZOLE			.002
SUBJ=KETO=CETIR	14	46.51						

¹SUBJECTS RECEIVED PLACEBO FOR THE FIRST FIVE DAYS AND THEN RECEIVED CETIRIZINE FOR AN ADDITIONAL TEN DAYS

²SUBJECTS RECEIVED KETOCONAZOLE FOR THE FIRST FIVE DAYS AND THEN RECEIVED COMBINATION FOR AN ADDITIONAL TEN DAYS

³SUBJECTS RECEIVED BOTH REGIMENS WITH INTERVENING WASHOUT IN CROSSOVER FASHION

⁴EFFECTS ARE TESTED AGAINST CORRESPONDING MS FOR INTERACTION WITH SUBJECT.

6. Also the hour 30, 36 and 48 post-dose recordings associated with treatment day 16 were redefined as hour 6, 12 and 24 of day 17. Note that day 17 was not a dosing day.

3. Statistical Methods for Change From Baseline

Changes in Hodges QTc, as well as changes in Bazett QTc, uncorrected QT and RR interval, were analyzed comparatively among treatments using analysis of variance procedures appropriate to a mixed random and fixed effects model. The analysis focused on the changes from day 1 to treatment day 6 and 16 since ECG recordings were made at every hour corresponding to baseline day (day 1). Day 6 is the last day of dosing with either placebo or ketoconazole alone, and day 16 is the last day of dosing after cetirizine was added to the treatment regimen for 10 days. For completeness, plots of mean Hodges QTc for each hour separately are provided in Appendix E.4, showing mean QTc for all days on which ECGs were recorded at the particular hour. The study design allowed for the parameterization of the statistical model as a factorial model consisting of an overall effect of ketoconazole, an overall effect of cetirizine, and the drug interaction effect of cetirizine and ketoconazole. These terms are defined as follows (refer to Table 3 for a diagrammatic representation).

As described in Section IV.A, each subject received both 15-day treatment regimens: placebo on treatment phase day 2 through 6 followed immediately by cetirizine alone on days 7 through 16; and ketoconazole alone on day 2 through 6 followed by combination treatment on days 7 through 16. The overall ketoconazole effect is the mean of the following two effect estimates: (K1) the mean difference between ketoconazole alone and placebo at day 6 when no cetirizine is present, and (K2) the mean difference between the combination and cetirizine alone at day 16. Similarly, the overall cetirizine effect is the mean of the following two effect estimates: (C1) the mean difference between cetirizine alone at day 16 and placebo at day 6 within the treatment regimen that does not include ketoconazole, and (C2) the mean difference between the combination at day 16 and ketoconazole alone at day 6 within the regimen including ketoconazole throughout. When the effects of K1 and K2 are identical then the overall effect estimate measures the ketoconazole effect independent of cetirizine. Likewise, when the effects of C1 and C2 are identical then the overall effect estimate measures the cetirizine effect independent of ketoconazole. Otherwise, the effect of component drug alone can only be estimated from K1 and C1.

The drug interaction term measures the amount by which the ketoconazole effect when cetirizine is present differs from the effect without concurrent cetirizine, and is estimated by $K2 - K1$. Identically, the drug interaction is the amount by which the cetirizine effect when ketoconazole is administered concurrently differs from the effect without ketoconazole present, and is identically estimated by $C2 - C1$. When the drug interaction term is equal to zero, the total effect of combination treatment on change in QTc is equal to the sum of the overall component effects.

It is important to note that the cetirizine effect cannot be separated from a serial measurement effect, i.e., a time effect from day 6 to day 16. Likewise, the drug interaction effect cannot be separated from a cumulative effect of fifteen days of ketoconazole treatment.

An initial statistical model was examined to ascertain whether effects were consistent over the eight recording hours. With respect to Hodges QTc change from baseline no significant variation across hours and no drug by hour interactions were statistically significant indicating that effects could be averaged over hours. Details of this analysis are provided in Appendix E.3.

Because of this consistency the change from baseline was averaged over hours and the average changes were analyzed (see Appendix F.1 for a listing of these averages on day 6 and day 16) in order to simplify the model. Therefore the primary model included the random effect of subject, the overall effect of ketoconazole, the overall effect of cetirizine, and the drug interaction along with the interactions of each fixed effect with subject. The error term for testing the significance of any effect in the model is the mean square for the corresponding interaction with subject. The ketoconazole effect, the cetirizine effect and the interaction effect were declared statistically significant if the associated F-statistic was greater than or equal to the 5% critical value of the F-distribution. The sums of squares in each analysis were computed using SAS PROC GLM.

4. QTc Prolongations of 10% Over Baseline

The number of subjects experiencing prolongations of 10% over baseline Hodges QTc was computed and summarized for each of the component treatments and the combination. Each subject was counted only once for each treatment regardless of the number of occurrences of 10% prolongation. However, the likelihood of observing at least one event is not constant among the treatments since only 10 ECG recordings were scheduled during the first 5 days of each treatment regimen when subjects were on placebo or ketoconazole only treatment, but 16 or 24 were scheduled during the next 10 days, during study phase I and study phase II respectively, when subjects received cetirizine or combination treatment. All 16 subjects who received study medication were included in this account, including subject 13 who discontinued early.

B. Adverse Experiences

All reported adverse experiences were coded according to the WHO dictionary preferred term and entered into the clinical database, along with the onset and resolution date, severity and probable cause. A summary table presenting the incidence of adverse experiences by study drug administered was prepared, and is discussed in Section VIII.C. In this table, adverse experiences are assigned to the treatment the subject was taking on the study date when the adverse experience occurred. If an adverse experience had a duration over several study dates on which the subject received different treatments, the adverse experience was counted once for each treatment. Multiple episodes of an adverse experience are counted once per

study phase I.

For the statistical analysis, the cetirizine and ketoconazole pharmacokinetic parameters were analyzed independently. Cetirizine parameters for cetirizine administered alone (day 16) were compared to those estimated on combination dosing (day 16), following ketoconazole pretreatment. Ketoconazole parameters were compared between ketoconazole alone (day 6) and with cetirizine added (day 16). For each parameter, only subjects with values for both treatments were used in the statistical analyses. The analysis of variance was performed on the logarithms of the pharmacokinetic parameters. The results of the ANOVA were used to compute 90% confidence intervals for the ratios of C_{max} and AUC(24) means between administration of each of the drugs alone and in combination.

A detailed description of the pharmacokinetic analysis and statistical analysis methodology are presented in Appendix L.

VI. Subject Disposition

Sixteen normal volunteers were randomized to treatment sequence groups. One subject (#13) was discontinued on the second day of study phase II because his baseline drug screen was positive (Table 1). All of the remaining 15 subjects completed the study.

VII. Subject Demographic and Baseline Characteristics

The study population consisted of 12 Hispanic males, 2 white males and 2 black males, between 22 and 40 years old with a mean age of 30.0 years. The average weight was 156.5 lbs, ranging from 142 to 182 lbs. At the screening visit all the subjects had normal blood pressures, between 98 and 130 mmHg systolic, and 66 and 84 mmHg diastolic; and normal heart rate, between 60 and 86 beats per minute. Table 2 shows demographic characteristics and screening vital signs for the subjects in the study.

VIII. Results

A. ECG Measurements

1. Mean QT Interval

Table 3 shows a synopsis of the results of the analysis of change from baseline Hodges QTc. Mean changes are shown for placebo, cetirizine alone, ketoconazole alone and combination treatment. The estimates of the ketoconazole effects (K1 and K2) and the cetirizine effects (C1 and C2) are shown along with the estimates of the overall effect of each drug and the estimate of the interaction effect. Details of the analysis are shown in Appendix E.1. Figure 1 shows a plot of mean Hodges QTc (not changes from baseline) for each treatment on day 6 and 16 and also for baseline placebo day 1 of each regimen.

There was no statistically significant drug interaction effect on the change from baseline Hodges QTc. The mean difference (C1) between treatment with cetirizine alone and placebo treatment was 7.07 msec as compared to the mean difference (C2) between combination treatment and treatment with ketoconazole alone of 9.24 msec. The estimated drug interaction effect is $9.24 \text{ msec} - 7.07 \text{ msec} = 2.17 \text{ msec}$. Similarly, the mean difference (K1) between ketoconazole alone and placebo was 7.23 msec compared to a mean difference (K2) of 9.40 msec between the combination and cetirizine alone, which alternatively estimate the interaction of 2.17 msec. The estimated drug interaction effect of 2.17 msec is not statistically significantly different from zero. This indicates that the overall component drug effects, 8.16 msec for cetirizine and 8.32 msec for ketoconazole estimate the effect of each component drug alone (respectively) independent of the presence of the other. Each overall effect estimate is significantly different from zero. Additionally, the total effect of combination treatment is characterized as an additive effect of the individual drugs, but having no enhanced effect over the sum, and is estimated by $8.16 \text{ msec} + 8.32 \text{ msec} = 16.48 \text{ msec}$.

2. Incidence of Prolongations of 10% Over Baseline Hodges QTc

Table 4 summarizes the subject incidence of at least one occurrence of a prolongation of 10% over baseline Hodges QTc. No subject experienced a 10% prolongation during the 5 day placebo treatment. Seven subjects experienced at least 1 prolongation. Two subjects (13.3%) experienced an event during the 10 day cetirizine treatment, 1 subject (6.3%) during the 5 day ketoconazole treatment and 5 subjects (31.3%) had an occurrence during combination treatment (2 in study phase I and 3 in study phase II). A list of specific subjects is provided in Table 5.

3. Clinical Significance

As reported, this analysis is based on Hodges correction. The literature on this subject has primarily reported QT changes corrected according to Bazett's formula. The following discussion of clinical relevance of study results will be based on QT corrected according to Bazett's formula, in order to facilitate literature comparison (*ref*: Appendix E.1 for statistical analysis and Appendix F.2 for data listing). Review of the literature shows that a normal human subject may have changes in QTc duration varying by 15 to 70 msec (*Am J Cardiol* 1991; 67:774). The maximum in Bazett QTc change for all subjects in this study was 57 msec (Subject #14, Phase 2, Day 16, Hour 0: QTc = 422 msec). This result is well within the normal range. Thus, neither cetirizine alone nor in combination with ketoconazole was associated with a clinically significant change in Bazett QTc.

The listing of ECG measurements and changes from baseline are shown in Appendix F2. Using the criterion of QTc > 440 msec (*Am J Cardiol* 1991; 67:774) to identify abnormal QTc results, three subjects met this criterion, as shown below. The QTc changes were not sustained and occurred during

Addendum #1 to Medical Officer Review dated 10/17/95

NDA 19835

ORIGINAL

Drug: Cetirizine tablets (Zyrtec)

Sponsor: Pfizer

Date: November 3, 1995

Subject: Revisions to Medical Officer Review dated 10/17/95 incorporating Dr. Marty Himmel's recommendations.

Review of the sponsor's response via telephone facsimile dated November 2, 1995 to our request for further information of a patient with elevated liver transaminases (annual report for IND dated 9/25/95).

Medical Officer Reviewer: Ana M. Saavedra-Delgado, M.D.

Section 1 of this addendum contains the revisions to the original ^{4/3/95} Medical Officer Review to the NDA dated 10/17/95. The original pages are followed by the revised pages. The changes made are bolded and underlined.

Section 2 describes the case with elevated transaminases and includes the review of the annual report to the IND as Appendix 1 and the sponsor's telephone facsimile response as Appendix 2.

See supervisor's memo in attached 11/8/95

CC:

Original NDA 19-835

HFD-570/D.V. Files

HFD-570/M. Himmel

HFD-570/A. Saavedra-Delgado

HFD-570/K. Lee

Section 1

Outline and Table of Contents of this review:

Section 1.

- I. Response to our clinical requests on the February 21, 1995 NDA approvable letter.

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- II. Relevant Additional Safety Update Information

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New

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Section 3

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- II. Reviewer's general comments and regulatory recommendations.

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No MO reviewer's comments were made to the sponsor's response to questions 4, 6b, 6d, and 6e, 9, 19 and 21 of the approvable letter; they were found to be acceptable. The sponsor's response or salient points of the response were included in these sections. Comments to the sponsor's response to questions 15, 17, 19 and 20 are part of the reviews from the pertinent disciplines (Pharmacology or Biopharm).

Incidence of psychiatric disorders adverse experiences in placebo controlled studies by duration of treatment.

Adverse experience	cet up to 2 wks No. Pts (%)	cet 3-4 wks	cet 5-12 wks	placebo up to 2 wks	placebo 3-4 wks	placebo 5-12 wks
Total No. of Pts	2676	1835	957	1671	1147	586
N. of Pts with any Psychiatric Disorders	425 (15.9%)	160 (8.7%)	82 (8.6%)	133 (8.0%)	45 (3.9%)	22 (3.8%)
Somnolence	374 (14.0%)	135 (7.4%)	71 (7.4%)	96 (5.8%)	32 (2.8%)	17 (3.0%)
Concentration impaired	5 (0.2%)	0 (0%)	1 (0.1%)	1 (0.1%)	0 (0%)	0 (0%)
Emotional lability	3 (0.1%)	2 (0.1%)	3 (0.3%)	0 (0%)	0 (0%)	0 (0%)
Depression	4 (0.2%)	2 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.2%)
Thinking abnormal	4 (0.2%)	3 (0.2%)	2 (0.2%)	0 (0%)	0 (0%)	0 (0.0%)

* A patient can have an adverse experience reported for more than one interval of cetirizine therapy.

Agree with the sponsor's conclusion that somnolence accounts with the majority of the incidence of the reports in this category. The above series of tables also demonstrate that at doses of 5 and 10 mg it is approximately double the reported incidence in placebo treated patients (Table F8. B2-B3) and that this incidence persists at the different time intervals: up to 2 weeks, 3-4 weeks and 5-12 weeks of treatment (Table F8. B-4).

The reported incidence rates of other adverse events such as: concentration impaired, emotional lability and thinking abnormal are less than 1% but they are reported more frequently and for a longer duration than in placebo treated patients.

NEW

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The reported incidence rates of other adverse events such as: concentration impaired, emotional lability and thinking abnormal are less than 1% but they are reported more frequently and for a longer duration than in placebo treated patients.

Even though the % of patients reporting increase in appetite is greater for those treated with 5 mg, the % of patients reporting a weight increase is greater for those patients that had been treated with the 10 mg tablet.

Adverse experience	Cet 5 mg up to 2 wks	Cet 5 mg 3-4 wks	Cet 5 mg 5-12 wks	Cet 5 mg 15wks to 6 mo
Total No. of pts	589	397	273	34
Total No. of pts with adverse experiences	214 (36.3%)	98 (24.7%)	75 (27.5%)	11 (32.4%)
fatigue	18 (3.1%)	9 (2.3%)	8 (2.9%)	0 (0%)
weight increase	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)
Adverse experience	Cet 10 mg up to 2 wks	Cet 10 mg 3-4 wks	Cet 10 mg 5-12 wks	Cet 10 mg 15wks to 6 mo
Total No. pts.	1961	1225	529	69
Total No. of pts with adverse experiences	758 (38.7%)	312 (25.5%)	139 (26.3%)	13 (18.9%)
fatigue	102 (5.2%)	48 (3.9%)	14 (2.7%)	1 (1.5%)
weight increase	9 (0.5%)	11 (0.9%)	10 (1.9%)	3 (4.4%)

The reports of weight increase during longer duration of treatment are more apparent in the higher dose group.

In these listings, the following are noted, in parenthesis, duration of exposure:

Diabetes Mellitus: 5mg dose at the 5-12 week interval (1)
 Polyuria: 10 mg (up to 2 wks) (4), (3-4 wks) (1)
 Purpura: 5 mg dose at the 3-4 week interval (1) and 5-12 wk interval (1)
 Purpura: 10 mg (up to 2 weeks) (1)
 Hematuria: 10 mg (3-4 weeks) (1)
 Ocular hemorrhage: 10 mg (up to 2 weeks) (1)
 visual field defect: 10 mg (up to 2 weeks) (1)
 vision abnormal: 5 mg (up to 2 wks) (2), (3-4 weeks) (1)
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 Tinnitus: 5 mg (up to 2 weeks) (1)
 Tinnitus: 10 mg (up to 2 weeks) (1), (3-4 wk) (1), 5-12 wks) (1)

New Reviewer's comments: Even though the % of patients reporting increase in appetite is greater for those treated with 5 mg, the % of patients reporting a weight increase is greater for those patients that had been treated with the 10 mg tablet.

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 Tinnitus: 5 mg (up to 2 weeks) (1)
 Tinnitus: 10 mg (up to 2 weeks) (1), (3-4 wk) (1), 5-12 wks) (1)

Scatterplots of BUN, creatinine, SGOT and SGPT by age, gender, race and dose did not reveal a clear trend between cetirizine and placebo.

Further information was requested from the sponsor regarding specific outliers in these scatterplots. The sponsor's response dated August 11, 1995 was reviewed. A alternative explanation as to the possible cause of lab abnormality was not found after review of the CRF for the following patients. These patients were required to have a baseline value within the normal range and at least one abnormal value after the start of treatment:

N-0047 84N0060/49

54 y/o white, female patient in SAR study. In CFR no record of concomitant drugs or illness. Patient received 10 mg cetirizine treatment from 9/19/84 to 9/26/94. Patient completed the study.

Prior to treatment	9/18/84	SGOT=31
		SGPT=27
		LDH=246
		T. bili=0.2
End of treatment	9/26/84	SGOT=80
		SGPT=108
		LDH=272
		T. bili=0.3
	10/3/84	SGOT=40
		SGPT=89
		LDH=235
		T. bili=not available in CFR
	10/9/84	SGOT=17
		SGPT=26
		LDH=not available in CFR
		T. bili=not available in CFR

N-0050 85N0044/5

35 y/o hispanic female patient in a 4 week chronic idiopathic urticaria study. In the CFR there is no record of concomitant drugs or illness. Patient received 10 mg cetirizine treatment from 9/19/84 to 9/26/94. Patient had received Benadryl for 9 mo. prior to study.

Prior to treatment	6/9/86	SGOT=23
		SGPT=24
		LDH=188
		T. bili=0.5
First Day of treatment	6/11/86	
End of week two	6/25/86	
		SGOT=82
		SGPT=70

New

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Prior to treatment 9/18/84	SGOT=31 SGPT=27 LDH=246
End of treatment 9/26/84	T. bili=0.2 SGOT=80 SGPT=108 LDH=272
10/3/84	T. bili=0.3 SGOT=40 SGPT=89 LDH=235
10/9/84	T. bili=not available in CFR SGOT=17 SGPT=26 LDH=not available in CFR
	T. bili=not available in CFR

N-0050 85N0044/5

35 y/o hispanic female patient in a 4 week chronic idiopathic urticaria study. In the CFR there is no record of concomitant drugs or illness. Patient received 10 mg cetirizine treatment from 6/11/86 to 7/9/86. Patient had received Benadryl for 9 mo. prior to study.

Prior to treatment 6/9/86	SGOT=23 SGPT=24 LDH=188
First Day of treatment 6/11/86	T. bili=0.5
End of week two 6/25/86	SGOT=82 SGPT=70

patients in both the NDA and cumulative database, the incidence for the term sinus infection are different:

For NDA database:cetirizine 1 (0.1%) placebo 0 (0.0%)

For Cumulative database:cetirizine 11(0.4%) placebo 0 (0%)

The incidence of menstrual cramps also increased 0-0.7% from the NDA to the cumulative database presumably due to the increased number of women enrolled in the cumulative database.

The CRF and additional information was requested from the sponsor regarding three patients listed as having intercurrent illnesses. The reported events for these patients were: abnormal EKG, premature cardiac beats, and syncopal episode. The sponsor response (BM-7/17/95) was reviewed.

Patient 87-N-0017/36: 44 y/o asian male, in seasonal asthma study, symptomatic premature beats. These decreased after rinsing mouth after using a beta agonist inhaler. ECG reported normal by investigator.

Patient 91-S-0033/304: 18 y/o hispanic female in SAR and asthma study; syncopal episode 4 days post treatment initiation, patient continued treatment; no recurrent events reported by the investigator.

Patient 89-N-0103/74: 51y/o caucasian female in PAR study, according to patient's primary physician, this patient had prior history of heart palpitations and shortness of breath not related to exercise, with 80% PFTs and was referred to the study investigator for asthma evaluation. The study investigator did not record any CV signs or symptoms in the initial screening hx and physical exam. During the course of treatment a routine ECG was done prior to a bunion operation which was abnormal: with T wave inversions and multiple PVCs. Echo revealed mitral prolapse and regurgitation as well as tricuspid regurgitation. The patient discontinued the study early.

Placebo controlled studies. "The overall incidence of intercurrent illnesses in the cumulative database in cetirizine treated patients (16.5%) and placebo treated patients (19.2%) were similar."

From Table P8.C, the number of patients with intercurrent

NEW

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The CRF and additional information was requested from the sponsor regarding three patients listed as having intercurrent illnesses. The reported events for these patients were: abnormal EKG, premature cardiac beats, and syncopal episode. The sponsor response (BM-7/17/95) was reviewed.

In the following case the adverse event appears to have been related to the use of beta agonist and not to an intercurrent illness.

Patient 87-N-0017/36: 44 y/o asian male, in seasonal asthma study, symptomatic premature beats. These decreased after rinsing mouth after using a beta agonist inhaler. ECG reported normal by investigator.

There was no characterization of the syncopal episode in the CRF for the following patient. Although cetirizine may not have been its cause, it should have been reported as an adverse event.

Patient 91-S-0033/304: 18 y/o hispanic female in SAR and asthma study; syncopal episode 4 days post treatment initiation, patient continued treatment; no recurrent events reported by the investigator.

For the following patient the mitral valve prolapse was the most likely cause for the reported palpitations. In this case the report of the adverse experience as an intercurrent illness was justified.

Patient 89-N-0103/74: 51y/o caucasian female in PAR study, according to patient's primary physician, this patient had prior history of heart palpitations and shortness of breath not related to exercise, with 80% PFTs and was referred to the study investigator for asthma evaluation. The study investigator did not record any CV signs or symptoms in the initial screening hx and physical exam. During the course of treatment a routine ECG was done prior to a bunion operation which was abnormal: with T wave inversions and multiple PVCs. Echo revealed mitral prolapse and regurgitation as well as tricuspid regurgitation. The patient discontinued the study early.

Placebo controlled studies. "The overall incidence of intercurrent illnesses in the cumulative database in cetirizine treated patients (16.5%) and placebo treated patients (19.2%) were similar."

From Table F8.C, the number of patients with intercurrent

52 msec?. The patient took the vistaril for inability to sleep. The dose: 1 capsule po q hs. The therapy dates: 12/25. Therapy duration 12/31. Event onset:12/31/92. Event duration: 1 day. Did event abate after stopping drug?: Yes. Did event reappear after reintroduction?:N/A. Date of report: 2/7/93. Physician: Dr. Keneth Ellenbogen, Medical College of Virginia, Box 53 Richmond Va, 23298, 804-786-7565. Stamped: Received on 93 Feb 16.

The patient had tolerated the concomitant medication regimen which included procainamide, lanoxin, diuretics and potassium supplements without a history of adverse events. We do not know the status of the patient's electrolytes at the time of torsades. In view that no additional information will be available in this case, it cannot be ruled out that hydroxyzine at normal doses did not contribute to the QT prolongation and torsades in this patient.

8. Please address the increased frequency of Category 9 adverse events (liver enzymes) in the erythromycin-cetirizine study for 4 out of 16 patients receiving the combination.

"Results falling outside the normal range were reviewed by the investigator for clinical significance and relationship to study drug. The abnormal results were later computer categorized as Category 9 were those that were considered to be clinically significant and possibly related to study medication. These in turn were blindly reviewed by a Pfizer physician and were either left as Category 9 or recategorized to one of the following: 5=documented lab. error, 6=likely due to concurrent illness, 7=likely due to concomitant medication."

See attached photocopy. (SU 4/25/95, vol 35.2, p9 61)

New 52 msec?. The patient took the vistaril for inability to sleep. The dose: 1 capsule po q hs. The therapy dates: 12/25. Therapy duration 12/31. Event onset: 12/31/92. Event duration: 1 day. Did event abate after stopping drug?: Yes. Did event reappear after reintroduction?: N/A. Date of report: 2/7/93. Physician: Dr. Kenneth Ellenbogen, Medical College of Virginia, Box 53 Richmond Va, 23298, 804-786-7565. Stamped: Received on 93 Feb 16.

The patient had tolerated the concomitant medication regimen which included procainamide, lanoxin, diuretics and potassium supplements without a history of adverse events. We do not know the status of the patient's electrolytes at the time of torsades. In view that no additional information will be available in this case, it cannot be ruled out that hydroxyzine at normal doses did not contribute to the QT prolongation and torsades in this patient.

8. Please address the increased frequency of Category 9 adverse events (liver enzymes) in the erythromycin-cetirizine study for 4 out of 16 patients receiving the combination.

"Results falling outside the normal range were reviewed by the investigator for clinical significance and relationship to study drug. The abnormal results were later computer categorized as Category 9 were those that were considered to be clinically significant and possibly related to study medication. These in turn were blindly reviewed by a Pfizer physician and were either left as Category 9 or recategorized to one of the following: 5=documented lab. error, 6=likely due to concurrent illness, 7=likely due to concomitant medication."

Refer to the sponsor's response in the following page-attached photocopy. (SU 4/25/95, vol 35.2, p9 61).

Reviewer's comments:

In this study that incorporated sequential measurements of liver transaminases the incidence of elevated SGPT is higher (4/16, 25%), than the reported incidence in the placebo controlled clinical study population. It is not completely clear in this study whether the elevations in SGPT are due to cetirizine or erythromycin alone or to the combination. This study was a cross-over study; there were no concurrent placebo, erythromycin or cetirizine controls. The data in two of the four patients (from the sequence: cetirizine for 5 days then add erythromycin) suggests that the combination may contribute to further elevate the SGPTs than when the drug is given alone.

The four patients listed had a normal SGPT at baseline. In three patients (#6, 16, and 102) the values from Day 5 on

NEW cetirizine alone to day 6 (first day on the combination) go from being within normal limits to = or >2x. It is unlikely that the addition of one day of erythromycin would have caused this effect on the liver if it had not been started earlier by the drug (cetirizine for 5 days) alone. The same can be said for the patient that started on erythromycin (patient #1) that has a >2x increase in SGPT from Day 5 (erythromycin for 5 days) to Day 6 (first day on the combination).

The elevations in SGPT for patients (#6 and # 16) in the first sequence are of clinical concern. They continue to increase on Day 8 (three days on the combination) to levels up to 6x the levels recorded at Day 5 when cetirizine was given alone. However, there is a decrease in the SGPT levels after both drugs are discontinued. Patient #16 is discontinued from the study and the last value recorded for SGPT is greater than the upper limit of normal. For patient #6 the SGPT values normalized during the wash-out period and both drugs are given again in the opposite sequence. The values in SGPT double again on Day 6, however this elevation is less than that reported for this patient in the previous sequence. Following the wash out period the SGPT decreases.

Since patient #16 did not receive the opposite sequence (erythromycin followed by cetirizine) and the reported values of patient (#6) do not include a value for Day #8 of the second sequence (erythromycin followed by cetirizine) it can only be suggested that clinically in terms of SGPT elevations, patient (#6) would tolerate better the second combination sequence (erythromycin follow by cetirizine) than viceversa.

9. As previously advised, your proposed name "Reactine" connotes usefulness in acute situations and implies lack of drowsiness. Your alternate proposed names "Ultreon" implies maximum strength or effectiveness as compared to related products and "Alacrin" appears to be derived from "alacrity" which denotes quickness and alertness. These three tradenames are not acceptable. Your alternate proposed name, "Zyrtec", is acceptable.

The sponsor accepted the trade name Zyrtec. Refer to proposed package insert.

10. Your proposed annotated package insert has been revised. Please refer to the attachment and note that our recommended additions to the labeling are underlined and in bold typeface and our comments are in brackets, caps, and bold typeface.

The proposed package insert was included in this submission. Specific comments regarding the proposed labeling are included in Section 2 of this review.

SGPT (U/L) Values

Pt.	Base line	Cet Day 5	Comb Day 6	Comb Day 8	Comb Day 10	Wash Day 2	Wash Day 4	Wash Day 7	Wash Day 19	Eryth Day 5	Comb Day 6	Wash Day 2	Wash Day 7
6													
16													
102													

Pt.	Base line	Ery Day 5	Comb Day 6	Comb Day 8	Comb Day 10	Wash Day 2	Wash Day 4	Wash Day 7	Wash Day 19	Cet Day 5	Comb Day 6	Wash Day 2
1												

One of the subjects demonstrated a maximal elevation of SGPT < 2x the upper limit of normal, another subject showed a maximal SGPT elevation between 2 and 4 times the upper limit of normal, and the other two subjects had maximum elevations >4X the upper limit of normal. All subjects were asymptomatic, and no subject discontinued for abnormal liver function tests. Two subjects (nos. 6 and 102) experienced elevations of SGPT on the combination of drugs following single administration of both cetirizine and erythromycin; subject 102 experienced an elevated SGPT on erythromycin alone as well. One patient (no. 16) experienced an abnormal SGPT on the combination following cetirizine, but he discontinued from the study prior to the second regimen for personal reasons. Subject 1 had an abnormal SGPT on combination treatment following initial treatment with erythromycin, but not on cetirizine alone or on the combination following initial treatment with cetirizine. In general, the SGPT returned to normal when the combined drugs were stopped during the three week washout phase.

Both cetirizine and erythromycin are known to be associated with abnormal transaminases in a small percent of patients. It is difficult to attribute the abnormalities observed in the small number of volunteers in this study to either the combination, cetirizine alone or erythromycin alone because of the sequential nature of the design and lack of concurrent placebo, erythromycin, and cetirizine controls. In addition, the abnormalities resolved during the washout period when both drugs were withdrawn. Therefore, we cannot attribute these abnormalities to concomitant administration of cetirizine and erythromycin. ■

SGPT (U/L) Values

Pt.	Base line	Cet Day 5	Comb Day 6	Comb Day 6	Comb Day 10	Wash Day 2	Wash Day 4	Wash Day 7	Wash Day 19	Eryth Day 5	Comb Day 6	Wash Day 7	Wash Day 7
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Pt.	Base line	Ery Day 5	Comb Day 6	Comb Day 8	Comb Day 10	Wash Day 2	Wash Day 4	Wash Day 7	Wash Day 19	Cet Day 5	Comb Day 6	Wash Day 2
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found in the cetirizine group are small and similar to the placebo group. The mean changes by dose do not suggest a relationship between cetirizine dose and change in vital sign parameter." **Appendix 1**

- B. Hydroxyzine/Meclizine and cardiovascular events (update) in Appendix F volume 35.4 -January 1, 1994 to April 19, 1995. The review identified 14 new hydroxyzine cases, one updated hydroxyzine case, and two new meclizine cases. Of these 16 were spontaneously reported and one was a literature report.

"The updated review of the new cases supports the previous conclusion that there is no indication that serious arrhythmias occur in association with hydroxyzine or meclizine when used in normal therapeutic doses in patients who are otherwise healthy." **Appendix 2.**

- C. Response to a consult request to the Division of Epidemiology and Surveillance, HFD-730 on Ketoconazole and Hydroxyzine drug interaction dated June 23, 1995.

Line-listing corresponding to the Spontaneous Reporting System reports where ketoconazole and Hydroxyzine are listed as concomitant drugs. Between 1982 and the present there have been 20 such reports in the SRS.

Demographics:

Outcome: 2 deaths; 5 hospitalizations; 1 disability

Origin: 18 domestic; 2 foreign

Sex: 6 female; 14 male

Age: range 6-90

Most often reported COSTART terms (2 or more cases each):

Liver function abnorm	5
Bilirubinemim	3
Phosphatase alk inc	3
Pruritus	3
Intracran hyperten	2
Jaundice cholestat	2
Rash	2
Rash mac pap	2

The ketoconazole labeling addresses hepatic adverse events. An interaction with hydroxyzine is not mentioned. In reviewing the report its important to remember the limitations associated with data derived from the Spontaneous Reporting System. **Appendix 3.**

- D. Update on cetirizine literature review in Appendix E, vol 4, SU 4/25/95 with copy of article in correspondence dated 8/8/95.

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- D. Update on cetirizine literature review in Appendix E, vol 4, SU 4/25/95 with copy of article in correspondence dated 8/8/95.

The photocopy of a case report suggestive of drug induced hepatitis is enclosed in **Appendix 4**.

New

found in the cetirizine group are small and similar to the placebo group. The mean changes by dose do not suggest a relationship between cetirizine dose and change in vital sign parameter." Appendix 1

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"The updated review of the new cases supports the previous conclusion that there is no indication that serious arrhythmias occur in association with hydroxyzine or meclizine when used in normal therapeutic doses in patients who are otherwise healthy." Appendix 2.

Reference is made to the review (MOR-2/27/94) of a series of patients identified by the sponsor (submission dated 1/20/94) as having reported a cardiovascular event that could relate to a prolonged QT and that had received treatment with hydroxyzine or meclizine. Of the 4/12 hydroxyzine cases with identified torsades, one was an overdose, and in the other three hydroxyzine was a concomitant medication with another drug that could produce torsades. Of the 6 meclizine cases, one patient developed torsades and in this case the dose was higher than recommended and the patient had concomitant heart failure and liver disease.

None of the cases that follow has the complete information or provides a clear cut evidence that hydroxyzine or meclizine can on their own at recommended doses produce a direct cardiac effect and prolong the QT interval to the point of producing serious arrhythmias. However, these cases as a group suggest that for both hydroxyzine and meclizine this effect is possible; the mechanism is not clear. They have been identified as a concomitant medication in ventricular arrhythmias in apparently healthy individuals, in patients with underlying cardiovascular disease and in patients with drug overdose. For the parenteral formulations of hydroxyzine symptomatic hypotension and bradycardia are also reported.

The list provided by the sponsor in this submission does not identify any patient with torsades. Of the new 14 hydroxyzine patients identified, cardiac arrest is reported in 4 of them (9501282-25 y/o male, 1250 mg po, intentional overdose, recovered; 9408568-unknown age and gender, concomitant venlafaxine, recovered; 950193, 4y/o, as dental anesthesia 50 mg po, concomitant diazepam and lidocaine, arrested following apneic episode, died; 9503398, 30 y/o,

NEW

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prior to surgery 50 mg po x 3 days, ventricular fibrillation following severe bronchospasm, arrested, died).

Symptomatic transient hypotension in a 36 y/o female (9400513) that received 100 mg IM along with meperidine for pain, was followed with ischemia in ECG leads and myocardial enzyme elevation; "cardiac catheterization and echo revealed a completely normal heart". Other cases that also reported hypotension were: 9503404, 32 y/o male, 150 mg IM and atropine 0.5 mg prior to surgery; and 9503403, 55 y/o female, 150mg IM along with atropine 0.5 mg prior to surgery.

Bradycardia was also reported by 9503404 and 9501282 as well as by 9503401, unknown age and gender and concomitant disease ("deficient heart state" an gastric cancer), hydroxyzine and amiodarone, bradycardia improved when hydroxyzine was discontinued; 9503397 and 9503400 patients of unknown age and gender, intravenous hydroxyzine, dose unknown.

One of the two reported meclizine patients 9401063, 42 y/o male, on unknown dose for vertigo for "a couple of weeks" had ventricular fibrillation, patient recovered, work up for cardiac disease was negative.

- C. Response to a consult request to the Division of Epidemiology and Surveillance, HFD-730 on Ketoconazole and Hydroxyzine drug interaction dated June 23, 1995. See Appendix 3.

The intent of the consult was to screen out if there were any other cases of cardiovascular events reported with the interaction. An additional case of torsades was produced by this search. However, the patient was hypocalcemic and was both on terfenadine (120mg po 15 days) and ketoconazole (400 mg po 14 days) in addition to hydroxyzine.

The findings of the consult point out to another effect, hepatic adverse events.

Ketoconazole has been associated with hepatic toxicity, including some fatalities, a warning box is included in the labeling. Hydroxyzine labeling does not mention the association with liver function abnormalities. The cases reported in this search had in addition to the ketoconazole hydroxyzine combination other concomitant medications. The duration of treatment that the patients received both drugs is not specified. Therefore, it is not clear what role hydroxyzine could have had in these cases.

New

- D. Copy of literature article reporting a case of hepatitis associated with the use of cetirizine. The article was mentioned in the update on cetirizine literature review in Appendix E, vol 4, SU 4/25/95 and the article was submitted in correspondence dated 8/8/95. Appendix 4.

the results using the combination are comparable with single dose administration data (azithromycin) from other studies.

Sponsor's conclusion:

The results indicate that cetirizine 20 mg QD administered for ten 10 does not affect the QT interval. There is no indication that concomitant administration of azithromycin and cetirizine produces any significant changes in QT interval. No pharmacokinetic interaction occurs when subjects who are taking cetirizine and have attained steady state levels of the drug are additionally administered the five-day recommended dosage regimen of azithromycin. Cetirizine alone and in combination with azithromycin was well tolerated in this study.

Reviewer's comments:

After reviewing the study the following questions were faxed to the Sponsor August 4, 1995. For clarity th'e questions are bolded and a summary of the response that was submitted and the amendment to the NDA dated, 8/11/95, follows.

- 1. Please provide the corresponding ECG values in the format of Appendix F.2 in vol 14, for the following ECGs with QTc prolongations that are listed in Table 1.5, vol 1:**

Cetirizine pt. # 25 Treatment Day 9 (Study Day 10) Hour 0
Day 10 : QTc 410 (Bazzet), 12.02% increase QTc Bazzet

Cetirizine pt. #38 Treatment Day 3 (Study Day 4) Hour 6
Day 4: QTc 436 (Bazzet), 10.66% increase QTc Bazzet

Cet/Azi pt. #35 Treatment Day 9 (Study Day 10) Hour 0
Day 10: QTc 427 (Bazzet), 17.96% increase QTc Bazzet

Cet/ Azi pt. #39 Treatment Day 9 (Study Day 10) Hour 0
Day 10: QTc 431 (Bazzet), 12.53% increase QTc Bazzet

Placebo pt. #12 Treatment Day 9 (Study Day 10) Hour 0
Day 10: QTc 435 (Bazzet), 12.40% increase QTc Bazzet

Placebo pt. # 33 Treatment Day 9 (Study Day 10) Hour 0
Day 10: QTc 433 (Bazzet), 13.05% increase QTc Bazzet

Please explain why the corresponding ECG values for the above patients were not included in the Appendix F.2 listing and what was the reason for obtaining these ECGs out of the regular protocol schedule. Please submit the listings for any other ECGs obtained out of the regular protocol

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Please explain why the corresponding ECG values for the above patients were not included in the Appendix F.2 listing and what was the reason for obtaining these ECGs out of the regular protocol schedule. Please submit the listings for any other ECGs obtained out of the regular protocol

Days	# of patients with QTc prolongation 10% or greater	# ECGs, QTc 10% or greater	# ECGs, QTc>440
1-5	4	4	1
6-9	3	3	0
10	7	12	5

Combination treatment:

Days	# of patients with QTc prolongation 10% or greater	# ECGs, QTc 10% or greater	# ECGs, QTc>440
5*	5	6	3
6-9	5	5	1
10	4	7	2

* Please note that from days 1-5 inclusive patients were receiving only cetirizine

In the attached Table E.2.2., the statistical difference between cetirizine and the combination is $p=0.02$ for the treatment effect from Day 6 to Day 11. We would have expected the patients for both cetirizine and combination to have approximate equal Day 6 change, since the two groups were receiving the same drug for those 5 days of treatment. However, the cetirizine only group had a lower increase in QTc, than the combination, in this reviewer agrees with the Sponsor's interpretation for Day 6, since in addition the baseline QTc for cetirizine was 425 msec and for the combination it was 429 msec.

However, when the treatment effect from Day 6 to Day 11 is calculated, (Day 11-Day 6) cetirizine group it is 13.41 msec, versus the -1.43 in the combination and 3.14 in the placebo treated group. Using the Hodges correction as depicted in Table E.1.3. p11 550 vol 35.14, the maxchange (Day 11-Day6) for cetirizine treated patients was 6.79, versus 0.43msec for the combination and 1.79 for placebo. The mean increase for cetirizine treated patients in the cetirizine -ketaconazole study (Hodges) at 10 days of treatment was 8.2 msec. The results of this study suggest that the combination of cetirizine/azithromycin is favorable in decreasing the expected increase in QTc that has been observed in cetirizine treated

New

Days	# of patients with QTc prolongation 10% or greater	# ECGs, QTc 10% or greater	# ECGs, QTc>440
1-5	4	4	1
6-9	3	3	0
10	7	12	5

Combination treatment:

Days	# of patients with QTc prolongation 10% or greater	# ECGs, QTc 10% or greater	# ECGs, QTc>440
5*	5	6	3
6-9	5	5	1
10	4	7	2

* Please note that from days 1-5 inclusive patients were receiving only cetirizine

In the attached Table E.2.2., there are no statistical significant differences at Day 6 among treatment groups including placebo. We would have expected the patients for both cetirizine and combination to have approximate equal Day 6 change, since the two groups were receiving the same drug for those 5 days of treatment. The cetirizine only group had a lower increase in QTc from baseline at Day 6 than the combination, however this change was not statistically significant.

When the treatment effect from Day 6 to Day 11 is calculated, (Day 11-Day 6), this difference for the cetirizine group is 13.41 msec, versus the -1.43 in the combination and 3.14 in the placebo treated group. There is a statistically significant difference between cetirizine and the combination, p=0.02, for the treatment effect from Day 6 to Day 11. However there is no difference between placebo and either cetirizine alone or the combination in treatment effect from Day 6 to Day 11.

Change from baseline for ECGs recorded within days 11-17 of first dose from Table 2.1:

Number of patients	Placebo 40	Cet 5 mg 35	Cet 10 mg 44	p-value
QTc (Bazett)				
Baseline	425.05 +/- 25.47	417.36 +/- 25.33	420.54 +/- 22.34	
Change	-0.79 +/- 24.25	-0.08 +/- 35.67	10.32 +/- 25.18	
(p-value within)	0.833	0.970	0.015	0.061
Adjusted change	1.77	-2.52	9.94	

Change from baseline for ECGs recorded last or maximum ECG recorded on treatment (11-17 Days ECGs), from Table 2.2:

Number of patients	Placebo 64	Cet 5 mg 64	Cet 10 mg 65	p-value
QTc (Bazett)				
Baseline	418.93 +/- 24.88	421.02 +/- 25.98	421.15 +/- 21.31	
Change	-5.89 +/- 27.21	-2.84 +/- 31.52	10.22 +/- 24.84	
(p-value within)	0.107	0.887	0.002	0.006
Adjusted change	4.92	-2.40	10.73	

Distribution of percent change from baseline for ECGs recorded within days 11-17 of first dose, from Table 2.4:

	under 5%	5- <10%	10- <20%
Placebo-# of pts.	32	6	2
Row %	80%	15%	5%
5 mg cet	27	4	4
Row %	77.14%	11.43%	11.43%
10 mg cet	31	7	6
Row %	70.45%	15.91%	13.64%

INTEROFFICE MEMO

Date: 11/2/95
To: Suzanne LoGalbo
From: Michael Widlitz, M.D. *MW*
Subject: FDA Medical Reviewers Comment Cetirizine APR
(1995)

The following summary is in response to Dr. Delgado's request for information concerning the cetirizine patient with the elevated SGPT.

The patient is identified as Patient No. 344, 93-S-0083, Protocol L-0270, a 26 yo healthy female with an unremarkable history and physical, except for a 22 year history of the disease under study (Seasonal allergic rhinitis). The patient met all inclusion/exclusion criteria and had an unremarkable clinical laboratory profile. The SGPT, SGOT and Bilirubin were 38 U/L, 24U/L, and 1.1 mg/DL, respectively. She had an uneventful course during the trial reporting two adverse events – mild headache for 2 days due to allergies which was treated successfully with ibuprofen, and mild nausea on 1 day, the cause of which was considered uncertain by the investigator. The event resolved following treatment with one dose of Dramamine. The physical examination following 2 weeks of treatment was again unremarkable. All clinical laboratory was normal except for SGPT and SGOT which were 210 U/L and 87 U/L, respectively. The Bilirubin was 1.2 mg/DL. These laboratory parameters were repeated and the results were normal. SGPT was 34 U/L, SGOT was 29 U/L, and Bilirubin was 1.2 mg/DL. No further work up was performed.

Attachments: Case Report Form

CETIRIZINE VS. LORATADINE & PLACEBO

CASE REPORT FORM

SEASONAL ALLERGIC RHINITIS

INVESTIGATOR <i>R. Dockhorn, M.D.</i>	STUDY NUMBER <i>93-5-0083</i>
PATIENT INITIALS	PATIENT NUMBER <i>2646 / 344</i>

**A DOUBLE-BLIND PARALLEL MULTICENTER STUDY OF THE SAFETY
AND EFFICACY OF CETIRIZINE VS LORATADINE AND
PLACEBO IN THE TREATMENT OF SEASONAL ALLERGIC RHINITIS
(Protocol Number L - 0270)**

93-5-0083
PT. 344

CONFIDENTIAL
344

CONFIDENTIAL



**Pfizer Labs
235 East 42nd Street
New York, New York 10017**



CETIRIZINE VS LORATADINE AND PLACEBO

SEASONAL ALLERGIC RHINITIS

INVESTIGATOR <u>R. Dockhorn M.D.</u>	STUDY NUMBER <u>93-5-0083</u>
PATIENT INITIALS	VISIT DATE (mo/day/yr) <u>05-18-94</u>
PATIENT NUMBER 1 <u>2646</u>	PATIENT NUMBER 2 <u>344</u>

VISIT 1

INFORMED CONSENT

Written informed consent obtained from patient? Yes No

If patient is a minor, informed consent form signed by legal representative? Yes No Not Applicable

Relationship of signer _____

Date written informed consent obtained: 05/18/94
MO DAY YR

DEMOGRAPHICS/HISTORY

Birth Date: 05/28/68
MO DAY YR

Sex: M F

If female: surgically sterilized

Race: White Black

postmenopausal
or practicing effective pregnancy prevention

Hispanic Asian

oral contraceptives

Other _____

(check two) cervical barrier
 spermicide
 condom

SKIN TESTING DOCUMENTATION

Date of Allergy Testing: 05/18/94
MO DAY YR

Check the method: RAST I.D. Prick

	Yes	No		Yes	No
Positive to grass	☒	☐	trees	☒	☐



INVESTIGATOR <i>R. Dockhorn, M.D.</i>		STUDY NUMBER <i>93-S-0083</i>
PATIENT INITIALS	PATIENT NUMBER I <i>2646</i>	VISIT DATE (m/d/yyyy) <i>05-18-97</i>
	II <i>344</i>	

VISIT 1

PATIENT SELECTION CHECKLIST - INCLUSIONS

	YES	NO
1. Patient is between the age of 12 and 70 years.	☒	☐
2. Patient is male; or female of nonchildbearing potential (postmenopausal or documented as surgically incapable of conception); or female of childbearing potential who agrees not to become pregnant during the study. When sexually active, females of childbearing potential must already be using oral contraceptives or agree to use at least any two of the following: a cervical barrier (diaphragm), spermicide, or condom. Females of childbearing potential less than 18 years of age may only be enrolled in the study if they already are using oral contraceptives. Premenarchal females are to be considered of childbearing potential and they may only be enrolled if they are already taking oral contraceptives. Abstinence is not an acceptable method of birth control.	☒	☐
3. Patient will have a negative serum pregnancy test if a female of childbearing potential.	☒	☐
4. Patient is an outpatient with a history of grass or tree seasonal rhinitis and which required pharmacologic therapy each year for at least 2 years.	☒	☐
5. Patient has a documented grass or tree allergy as confirmed by a recognized skin test (prick, I.D., or RAST) of moderate or greater reaction at Visit 1 or within the last year.	☒	☐
6. Patient is someone from whom the principal investigator or study personnel would expect conscientious cooperation over the duration of the study.	☒	☐
7. Patient is able to execute a written informed consent document at Visit 1. Written consent of a parent or legal guardian is also required for patients under the age of consent.	☒	☐

A NEGATIVE ANSWER TO ANY OF THE ABOVE
RENDERS THE PATIENT INELIGIBLE FOR STUDY ENTRY
UNLESS PRIOR APPROVAL FROM SPONSOR IS OBTAINED.



INVESTIGATOR <i>R. Dockhorn, M.D.</i>	STUDY NUMBER <i>93-5-003</i>
PATIENT INITIALS	PATIENT NUMBER <i>2644</i> <i>344</i>
	VISIT DATE (m/d/yyyy) <i>05-18-94</i>

VISIT 1

PATIENT SELECTION CHECKLIST - EXCLUSIONS

	YES	NO
1. Patient is pregnant, lactating or not employing appropriate contraceptive measures to ensure that pregnancy will not occur during the study.	☐	☒
2. Patient has clinically significant nasal anatomical deformities (septal defects, polyps).	☐	☒
3. Patient has experienced an episode of acute sinusitis within 30 days of Visit 1.	☐	☒
4. Patient is initiating or advancing an immunotherapy regimen during the course of the study.	☐	☒
5. Patient has impaired hepatic function (alcohol cirrhosis, hepatitis), glaucoma, cancer, acute respiratory infection (including the common cold), any systemic infection, any clinically significant hematologic, renal, endocrine (except for controlled diabetes mellitus, post-menopausal symptoms or hypothyroidism), or gastrointestinal disease, and/or neuropsychiatric disorders with or without drug therapy.	☐	☒
6. Patient has a history of malignancy (except basal cell carcinoma), epilepsy or seizures, excessive alcohol intake or drug addiction, coronary artery disease, uncontrolled hypertension, or other clinically significant cardiovascular disease.	☐	☒
7. Patient has a physical examination abnormality considered to be clinically significant and limiting to the study's conduct by the investigator unless the abnormality is related to underlying allergic rhinitis:	☐	☒
8. Patient has an intolerance to antihistamines.	☐	☒
9. Patient has used chronic anti-asthma medication for at least 24 consecutive months prior to study entrance.	☐	☒
10. Patient has used inhaled and/or topical (intranasal or ophthalmic) corticosteroids within 14 days or systemic (intramuscular and/or intravenous and/or oral) corticosteroids within 30 days of Visit 1.	☐	☒
11. Patient has used intranasal cromolyn (Nasalbrom™), optical cromolyn (Opticrom™), MAO inhibitors, reserpine, or beta blockers within 14 days of Visit 1.	☐	☒
12. Patient has received astemizole within 90 days of Visit 1.	☐	☒
13. Patient has used H ₁ -receptor antagonists or decongestants within 48 hours of Visit 1.	☐	☒
14. Patient has participated in a clinical protocol within 30 days of Visit 1 or have ever participated in a cetirizine clinical trial.	☐	☒

A POSITIVE ANSWER TO ANY OF THE ABOVE RENDERS THE PATIENT INELIGIBLE FOR STUDY ENTRY UNLESS PRIOR APPROVAL FROM SPONSOR IS OBTAINED.



CETIRIZINE VS LORATADINE AND PLACEBO

SEASONAL ALLERGIC RHINITIS

INVESTIGATOR <i>R. Dockhorn M.D.</i>	STUDY NUMBER <i>93-5-0083</i>
PATIENT INITIALS	VISIT DATE (mo/day/yr) <i>05-18-94</i>
PATIENT NUMBER <i>2646 / 344</i>	

VISIT 1 LABORATORY EVALUATIONS

Lab Requisition Number 576516

UPON REVIEW OF ALL LAB RESULTS, WERE THERE ANY LAB ABNORMALITIES AT THIS VISIT? Yes No

IF YES, ARE ANY OF THE ABNORMAL LABORATORY VALUES FOR THIS VISIT CLINICALLY SIGNIFICANT? Yes No

IF YES, EXPLAIN BELOW:

Date Specimen Taken: <u> </u> / <u> </u> / <u> </u> MO DAY YR (if different from visit date)		Specify cause of abnormality: 1 = Study drug 2 = Concurrent drug 3 = Concurrent illness 4 = Other known cause 5 = Unknown	If causes 2, 3 or 4 were specified, please comment below
Laboratory Test	Lab Value		

Comments: _____



CETIRIZINE VS LORATADINE AND PLACEBO

SEASONAL ALLERGIC RHINITIS

INVESTIGATOR <i>R. Dockhorn, M.D.</i>	STUDY NUMBER <i>93-S-0083</i>
PATIENT INITIALS	PATIENT NUMBER <i>2646 / 344</i>
	VISIT DATE (month/year) <i>05-18-94</i>

VISIT 1

ALLERGIC HISTORY	
Duration of this episode of Seasonal Allergic Rhinitis (weeks):	<u>4</u>
Duration of history of Seasonal Allergic Rhinitis (years):	<u>22</u>
Drug allergy history? ☒ Yes ☐ No If yes, specify:	<u>PENICILLIN</u>

PAST MEDICAL/SURGICAL HISTORY			
	No	Yes	Yes, give details and dates:
DERMATOLOGICAL	☒	☐	
ALLERGIC/IMMUNOLOGICAL	☒	☐	(other than SAR)
EYES/EARS/NOSE/THROAT	☒	☐	
ENDOCRINE	☒	☐	
HEMATOLOGICAL	☒	☐	
RESPIRATORY (including asthma)	☒	☐	
CARDIOVASCULAR	☒	☐	
GASTROINTESTINAL	☒	☐	
GENITOURINARY	☒	☐	
HEPATOBIILIARY	☒	☐	
MUSCULOSKELETAL	☒	☒	<i>PKA 5-8-94 Surgery for pinched NERVE @ elbow, 1-87</i>
NEUROLOGICAL	☐	☒	<i>ALLERGY HEADACHES - 1972</i>
GYNECOLOGICAL	☒	☐	
OTHER (specify)	☒	☐	



CETIRIZINE VS LORATADINE AND PLACEBO

SEASONAL ALLERGIC RHINITIS

INVESTIGATOR <i>R. Dockhorn, M.D.</i>	STUDY NUMBER <i>93-5-0083</i>
PATIENT INITIALS	PATIENT NUMBER I <i>2646</i>
	PATIENT NUMBER II <i>347</i>
	VISIT DATE (mo/day/yr) <i>05-18-94</i>

VISIT 1

PHYSICAL EXAMINATION				
HEIGHT	WEIGHT	TEMPERATURE	PULSE	BLOOD PRESSURE
<i>66</i> in	<i>160</i> lb	<i>99</i> °F	<i>76</i>	<i>108/76</i>
	NORMAL	ABNORMAL	NOT DONE	Describe Abnormalities
SKIN	☒	☐	☐	
HEAD/NECK	☒	☐	☐	
EENT	☐	☒	☐	<i>NASAL MEMBRANES EDEMATOUS</i>
LUNGS	☒	☐	☐	
HEART	☒	☐	☐	
ABDOMEN	☒	☐	☐	
EXTREMITIES	☒	☐	☐	
NEUROLOGICAL	☒	☐	☐	
LYMPH NODES	☒	☐	☐	
Visit Comments				

PRINCIPAL INVESTIGATOR'S SIGNATURE <i>T. Rausch, M.D.</i>	DATE <i>5/18/94</i>

111-853 (Rev. 0)

8



CETIRIZINE VS LORATADINE AND PLACEBO

SEASONAL ALLERGIC RHINITIS

INVESTIGATOR <i>R. Dockhorn, M.D.</i>		STUDY NUMBER <i>93-5-0083</i>
PATIENT INITIALS	PATIENT NUMBER <i>244 / 344</i>	VISIT DATE (mo/day/yr) <i>05-18-94</i>

VISIT 1

YES NO

- Was the patient diary dispensed after instructing the patient to complete every morning?
- Was study medication dispensed and the patient instructed to take 1 tablet and 1 capsule each morning?
- Was an appointment scheduled to return in 7 (±2) days?

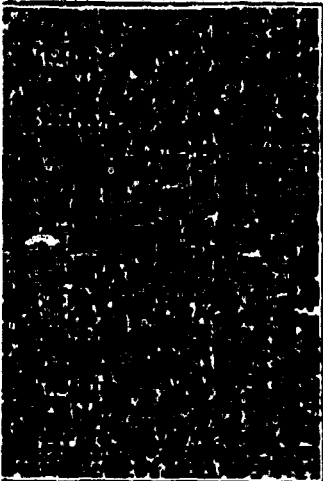
ATTACH THE TEAR-OFF PORTION OF THE LABEL BELOW

Pfizer Inc., New York, NY 10017

PROTOCOL NO.: L-0270
 PHASE I NO.: 2646
 VISIT: 1
 CAPSULES: 10 TABLETS: 10
 STUDY NO.: *93-5-0083*
 INVESTIGATOR: *DOCKHORN*
 PATIENT INITIALS: _____
 DIRECTIONS: TAKE ONE (1) TABLET FROM COLUMN 1 AND ONE (1) CAPSULE FROM COLUMN 2 EACH MORNING.
 STORAGE: STORE BETWEEN 36 DEG. F AND 86 DEG. F (2 DEG. C AND 30 DEG. C) PROTECT FROM EXCESSIVE MOISTURE.
 DRUG RETURN: THIS CARD, INCLUDING ANY UNUSED MEDICATION MUST BE RETURNED TO YOUR PHYSICIAN.

TEAR OFF AT PERFORATION AND AFFIX TO CASE REPORT

OPEN ONLY IN CASE OF EMERGENCY



DRUG INFORMATION INSIDE

CUT ON GREEN LINES TO OPEN

Cetirizine HCl Drug - Labeled by Federal Bureau of Investigation and FDA

Visit Comments _____

I affirm by my signature that the information reflected on all pages of the case report form for this visit have been personally reviewed by me and deemed accurate.

PRINCIPAL INVESTIGATOR'S SIGNATURE <i>William A. Dockhorn, M.D.</i>	DATE <i>5/18/94</i>



CETIRIZINE VS LORATADINE AND PLACEBO

SEASONAL ALLERGIC RHINITIS

INVESTIGATOR <u>R. Dosikhorn, M.D.</u>	STUDY NUMBER <u>93-5-0083</u>
PATIENT INITIALS <u>344</u>	PATIENT NUMBER II <u>344</u>
	VISIT DATE (month/year) <u>05-18-94</u>

VISIT 2

05-31-94
29

	YES	NO
1. Have there been any Adverse Experiences since the last visit? If yes, record on the Adverse Experience Record page 23.	☐	☒
2. Have there been any changes in the Concomitant Medications since the last visit? If yes, record on page 24.	☐	☒
3. Have there been any Concurrent Illnesses since the last visit? If yes, record on page 25.	☐	☒

INSTRUCTIONS FOR RETURNING MEDICATION AND DIARY

- Medication from Visit 1 should be returned and inventoried at this visit.
- Record the number of tablets and capsules taken and returned and check to see if doses taken are consistent with the diary entries.
- Returned medication should be retained in the original blister cards.

MEDICATION INVENTORY REVIEW

Was medication returned from Visit 1?

Yes, date returned: 05/25/94
MO DAY YR

No, comment: _____

Number of tablets/capsules
DISPENSED AT
LAST VISIT

10	10
7	7
3	3

Number of tablets/capsules
TAKEN

First Dose Taken: 05/18/94 (PK) 5-25-94
MO DAY YR

Number of tablets/capsules
RETURNED

Last Dose Taken: 05/25/94
MO DAY YR

Was there missed doses or loss of any medication? Yes No

Yes, comment (note date): _____

If the number of tablets/capsules taken plus number of tablets/capsules returned does not equal the number originally dispensed, please explain discrepancy: _____



INVESTIGATOR

K. Dockhorn, M.D.

STUDY NUMBER

93-J-0083

PATIENT INITIALS

PATIENT NUMBER II

344

VISIT DATE (month/year)

05-25-94

VISIT 2

PATIENT SELECTION CHECKLIST - INCLUSIONS

	YES	NO
1. Patient is between the age of 12 and 70 years.	☒	☐
2. Patient is male; or female of nonchildbearing potential (postmenopausal or documented as surgically incapable of conception); or female of childbearing potential who agrees not to become pregnant during the study. When sexually active, females of childbearing potential must already be using oral contraceptives or agree to use at least any two of the following: a cervical barrier (diaphragm), spermicide, or condom. Females of childbearing potential less than 18 years of age may only be enrolled in the study if they already are using oral contraceptives. Premenarchal females are to be considered of childbearing potential and they may only be enrolled if they are already taking oral contraceptives. Abstinence is not an acceptable method of birth control.	☒	☐
3. Patient will have a negative serum pregnancy test if a female of childbearing potential.	☒	☐
4. Patient is an outpatient with a history of grass or tree seasonal rhinitis and which required pharmacologic therapy each year for at least 2 years.	☒	☐
5. Patient has a documented grass or tree allergy as confirmed by a recognized skin test (prick, I.D., or RAST) of moderate or greater reaction at Visit 1 or within the last year.	☒	☐
6. Patient diary shows the sum of the morning rhinitis symptom severity scores of the major symptom complex (sneezes, runny nose/sniffles, nose blows, itchy nose, and watery eyes) must be ≥ 7 on at least 4 days of the 1-week baseline single-blind period.	☒	☐
7. Patient diary shows at least two of these major complex symptoms must be of moderate or greater (≥ 3) intensity on at least one recording on each of those 4 days. The same symptom need not be of moderate or greater intensity as long as one of the symptoms is of moderate or greater intensity.	☒	☐
8. Patient is someone from whom the principal investigator or study personnel would expect conscientious cooperation over the duration of the study.	☒	☐
9. Patient is able to execute a written informed consent document at Visit 1. Written consent of a parent or legal guardian is also required for patients under the age of consent.	☒	☐

A NEGATIVE ANSWER TO ANY OF THE ABOVE
RENDERS THE PATIENT INELIGIBLE FOR STUDY ENTRY
UNLESS PRIOR APPROVAL FROM SPONSOR IS OBTAINED.



INVESTIGATOR <i>R. Dockhorn, M.D.</i>	STUDY NUMBER <i>93-5-0083</i>
PATIENT INITIALS	VISIT DATE (month/year) <i>05-25-94</i>
PATIENT NUMBER II <i>344</i>	

VISIT 2

PATIENT SELECTION CHECKLIST - EXCLUSIONS

	YES	NO
1. Patient is pregnant, lactating or not employing appropriate contraceptive measures to ensure that pregnancy will not occur during the study.	☐	☒
2. Patient has clinically significant nasal anatomical deformities (septal defects, polyps).	☐	☒
3. Patient has experienced an episode of acute sinusitis within 30 days of Visit 1.	☐	☒
4. Patient is initiating or advancing an immunotherapy regimen during the course of the study.	☐	☒
5. Patient has impaired hepatic function (alcohol cirrhosis, hepatitis), glaucoma, cancer, acute respiratory infection (including the common cold), any systemic infection, any clinically significant hematologic, renal, endocrine (except for controlled diabetes mellitus, post-menopausal symptoms or hypothyroidism), or gastrointestinal disease, and/or neuropsychiatric disorders with or without drug therapy.	☐	☒
6. Patient has a history of malignancy (except basal cell carcinoma), epilepsy or seizures, excessive alcohol intake or drug addiction, coronary artery disease, uncontrolled hypertension, or other clinically significant cardiovascular disease.	☐	☒
7. Patient has an abnormal laboratory test considered to be clinically significant by the investigator unless the abnormality is related to underlying allergic rhinitis (e.g., eosinophilia).	☐	☒
8. Patient has a physical examination abnormality considered to be clinically significant and limiting to the study's conduct by the investigator unless the abnormality is related to underlying allergic rhinitis.	☐	☒
9. Patient has an intolerance to antihistamines.	☐	☒
10. Patient has used chronic anti-asthma medication for at least 24 consecutive months prior to study entrance.	☐	☒
11. Patient has used inhaled and/or topical (intranasal or ophthalmic) corticosteroids within 14 days or systemic (intramuscular and/or intravenous and/or oral) corticosteroids within 30 days of Visit 1.	☐	☒
12. Patient has used intranasal cromolyn (Nasal crom™), optical cromolyn (Opticrom™), MAO inhibitors, reserpine, or beta blockers within 14 days of Visit 1.	☐	☒
13. Patient has received astemizole within 90 days of Visit 1.	☐	☒
14. Patient has used H ₁ -receptor antagonists or decongestants within 48 hours of Visit 1.	☐	☒
15. Patient has participated in a clinical protocol within 30 days of Visit 1 or have ever participated in a cetirizine clinical trial.	☐	☒

A POSITIVE ANSWER TO ANY OF THE ABOVE RENDERS THE PATIENT INELIGIBLE FOR STUDY ENTRY UNLESS PRIOR APPROVAL FROM SPONSOR IS OBTAINED.



CETIRIZINE VS LORATADINE AND PLACEBO

SEASONAL ALLERGIC RHINITIS

INVESTIGATOR <i>R. Deckhorn, M.D.</i>	STUDY NUMBER <i>93-S-0083</i>
PATIENT INITIALS	PATIENT NUMBER II <i>344</i>
	VISIT DATE (m/d/y) <i>05-25-94</i>

VISIT 2 INVESTIGATOR EVALUATION

SYMPTOMS OF ALLERGIC RHINITIS	
Sneezing	
Absent	Frequent
Runny Nose	
Absent	Constant
Nasal Itching	
Absent	Constant
Eye Symptoms	
Absent	Constant
Nasal Blockage	
Breathing Freely	Completely Blocked

PRINCIPAL INVESTIGATOR'S SIGNATURE <i>R. Deckhorn</i>	DATE <i>5/25/94</i>



CETIRIZINE VS LORATADINE AND PLACEBO

SEASONAL ALLERGIC RHINITIS

INVESTIGATOR <u>R. Dockhorn, M.D.</u>	STUDY NUMBER <u>93-5-0083</u>
PATIENT INITIALS	VISIT DATE (mo/day/yr) <u>05.25.94</u>
PATIENT NUMBER # <u>344</u>	

VISIT 2

YES NO

- Was the patient diary dispensed after instructing the patient to complete every morning? YES NO
- Was study medication dispensed and the patient instructed to take 1 tablet and 1 capsule each morning? YES NO
- Was an appointment scheduled to return in 7 (±2) days? YES NO

ATTACH THE TEAR-OFF PORTION OF THE LABEL BELOW

PFIZER INC., NEW YORK, NY 10017

PROTOCOL NO.: L-0270
 PHASE 2 NO.: 344
 VISIT: 2
 CAPSULES: 10 TABLETS: 10
 STUDY NO.: 93-5-0083
 INVESTIGATOR: Dockhorn R
 PATIENT INITIALS: _____

▲ TEAR OFF HERE ▲ DIRECTIONS: TAKE ONE (1) TABLET FROM COLUMN 1 AND ONE (1) CAPSULE FROM COLUMN 2 EACH MORNING.
 STORAGE: STORE BETWEEN 36 DEG. F AND 86 DEG. F (2 DEG. C AND 30 DEG. C) PROTECT FROM EXCESSIVE MOISTURE.
 DRUG RETURN: THIS CARD, INCLUDING ANY UNUSED MEDICATION MUST BE RETURNED TO YOUR PHYSICIAN.

TEAR OFF AT PERFORATION AND AFFIX TO CASE REPORT

Discontinue Non-Drug • Limited by Federal law to investigational use only.

OPEN ONLY IN CASE OF EMERGENCY



CUT ON GREEN LINES TO OPEN

DRUG INFORMATION INSIDE

Visit Comments _____

"I affirm by my signature that the information reflected on all pages of the case report form for this visit have been personally reviewed by me and deemed accurate."

PRINCIPAL INVESTIGATOR'S SIGNATURE <u>[Signature]</u>	DATE <u>5/25/94</u>



CETIRIZINE VS LORATADINE AND PLACEBO

SEASONAL ALLERGIC RHINITIS

INVESTIGATOR <u>R. Dockhorn, M.D.</u>	STUDY NUMBER <u>93-S-0083</u>
PATIENT INITIALS	PATIENT NUMBER II <u>344</u>
	VISIT DATE (m/d/yyyy) <u>06-01-94</u>

VISIT 3

- Have there been any Adverse Experiences since the last visit?
If yes, record on the Adverse Experience Record page 23.
- Have there been any changes in the Concomitant Medications since the last visit?
If yes, record on page 24.
- Have there been any Concurrent Illnesses since the last visit?
If yes, record on page 25.

6-1-94
 YES NO
 6-1-94

INSTRUCTIONS FOR RETURNING MEDICATION AND DIARY

- Medication from Visit 2 should be returned and inventoried at this visit.
- Record the number of tablets and capsules taken and returned and check to see if doses taken are consistent with the diary entries.
- Returned medication should be retained in the original blister cards.

MEDICATION INVENTORY REVIEW

Was medication returned from Visit 2?

Yes, date returned: 06/01/94
MO DAY YR

No, comment: _____

Number of tablets/capsules
DISPENSED AT
LAST VISIT

10	10
7	7
3	3

Number of tablets/capsules
TAKEN

First Dose Taken: 05/26/94
MO DAY YR

Number of tablets/capsules
RETURNED

Last Dose Taken: 06/01/94
MO DAY YR

Was there missed doses or loss of any medication? Yes No

Yes, comment (note date): _____

If the number of tablets/capsules taken plus number of tablets/capsules returned does not equal the number originally dispensed, please explain discrepancy: _____



CETIRIZINE VS LORATADINE AND PLACEBO

SEASONAL ALLERGIC RHINITIS

INVESTIGATOR <u>R. Dockhorn, M.D.</u>		STUDY NUMBER <u>93-5-0083</u>
PATIENT INITIALS	PATIENT NUMBER # <u>344</u>	VISIT DATE (mo/day/yr) <u>06-01-94</u>

VISIT 3

	YES	NO
1. Was the patient diary dispensed after instructing the patient to complete every morning?	☒	☐
2. Was study medication dispensed and the patient instructed to take 1 tablet and 1 capsule each morning?	☒	☐
3. Was an appointment scheduled to return in 7 (±2) days?	☒	☐

ATTACH THE TEAR-OFF PORTION OF THE LABEL BELOW

PFIZER INC., NEW YORK, NY 10017

PROTOCOL NO.: L-0270
 PHASE 2 NO.: 344
 VISIT: 3

CAPSULES: 10 TABLETS: 10
 STUDY NO.: 93-5-0083
 INVESTIGATOR: DOCKHORN
 PATIENT INITIALS: _____

▲ TEAR OFF HERE ▲
 DIRECTIONS: TAKE ONE (1) TABLET FROM COLUMN 1 AND ONE (1) CAPSULE FROM COLUMN 2 EACH MORNING.
 STORAGE: STORE BETWEEN 36 DEG. F AND 86 DEG. F (2 DEG. C AND 30 DEG. C)
 PROTECT FROM EXCESSIVE MOISTURE.
 DRUG RETURN: THIS CARD, INCLUDING ANY UNUSED MEDICATION MUST BE RETURNED TO YOUR PHYSICIAN.

TEAR OFF AT PERFORATION AND APPLY TO CASE REPORT

OPEN ONLY IN CASE OF EMERGENCY



CUT ON GREEN LINES TO OPEN

Cut-off portion of label to be attached to Investigator's Case Report

Visit Comments _____

"I affirm by my signature that the information reflected on all pages of the case report form for this visit have been personally reviewed by me and deemed accurate."

PRINCIPAL INVESTIGATOR'S SIGNATURE <u>R. Dockhorn</u>	DATE <u>6/01/94</u>



CETIRIZINE VS LORATADINE AND PLACEBO

SEASONAL ALLERGIC RHINITIS

INVESTIGATOR <u>R. Dookhorn, M.D.</u>	STUDY NUMBER <u>93-5-6083</u>
PATIENT INITIALS	PATIENT NUMBER <u>344</u>
	VISIT DATE (month/year) <u>06-08-94</u>

VISIT 4

	YES	NO
1. Have there been any Adverse Experiences since the last visit? If yes, record on the Adverse Experience Record page 23.	☒	☒ <i>PK</i>
2. Have there been any changes in the Concomitant Medications since the last visit? If yes, record on page 24.	☒	☒ <i>PK</i>
3. Have there been any Concurrent Illnesses since the last visit? If yes, record on page 25.	☐	☒ <i>PK</i>

INSTRUCTIONS FOR RETURNING MEDICATION AND DIARY

- Medication from Visit 3 should be returned and inventoried at this visit.
- Record the number of tablets and capsules taken and returned and check to see if doses taken are consistent with the diary entries.
- Returned medication should be retained in the original blister cards.

MEDICATION INVENTORY REVIEW

Was medication returned from Visit 3?

Yes, date returned: 06 18 194
MO DAY YR

No, comment: _____

Number of
tablets/capsules
DISPENSED AT
LAST VISIT

	10	10
Number of tablets/capsules TAKEN	7	7
Number of tablets/capsules RETURNED	3	3

First Dose Taken: 06 102 194
MO DAY YR

Last Dose Taken: 06 108 194
MO DAY YR

Was there missed doses or loss of any medication? Yes No

If Yes, comment (note date): _____

If the number of tablets/capsules taken plus number of tablets/capsules returned does not equal the number originally dispensed, please explain discrepancy: _____

New

Change from baseline for ECGs recorded within days 11-17 of first dose from Table 2.1:

Number of patients	Placebo 40	Cet 5 mg 35	Cet 10 mg 44	p-value
QTc (Bazett) Baseline	425.05 +/- 25.47	417.36 +/- 25.33	420.54 +/- 22.34	0.061
Change	-0.79 +/- 24.25	-0.08 +/- 35.67	10.32 +/- 25.18	
(p-value within)	0.833	0.970	0.015	
Adjusted change	1.77	-2.52	9.94	

Change from baseline for maximum ECG recorded on treatment (11-17 Days ECGs), from Table 2.2:

Number of patients	Placebo 64	Cet 5 mg 64	Cet 10 mg 65	p-value
QTc (Bazett) Baseline	418.93 +/- 24.88	421.02 +/- 25.98	421.15 +/- 21.31	0.006
Change	5.89 +/- 27.21	-2.84 +/- 31.52	10.22 +/- 24.84	
(p-value within)	0.107	0.887	0.002	
Adjusted change	4.92	-2.40	10.73	

Distribution of percent change from baseline for ECGs recorded within days 11-17 of first dose, from Table 2.4:

	under 5%	5- <10%	10- <20%
Placebo-# of pts.	32	6	2
Row %	80%	15%	5%
5 mg cet	27	4	4
Row %	77.14%	11.43%	11.43%
10 mg cet	31	7	6
Row %	70.45%	15.91%	13.64%

Section 2

Reference is made to the MO review (10/30/95-in **Appendix 1**) of the annual report to the IND dated 9/25/95.

Reference is also made to the sponsor's response in the telephone facsimile dated 11/2/95 in **Appendix 2**. The information requested refers to a case of a 26 y/o female patient that participated in study L-0270 for seasonal allergic rhinitis. In addition, this patient had history of allergy headaches. The patient completed the study. Treatment with cetirizine began on 5/18/94 and ended on 6/8/94. The patient experienced sinus headache on 5/29/94 and 5/30/94 that was treated with ibuprofen and nausea on 6/5/95 treated with Dramamine.

Laboratory results pretreatment on 5/18/94: SGOT=24 U/L
SGPT=38 U/L
T.Bili=1.1 mg/dl

At the end of treatment 6/8/94: SGOT=87 U/L
SGPT=210 U/L
T. Bili=1.2 mg/dl

Follow up repeat labs 6/23/94: SGOT=29 U/L
SGPT=34 U/L
T. Bili=1.2 mg/dl

Reviewer's comments:

Three days prior to the end of 3 weeks of treatment this patient felt nauseous for 1 day. Three days later, at the end of study evaluation the elevation of liver transaminases and an increase in total bilirubin (that was within the lab normal limits) was noted; no other symptoms were recorded in the CFR. Fifteen days after the drug had been stopped a lab retest was done and the liver enzymes had returned to normal values; a positive dechallenge. The CRF does not record a history of a concomitant illness, concomitant use of medications or other abnormal labs that would account for the abnormal enzyme elevations. It is very likely that the liver enzyme elevation in this patient was related to the use of cetirizine.

Appendix 1

Medical Officer Review

IND

Drug: Cetirizine tablets

Correspondence: N228YY-annual report 2/27/94-2/26/95

Document date: September 14, 1995

Date of review: October 30, 1995

Medical Officer Reviewer: Ana M. Saavedra-Delgado, M.D.

The following items that were not included in the 4/25/95 safety update are noted:

In Table 3, the incidence of adverse experiences in U.S. pharmaceutical studies during the reporting period is displayed for multiple dose, open-label/single blind/unblinded studies is displayed. For patients treated with cetirizine=474, loratadine=194 and placebo=197, the incidence of adverse experiences was 47%, 35% and 35% respectively.

In Table 4, the incidence of intercurrent illnesses in U.S. pharmaceutical studies during the reporting period is displayed for multiple dose, open-label/single blind/unblinded studies is displayed. For patients treated with cetirizine=381, loratadine=101 and placebo=104, the incidence of intercurrent illnesses was 19%, 17% and 13% respectively.

For future annual reports we would want to see the adverse events associated with intercurrent illnesses integrated in the adverse event database and presented to us as a single table.

The following items that were included in the 4/25/95 safety update are also noted:

In the listing providing serious spontaneous adverse events from non-clinical trial, four cases are reported with ventricular tachycardia and or fibrillation. A clear relation to the drug was not apparent in any of these cases, since either there were pre-existing conditions, electrolyte deficiencies or concomitant medications that could have been responsible for the event. The four cases resolved and cetirizine was permanently stopped. The summary of these four cases from the 4/25/95 safety update is attached.

More information is needed on the following patient(s):

In Table 5, the incidence of clinically significant

A. Saavedra-Delgado MD 10/30/95
medical officer should be sponsor to request information in request #2.
an Abonne 10/30/95
Request was faxed on 10-31-95
Comments: int. to Mr. Saavedra
Labels of 10-31-95
via telephone
KL
10-31-

laboratory abnormalities in U.S. pharmaceutical studies is displayed for protocol L-0270 (patients active during the reporting period). In this table, for cetirizine treated patients N=1 is listed for increase >3x ULN in SGPT and T. bili.

Study L-0270 was initiated after 2/26/95, and was included in the 4/25/95 safety update for serious adverse events discussion only. Under this definition the patient must have not needed hospitalization. However, more information is needed to assess the cause of the rise in liver enzymes.

The following information will be requested: patient ID, gender, age, treatment dose at onset of event, duration of treatment at onset of event, concomitant therapy or illnesses, follow up lab results, continuation of treatment, and resolution.

Recommendations to Sponsor:

We have completed the review of your annual report for IND dated September 14, 1995. We have the following requests:

1. For future annual reports we would want to see the adverse events associated with intercurrent illnesses integrated in the adverse event database and presented as a single table.
2. In Table 5, the incidence of clinically significant laboratory abnormalities in U.S. pharmaceutical studies is displayed for protocol L-0270 (patients active during the reporting period). In this table, for cetirizine treated patients N=1 is listed for increase >3x ULN in SGPT and T. bili. Please provide patient ID, gender, age, treatment dose at onset of event, duration of treatment at onset of event, concomitant therapy or illnesses, follow up lab results, whether treatment was continued, and resolution of event.

cc: original IND

HFD-570/Div files

HFD-570/K.Lee/Saavedra-Delgado

TABLE 5. CETIRIZINE - INCIDENCE OF CLINICALLY SIGNIFICANT LABORATORY ABNORMALITIES
 U.S. PHARMACEUTICALS STUDIES
 PROTOCOL L-0270 (PATIENTS ACTIVE DURING THE REPORTING PERIOD 27FEB94 TO 26FEB95)

NUMBER OF SUBJECTS:				CETIRIZINE			LORATADINE			PLACEBO		
EVALUABLE FOR LABORATORY ABNORMALITIES				95			99			98		
WITH CLINICALLY SIGNIFICANT LABORATORY ABNORMALITIES				21			13			13		
GROUP	PARAMETER	UNITS	CRITERIA	SUBJECTS WITH ABNORMALITIES			SUBJECTS WITH ABNORMALITIES			SUBJECTS WITH ABNORMALITIES		
				N	n	%	N	n	%	N	n	%
HEMATOLOGY	HGB (F)	G/DL	> 20% DECREASE*	55	0	0.0	51	0	0.0	56	0	0.0
	HGB (M)	G/DL	> 20% DECREASE*	39	0	0.0	47	0	0.0	40	0	0.0
	HCT (F)	%	> 20% DECREASE*	55	0	0.0	51	0	0.0	56	0	0.0
	HCT (M)	%	> 20% DECREASE*	39	0	0.0	47	0	0.0	40	0	0.0
	WBC	THOU/MCL	< 2.5	94	0	0.0	98	0	0.0	96	0	0.0
			> 17.5	94	0	0.0	98	0	0.0	96	0	0.0
	NEUTROS	THOU/CMM	< 1	94	1	1.1	98	0	0.0	96	0	0.0
	EOS	%	>= 10	94	10	10.6	99	7	7.1	96	5	5.2
LIVER FUNCTION	SGOT	U/L	> 3 X ULM	94	0	0.0	99	0	0.0	96	0	0.0
	SGPT	U/L	> 3 X ULM	94	1	1.1	99	0	0.0	96	0	0.0
	T.BILI.	MG/DL	> 1.5 X ULM	94	1	1.1	99	0	0.0	96	0	0.0
RENAL FUNCTION	BUN	MG/DL	> 1.3 X ULM	94	0	0.0	99	0	0.0	96	0	0.0
	CREATININE	MG/DL	> 1.3 X ULM	94	0	0.0	99	0	0.0	96	0	0.0
URINALYSIS	BILIRUBIN		>= 1+	95	0	0.0	99	0	0.0	98	0	0.0
	GLUCOSE		>= 2+	95	0	0.0	99	0	0.0	98	1	1.0
	KETONE		>= 1+	95	0	0.0	99	0	0.0	98	1	1.0
	PH (REACTION)		< 0.9 X LLM	95	0	0.0	99	0	0.0	98	0	0.0
			> 1.1 X ULM	95	0	0.0	99	0	0.0	98	0	0.0
	PROTEIN		>= 2+	95	1	1.1	99	0	0.0	98	0	0.0
	RBC/NPF		>= 6	95	4	4.2	99	4	4.0	97	3	3.1
	SPEC.GRAV.		< 1	95	0	0.0	99	0	0.0	98	0	0.0
			> 1.035	95	0	0.0	99	0	0.0	98	0	0.0
	WBC/NPF		>= 6	95	4	4.2	99	4	4.0	97	3	3.1

NOTE: N = TOTAL NUMBER OF SUBJECTS WITH AT LEAST ONE OBSERVATION OF THE GIVEN LAB PARAMETER WHILE ON STUDY TREATMENT
 n = NUMBER OF SUBJECTS WITH A CLINICALLY SIGNIFICANT ABNORMALITY
 * = CHANGE FROM BASELINE

RUN DATE: 27JUL95

89. 9410358	A congenital anomaly of a spinal malformation was reported by the Norwegian Medicines Control Authority. The registry felt that cetirizine could possibly be causal in this malformation. No further information is available.	Norway
90. 9500834	A female infant was born prematurely at 33 weeks of gestation with multiple malformations (Pierre Robin Syndrome) with streptococcal septicemia, and died. The mother had taken cetirizine 5-10 mg daily during weeks 5-7 of pregnancy. The Swiss Regulatory Authority felt it unlikely that the malformations were attributable to cetirizine.	Switzerland
91. 9500835	A 69 year old polymedicated woman with a known history of cardiac disease and a prior myocardial infarction developed ventricular tachycardia while taking 10 mg of cetirizine daily for urticaria. The cetirizine was permanently stopped although underlying cardiac disease was most likely the reason for the event. Concomitant medications included indomethacin, cinnarizine, clonazepam, amiloride, isosorbide, enalapril, and nitroglycerine. The events resolved.	United Kingdom ✓
92. 9500836	A 67 year old woman, who had been taking 10 mg of cetirizine daily for rhinitis, developed sudden dizziness followed by shortness of breath and chest pain. She was hospitalized. An ECG showed rapid ventricular tachycardia, which was successfully treated with lignocaine infusion. However, occasional ectopic beats were still noted; it is not known if the ectopics ever completely disappeared. Echocardiogram showed an akinetic segment of the heart with blood clot, which was felt by her physician to be related to the arrhythmia. Additionally, the patient was taking brompheniramine, had been taking terfenadine until two weeks before the event, and used a terbutaline turbohaler as necessary. Although the cetirizine was permanently discontinued, it was not felt to have been related to the arrhythmia.	United Kingdom ✓

96. 9501280	A 55 year old man with a prior history of ischemic heart disease, a coronary artery bypass graft, and poor left ventricular function developed ventricular tachycardia and ventricular fibrillation. He was hospitalized and treated with electric shocks. He was taking 10 mg of cetirizine intermittently for hay fever. Other medications included captopril, acetylsalicylic acid, furosemide, and another unspecified medication. Pfizer felt that the underlying heart disease seemed a more likely cause of the cardiac arrhythmia than cetirizine.	Unknown ✓
97. 9501420	A 48 year old polymedicated man developed ventricular fibrillation and ventricular ectopic beats successfully treated by defibrillation and lidocaine. On admission to the hospital he was severely hypokalemic and anemic. He was taking cetirizine 10 mg daily and paroxetine 20 mg daily. Both drugs were discontinued and suspected to have contributed to his arrhythmia, in addition to the hypokalemia and anemia.	Sweden ✓
98. 9500909	An 80 year old man developed urinary retention after the ingestion of a single intake of 150 mg of cetirizine (accidental overdose). The patient was not hospitalized but the event necessitated catheterization.	France

**Serious foreign clinical trial adverse experiences.

¹ This case does not meet FDA criteria for serious, but was noteworthy.

Appendix 2

To: K. Lee, Consumer Safety Officer, Division of Pulmonary
Drug Products

Fax: 13018271271

From: Suzanne E. LoGalbo

Date: November 2, 1995

Pages: 35, including cover sheet. As requested, attached please
find information about patient no. 344 from study no. L-
0270.

fax

From the desk of...

Suzanne E. LoGalbo
Associate Director, Drug Regulatory Affairs
Pfizer Inc
235 East 42nd Street
NY NY 10017

212 573 2950
Fax: 212 573 1563



INVESTIGATOR R. Dockhorn, M.D.

STUDY NUMBER 93-5-0083

PATIENT INITIALS

PATIENT NUMBER II 344

VISIT DATE (mm/dd/yy) 06-08-94

VISIT 4

PATIENT GLOBAL EVALUATION

Without reference to diary cards, have patient assess his/her therapeutic regimen during the previous two weeks:

1. How effective was the treatment in managing your rhinitis symptoms.

- Excellent - 1
- Very Good - 2
- Good - 3
- Fair - 4
- Poor - 5

2. How satisfied were you with the treatment?

- Exceptionally Satisfied - 1
- Very Satisfied - 2
- Satisfied - 3
- Neutral - 4
- Unsatisfied - 5

3. Would you continue to use this medication if available?

- Definitely - 1
- Probably - 2
- Unsure - 3
- No - 4



CETIRIZINE VS LORATADINE AND PLACEBO

SEASONAL ALLERGIC RHINITIS

INVESTIGATOR	R. Dockhorn, M.D.	STUDY NUMBER	93-S-0083
PATIENT INITIALS		PATIENT NUMBER II	344
		VISIT DATE (m/d/yyyy)	06-08-94

VISIT 4

INVESTIGATOR GLOBAL EVALUATION

Without reference to patient diary cards, please assess the therapeutic regimen's efficacy in managing symptoms of patient's rhinitis during the previous weeks:

- Complete Resolution of Symptoms - 1
- Marked Improvement of Symptoms - 2
- Moderate Improvement of Symptoms - 3
- Slight Improvement of Symptoms - 4
- No Improvement of Symptoms - 5

Visit Comments: _____

"I affirm by my signature that the information reflected on all pages of the case report form for this patient visit have been personally reviewed by me and deemed accurate."

PRINCIPAL INVESTIGATOR'S SIGNATURE	<i>R. Dockhorn</i>	DATE	6/8/94



CETIRIZINE VS LORATADINE AND PLACEBO

SEASONAL ALLERGIC RHINITIS

INVESTIGATOR R. Duckhorn, M.D.	STUDY NUMBER 93-5-0083
PATIENT INITIALS	PATIENT NUMBER 2646 / 344

RECORD OF ADVERSE DRUG EXPERIENCES

Adverse Experiences	Duration of Experience						Severity 1 = Mild 2 = Moderate 3 = Severe	In the physician's judgement, the cause of the adverse experience was: 1 = Study drug 2 = Concurrent drug 3 = Concurrent illness 4 = Other known cause 5 = Uncertain	If cause was chosen, specify	Action Taken (LIST ALL that apply) 1 = None 2 = Decreased dosage 3 = Symptomatic therapy required 4 = Study drug discontinued	Outcome (Check only one) 1 = Recovered 2 = Aband w/ decreased dose 3 = Alive with sequelae 4 = Under treatment 5 = Death	Hospitalized 1 = Yes 2 = No
	FROM			TO								
	MO	DAY	YR	MO	DAY	YR						
<i>9c</i> <i>07-11-94</i> Allergic rhinitis Headache	5	29	94	5	31	94	1	4	Allergies	1	1	2
<i>6-10-94</i> Headache												
<i>4-11-94</i> Headache	6	5	94	6	5	94	1	5		1	1	2

NO ADVERSE EXPERIENCES OCCURRED DURING THE COURSE OF THE STUDY

PRINCIPAL INVESTIGATOR'S SIGNATURE <i>[Signature]</i>	DATE 6/28/94



CETIRIZINE VS LORATADINE AND PLACEBO

SEASONAL ALLERGIC RHINITIS

INVESTIGATOR <u>R. Dockhorn, M.D.</u>		STUDY NUMBER <u>93-5-0083</u>
PATIENT INITIALS	PATIENT NUMBER I <u>2646</u> II <u>344</u>	VISIT DATE (m/d/yyyy) <u>06-23-94</u>

REFEAT LABORATORY EVALUATIONS

Not Done

Lab Requisition Number 805795

UPON REVIEW OF ALL LAB RESULTS, WERE THERE ANY LAB ABNORMALITIES AT THIS VISIT? Yes No

IF YES,

ARE ANY OF THE ABNORMAL LABORATORY VALUES FOR THIS VISIT CLINICALLY SIGNIFICANT? Yes No

IF YES, EXPLAIN BELOW:

Date Specimen Taken: <u> </u> / <u> </u> / <u> </u> MO DAY YR		Specify cause of abnormality: 1 = Study drug 2 = Concurrent drug 3 = Concurrent illness 4 = Other known cause 5 = Unknown	If causes 2, 3 or 4 were specified, please comment below
Laboratory Test	Lab Value		

Comments: _____



CETIRIZINE VS LORATADINE AND PLACEBO

SEASONAL ALLERGIC RHINITIS

INVESTIGATOR <u>R. Dockhorn, M.D.</u>		STUDY NUMBER <u>93-5-0083</u>
PATIENT INITIALS	PATIENT NUMBER I <u>2646 / 344</u>	

CLINICAL SUMMARY

Date of last dose of study drug: 06/08/94 (Date of last dose)

Did the patient complete the study? Yes 06/08/94 (Date completed)

No _____ (Date discontinued)

If No, what was the reason for discontinuation? Please check one:

1. Lack of efficacy _____
2. Adverse experience (specify) _____
3. Administrative decision (specify) _____
4. Non-study drug related concurrent illness (specify) _____
5. Protocol violation (specify) _____
6. Poor compliance _____
7. Lost to follow-up _____
8. Other (specify) _____

Comments: _____

I affirm by my signature below, that I have reviewed all of the information on all pages of the Case Report Form and assume responsibility for the accuracy and completeness of the data.

PRINCIPAL INVESTIGATOR'S SIGNATURE <u>[Signature]</u>	DATE <u>6/28/94</u>

DOCKHORN MD, ROBERT J
 BARBARA BURGER
 5300 W 94TH TERRACE
 RAIKIE VILLAGE

KS 66207

26101415 ROUTE K04 STOP

PATIENT NAME		PATIENT ID 2646		ROOM NO.	AGE 25	SEX F	PHYSICIAN	
PAGE 1	ASSIGNMENT NO. 576516	ACCESSION NO.	LAB REF. #	COLLECTION DATE & TIME 05/18/94 15:10		LOG-IN DATE 05/20/94	REPORT DATE 05/21/94	TIME 20:10

REMARKS

26101415 576516

REPORT STATUS	TEST	RESULT	UNITS	REFERENCE RANGE	SITE CODE
FINAL	TEST	IN RANGE			
	TESTS ORDERED:	COMPLETE BLOOD COUNT; URINALYSIS, ROUTINE; CHEM PANEL			
		HCG QL (PREG SCREEN)			
	STUDY:	CETIRIZINE			
	PROTOCOL:	L-0270			
	INVESTIGATOR:	DOCKHORN			
	STUDY NO:	93-S-0083			
	SCREENING #:	2646			
	RANDOMIZATION#:				
	BIRTHDATE:	05/28/68			
	VISIT NUMBER:	1			
	COMPLETE BLOOD COUNT				VN
	HEMOGLOBIN				
	HEMATOCRIT				
	WHITE CELL COUNT				
	NEUTROPHIL, SEGS				
	LYMPHOCYTES				
	MONOCYTES				
	EOSINOPHILS				
	BASOPHILS				
	URINALYSIS, ROUTINE				VN
	COLOR				
	APPEARANCE				
	SPECIFIC GRAVITY			1.025	
	REACTION PH				
	GLUCOSE				
	PROTEIN				
	KETONE				
	OCCULT BLOOD				
	BILIRUBIN				
	RBC/HPF				
	WBC/HPF				
	BACTERIA				
	CHEM PANEL				VN
	UREA NITROGEN				
	CREATININE				
	BILIRUBIN, TOTAL				
	AST (SGOT)				

DOCKHORN MD, ROBERT J
BARBARA BURGER
5300 W 94TH TERRACE
RAIRIE VILLAGE
KS 66207
26101415 ROUTE K04 STOP

PATIENT NAME		PATIENT ID 2646		ROOM NO.	AGE 25	SEX F	PHYSICIAN	
PAGE 2	ACQUISITION NO. 576516	ACCESSION NO.	LAB REP. #	COLLECTION DATE & TIME 05/18/94 15:10		LOG-IN DATE 05/20/94	REPORT DATE 05/21/94	& TIME 20:10

REMARKS

26101415 576516

REPORT STATUS	TEST	RESULT	UNITS	REFERENCE RANGE	SITE CODE
FINAL					JN
OUT OF RANGE ANALYTES NO ANALYTES APPROPRIATE FOR THIS SUMMARY SIGNATURE _____ MD DATE 5/21/94					

DOCKHORN MD, ROBERT J
 BARBARA BURGER
 5300 W 94TH TERRACE
 PRAIRIE VILLAGE
 KS 66207
 26101415 ROUTE K04 STOP

PATIENT NAME		PATIENT ID 344	ROOM NO.	AGE 26	SEX F	PHYSICIAN	
PAGE 1	ACQUISITION NO. S05781	ACCESSION NO.	LAB REF. #	COLLECTION DATE & TIME 06/08/94 14:10	LOG-IN DATE 06/09/94	REPORT DATE 06/13/94	TIME 08:00

REMARKS

26101415 S05781

REPORT STATUS	AMENDED	TEST	RESULT	UNITS	REFERENCE RANGE	SITE CODE
			IN RANGE			COB
			OUT OF RANGE			

TESTS ORDERED: COMPLETE BLOOD COUNT; URINALYSIS, ROUTINE; CHEM PANEL
 HCG QL (PREG SCREEN)

CORRECTED REPORT- PATIENT INFORMATION

STUDY: CETIRIZINE
 PROTOCOL: L-0270
 INVESTIGATOR: DOCKHORN
 STUDY NO: 93-S-0083
 SCREENING #: 2646
 RANDOMIZATION#: 344
 BIRTHDATE: 05/28/68
 VISIT NUMBER: 4

COMMENTS: AMENDED REPORT-VISIT NUMBER INFORMATION PER IRENE
 AT SITE.6/13/94(TD)

COMPLETE BLOOD COUNT

HEMOGLOBIN
 HEMATOCRIT
 WHITE CELL COUNT
 NEUTROPHIL, SEGS
 LYMPHOCYTES
 MONOCYTES
 EOSINOPHILS
 BASOPHILS

VN

URINALYSIS, ROUTINE

COLOR
 APPEARANCE
 SPECIFIC GRAVITY
 REACTION PH
 GLUCOSE
 PROTEIN
 KETONE
 OCCULT BLOOD
 BILIRUBIN
 RBC/HPF
 WBC/HPF
 SQUAMOUS EPITH CELLS

VN

S

CHEM PANEL

UREA NITROGEN

VN

DOCKHORN MD, ROBERT J
BARBARA BURGER
5300 W 94TH TERRACE
PRAIRIE VILLAGE

KS 66207
26101415 ROUTE K04 STOP

PAGE 2 OF 2

PATIENT NAME		PATIENT ID 344	ROOM NO.	AGE 26	SEX F	PHYSICIAN		
PAGE 2	REQUISITION NO. 805781	ADMISSION NO.	LAB REF. #	COLLECTION DATE & TIME 06/08/94 14:10		LOG-IN DATE 06/09/94	REPORT DATE 06/13/94	TIME 08:00

REMARKS

26101415 805781

REPORT STATUS	TEST	RESULT	UNITS	REFERENCE RANGE	SITE CODE
AMENDED	CREATININE				
	BILIRUBIN, TOTAL				
	AST (SGOT)				
	ALT (SGPT)				
	HCG QL (PREG SCREEN)				VN
	HCG QUAL				
	OUT OF RANGE ANALYTES				
	CHEM PANEL				
	AST (SGOT)				
	ALT (SGPT)				
	SIGNATURE	<i>J. Allen</i>			MD
	DATE	6/11/94			

DOCKHORN MD, ROBERT J
BARBARA BURGER
5300 W 94TH TERRACE
RAIRIE VILLAGE
KS 66207

26101415 ROUTE K04 STOP

PAGE 1 OF 1

PATIENT NAME		PATIENT ID	ROOM NO.	AGE	SEX	PHYSICIAN
		344		26	F	
PAGE	REQUISITION NO.	ACCESSION NO.	LAB REF. #	COLLECTION DATE & TIME	LOG-IN DATE	REPORT DATE & TIME
1	805795			06/23/94 15:15	06/24/94	06/25/94 18:00

REMARKS

26101415 805795

REPORT STATUS	TEST	RESULT	UNITS	REFERENCE RANGE	SITE CODE
FINAL	*TEST				
TESTS ORDERED: CHEM PANEL					
STUDY: CETIRIZINE					
PROTOCOL: L-0270					
INVESTIGATOR: DOCKHORN					
STUDY NO: 93-S-0083					
SCREENING #: 2646					
RANDOMIZATION#: 344					
BIRTHDATE: 05/28/68					
VISIT NUMBER: 4					
VISIT TYPE: RETEST					
EM PANEL					
UREA NITROGEN					
CREATININE					
BILIRUBIN, TOTAL					
AST (SGOT)					
ALT (SGPT)					
VN					
OUT OF RANGE ANALYTES					
=====					
NO ANALYTES APPROPRIATE FOR THIS SUMMARY					
SIGNATURE				MD	
DATE				06/25/94	

END

MD

J.H.M. Research & Development, Inc., 5776 Second Street, N.E., Washington, D.C. 20011

19835 MEMO 11/21/95

1 OF 1

19835

Memo

11/21/95

ORIGINAL

MEMORANDUM

NOV 21 1995

DATE: November 21, 1995

TO: NDA 19-835

FROM: John K. Jenkins, M.D.
Director, Division of Pulmonary Drug Products HFD-570

SUBJECT: Overview of NDA Review Issues

Administrative

NDA 19-835 for cetirizine tablets was originally submitted by Pfizer, Inc. on July 1, 1988. The NDA was presented for discussion at a Pulmonary and Allergy Drugs Advisory Committee (PADAC) meeting on April 26, 1993. An APPROVABLE letter was issued on February 21, 1995; the letter contained clinical, pharmacology/toxicology, biopharmaceutics, CMC, and labeling deficiencies. The sponsor submitted their response to the approvable letter on June 22, 1995. The current regulatory (non-User Fee) due date is December 19, 1995.

Clinical

The proposed indications for cetirizine tablets in this NDA are seasonal and perennial allergic rhinitis and chronic idiopathic urticaria. In support of these indications, the sponsor submitted nine multicenter, randomized, double-blind, placebo-controlled trials of cetirizine at doses of 5 to 20 mg/day in adults and children age 12 and older with seasonal or perennial allergic rhinitis. Five of these trials demonstrated significant effectiveness of cetirizine; three trials of one to 4 weeks duration in seasonal allergic rhinitis and two trials of up to 8 weeks duration in perennial allergic rhinitis. The sponsor also submitted two 4-week, randomized, double-blind, placebo-controlled trials of cetirizine at doses of 5 to 20 mg/day in adults and children age 12 or older with chronic idiopathic urticaria. Both of these trials demonstrated significant improvement for cetirizine-treated patients versus placebo. In general, the 10 mg dose was more effective than the 5 mg dose (which was also effective versus placebo); the 20 mg dose gave no added benefit. The PADAC recommended approval of cetirizine for the indications requested at the April 26, 1993 meeting and did not suggest that additional efficacy studies were required.

The doses and dosing interval proposed for marketing (i.e., 5 or 10 QD) appears justified based on the following information; 1) the seven to nine hour half-life of cetirizine in plasma, 2) the fact that cetirizine inhibits the skin wheal and flare response to histamine for up to 24 hours in humans, and 3) the fact that the 5 and 10 mg QD regimens were consistently demonstrated to be effective in the above referenced 7 clinical trials.

The safety database for cetirizine includes over 3900 patients from controlled and uncontrolled clinical trials conducted in the United States and Canada who were exposed to cetirizine at doses of 5 to 20 mg/day. The duration of treatment ranged from one week to 6

months, with a mean duration of exposure of 30 days. In addition, the safety database includes a rather large post-marketing experience for cetirizine and hydroxyzine (cetirizine is the major human metabolite of hydroxyzine) worldwide.

The adverse event profile for cetirizine is similar to that of other currently available antihistamines; the most commonly reported adverse reactions in clinical trials were somnolence, fatigue, and dry mouth.

Safety concerns which were raised in the Medical Officers's (Dr. Saavedra-Delgado) reviews are summarized and discussed in the Group Leader's (Dr. Himmel) memorandum of November 9, 1995. Please also refer to the Office Director's memorandum to Dr. Himmel dated November 17, 1994 which addresses many of the same safety concerns raised by the Medical Officer. I concur with the assessments made by Dr. Himmel and Dr. Temple in those memoranda and will only further address the cardiac safety issue in this memorandum.

Cardiac effects of cetirizine:

As summarized in Dr. Himmel's memo, the sponsor conducted four clinical trials specifically designed to evaluate the potential effect of cetirizine on cardiac repolarization as measured by the corrected QT interval (QTc). Three of these studies (92CK16-0604, 90CK16-0497, and 93-N-0096) demonstrated no significant effect on the QTc for 20 mg of cetirizine administered for up to 15 days alone or in combination with erythromycin or azithromycin and for 60 mg of cetirizine (6 times the maximum recommended daily dose) administered for 7 days. In study 90CK17-0497, the mean change from baseline in QTc was -3.1 msec for placebo, -2.6 msec for cetirizine 20 mg, and -2.5 msec for cetirizine 60 mg. The fourth study, a ketoconazole interaction study, demonstrated a 9.1 msec increase versus placebo (statistically significant) in QTc for cetirizine 20 mg and an 8.3 msec increase (statistically significant) versus placebo in QTc for ketoconazole 400 mg/day. The combination of cetirizine and ketoconazole was associated with a 17.4 msec increase (statistically significant) in QTc versus placebo; the effect was essentially equal to the sum of the individual effects seen for cetirizine and ketoconazole. No significant pharmacokinetic interaction was observed for cetirizine with ketoconazole, erythromycin, or azithromycin. As noted by the Medical Officer, there was a higher frequency of individual episodes of QTc > 10% of baseline for cetirizine and combination treated patients in the ketoconazole and erythromycin interaction trials. The absolute magnitude of the QTc increases of > 10% from baseline, however, were similar between the cetirizine or combination treated patients and placebo treated patients. In addition, as pointed out by Dr. Himmel, many more ECGs were performed during the cetirizine and combination treatment periods of these studies than during the placebo treatment periods and the placebo treatment periods were only 1 to 6 days in duration; these factors may tend to bias the incidence of QTc increases > 10% against the active treatment arms given the known high degree of variability of QTc in normal subjects. It is also noteworthy that in the ketoconazole interaction trial a statistically significant increase in QTc, of a similar magnitude to that observed for cetirizine 20 mg, was observed for ketoconazole. This finding is typical of ketoconazole trials that the Division has seen over the past few years, however, as

pointed out by the Medical Officer, there is a report in abstract form (the data has not been published as a manuscript) that ketoconazole 400 mg/day for 4 days was associated with a 5.5 msec increase in QTc versus placebo in 6 subjects.

In an effort to further explore the potential effects of cetirizine on QTc suggested by the ketoconazole interaction trial, additional databases and sources of information have been considered:

- a. Evaluation of the preclinical toxicology studies conducted with cetirizine and its two enantiomers by Dr. Joseph Sun and Dr. Mark Vogel (see reviews dated February 23, 1994 and October 11, 1995) revealed no clinically significant effect of cetirizine or its enantiomers on the QTc in monkeys and dogs following up to one year of dosing at daily doses which produced plasma concentrations approximately 6 and 80-110 times, respectively, greater than the plasma concentrations observed in humans at the maximum recommended daily dose of cetirizine (i.e., 10 mg/day).
- b. Evaluation by the Medical Officer of ECG data obtained from efficacy trials (SAR/Lor, SAR 8, and 9 UCB sponsored long term uncontrolled trials) demonstrated isolated occurrences of patients with QTc prolongations of >10% over baseline and patients with QTc prolongations >10% over baseline and an absolute value >440 msec in cetirizine, terfenadine, and placebo treatment groups. It is important to note that none of these trials were specifically designed to evaluate the ECG effects of cetirizine, therefore, the timing of ECGs in relation to dose or plasma concentration determinations were not standardized. The absolute magnitude of the increases in QTc over baseline for cetirizine 10 mg QD and terfenadine 60 mg BID were similar, however, it is important to note also that the changes of >10% over baseline observed in the placebo group were also of a similar magnitude. None of the ECGs identified by this screening criteria demonstrated other evidence of changes associated with delayed repolarization (i.e., altered T and U wave morphology) and none of the patients developed arrhythmias.
- c. Evaluation of the Peds-4 study comparing all treatment ECGs with those obtained at baseline showed a mean maximum change in QTc of 4.92 msec for placebo, -2.40 msec for cetirizine 5 mg, and 10.73 msec for cetirizine 10 mg. The overall p value was 0.006, however, the pairwise comparisons of cetirizine 5 or 10 mg versus placebo were not statistically significant. As pointed out in the Medical Officer's review, analysis of the individual cases of QTc >10% change from baseline and >440 msec showed that a few patients from all treatment groups met this criteria; the absolute maximum QTc observed in these cases was similar between the placebo group and the two cetirizine treated groups.
- d. A review of the available post-marketing adverse experience database for hydroxyzine and cetirizine as well as a consult to the Division of Epidemiology regarding a possible interaction between hydroxyzine and ketoconazole failed to identify a clear association between either drug and adverse events secondary to delayed cardiac repolarization.

In summary, the overall database available to evaluate the potential effects of cetirizine on cardiac repolarization does not demonstrate that cetirizine at the doses to be marketed; i.e., 5 and 10 mg QD effects a clinically significant increase in the QTc. The isolated statistically significant findings and possible trends highlighted by the Medical Officer in her review, even if they are real effects of cetirizine on the ECG, have not been shown to be clinically relevant. This conclusion is supported by the following observations; 1) the absence of an identified cardiac risk for hydroxyzine despite a long and extensive marketing history at doses which result in substantially higher plasma levels of cetirizine than when cetirizine is administered at doses of 5 or 10 mg a day, 2) the absence of identification of a cardiac risk for cetirizine from the extensive foreign post-marketing history despite the increased awareness of the potential cardiac adverse effects of antihistamines, 3) the absence of any clinically significant cardiac adverse events or ECG findings from the cetirizine NDA database, 4) the absence of clinically significant effects of cetirizine or its enantiomers on the ECG in monkeys and dogs at plasma exposures equivalent to approximately 6 and 80-110 times the exposure achieved in humans at a daily dose of 10 mg, and 5) the absence of an effect of cetirizine at 6 times the maximum recommended daily dose in study 90CK16-0497. The proposed labeling adequately describes the currently available data regarding the effects of cetirizine on QTc and no additional warnings or precautions are warranted.

Preclinical

Please see comments above regarding preclinical findings relative to the cardiac effects of cetirizine and its enantiomers. Cetirizine is non-mutagenic and has been associated with only benign liver tumors in male mice in two year rodent carcinogenicity studies. The clinical significance of this findings is unknown. Target organs of toxicity in the rodent and dog studies included the liver, kidney, and gastrointestinal tract. There were no significant differences in the toxicity profile of the two enantiomers of cetirizine or between the enantiomers and the racemate.

CMC

Cetirizine is a racemate and is proposed for marketing as 5 and 10 mg film-coated tablets. There are no outstanding CMC issues that remain to be resolved prior to approval. The sponsor has agreed to tighten the specifications for impurities in the drug product and has committed to monitor the levels of impurities in the first three production batches of drug product and to tighten the specification post-approval if necessary (see memo dated November 17, 1995 from Koung Lee, CSO).

Biopharmaceutics

Drug interaction studies have been conducted with cetirizine and theophylline, azithromycin, pseudoephedrine, ketoconazole, and erythromycin. The only significant interaction that was observed was a small decrease in clearance of cetirizine in the presence of a low dose of theophylline (400 mg QD); it is possible that at higher doses of theophylline a larger decrease in clearance of cetirizine could be observed. This observations is included in the Precautions section of the labeling. There are no outstanding biopharmaceutics review issues.

Data Verification

The Division of Scientific Investigations (DSI) completed audits at a total of 7 clinical sites, including 4 sites from the pivotal efficacy trials. One site was judged "NAI", the remaining 6 sites were judged "VAI". The observed deficiencies, as reported in the Medical Officer review dated May 12, 1994, are not of sufficient magnitude or frequency to raise serious questions regarding the integrity of the NDA database or the overall conduct of the clinical trials which support the efficacy and safety of cetirizine in patient with allergic rhinitis and chronic idiopathic urticaria.

Labeling

The proposed tradename, Zyrtec, was found to be acceptable by the Nomenclature Committee and is acceptable to the Division. The draft labeling included in this package has been carefully reviewed by the Division and accurately reflects the available information for cetirizine tablets.

Conclusion

This application is APPROVABLE. There are not outstanding deficiencies that must be resolved prior to approval. Other than the commitment made by the sponsor to revisit the specifications for impurities in the drug product after review of the data from the first three production batches, there are no required Phase 4 studies or commitments that should be made at the time of approval.

cc:

NDA 19-835

HFD-570 Division Files

HFD-570/Jenkins

HFD-570/Lee

HFD-570/Himmel

NDA 19-835
Pfizer Pharmaceuticals
New York, NY 10017

Review # 1

Date of Submission: June 30, 1988

Date of Review: April 11, 1989

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Initial Submission of June 30, 1988
Original Summary

Drug:

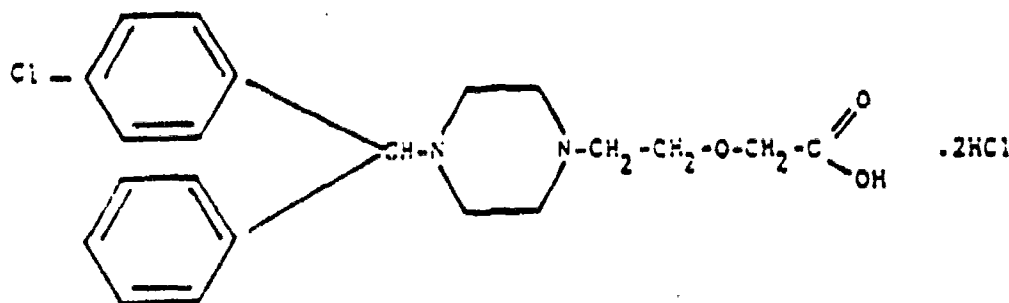
Trade name: Not established

Code name: UCBP071

Generic name: cetirizine HCl

Chemical name, empirical formula, molecular weight and structure:

2-[2-[4-[(4-chlorophenyl) phenylmethyl]-1-piperazinyl] ethoxy] acetic acid, dihydrochloride.



Molecular Formula: $C_{21}H_{25}N_2O_3Cl \cdot 2HCl$

Molecular Weight: 461.8

Dosage form: Tablets at 5, 10
Category: Antihistamine

Proposed indication:

Seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria.

Proposed dosage:

The recommended daily dose is 5 to 10 mg given as a single dose with or without food. If sufficient response is not obtained, the maximum daily dose is 20 mg.

Compositions:

Components	mg/tablet	
	5 mg	10 mg

Related drugs/INDs/NDAs/MFs:

IND

NDA

Pertinent memos/correspondence:

End of phase II meeting: IND of June 16, 1986

Preclinical studies and testing laboratories:

(1)

(2)

(3)

From page 4-15, summary tables are copied from NDA submission.
The tables included brief summaries of studies and principal findings.

- I. PHARMACOLOGY STUDIES (p. 4-6)
- II. TOXICOLOGY STUDIES (p. 7-9)
 - (A) ACUTE TOXICITY STUDIES (P. 7)
 - (B) SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY STUDIES (p. 7-9)
 - (C) CARCINOGENICITY STUDIES (p. 10)
 - (D) REPRODUCTION STUDIES (p. 10-11)
 - (E) GENETIC TOXICOLOGY STUDIES (p. 11)
- III. ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION STUDIES (p. 12-15)

From page 16 to 88, the summaries of I-III were prepared by this reviewer from individual study reports.

- I. PHARMACOLOGY STUDIES (p. 16-22)
- II. TOXICOLOGY STUDIES (p. 23-88)
 - (A) ACUTE TOXICITY STUDIES (P.24)
 - (B) SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY STUDIES (p.25-60)
 - (C) CARCINOGENICITY STUDIES (p.61-67)
 - (D) REPRODUCTION STUDIES (p.68-87)
 - (E) GENETIC TOXICOLOGY STUDIES (p.88)
- III. ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION (p.89-100) copied from NDA submission.

I. PHARMACOLOGY STUDIES:

CETIRIZINE HDA
ITEM 3a Molecular Pharmacology and Toxicology
I. Pharmacology
B. Summary Table

Table 1. Antihistaminic Activity In Vivo

NDA Report No.	Animal Species/Sex	Study Design	Number of Animals	Treatment/Dose (mcmol/kg) ^a	Route of Administration/ Duration of Treatment	Time of Testing After Last Dose	Results
1. General Antihistaminic Activity							
NP-1b	Sprague-Dawley Rats/ Male	Antagonism of 08/80-induced lethality	10 per group	Cetirizine (0.016, 0.16, 1.6 mg/kg) Hydroxyzine (0.06, 0.6, 6 mg/kg) Placebo	p.o./acute p.o./acute	2 Hrs	Cetirizine inhibited 08/80 induced lethality in rats (ED 50 = 0.016-0.16 mg/kg) and was more potent than hydroxyzine (ED 50 greater than 6 mg/kg)
NP-2	Hartley Guinea Pigs/ Male/Female	Antagonism of histamine induced lethality	8-10 per group	Cetirizine (0.01-0.12 mg/kg) Placebo	p.o./acute	1-96 Hrs	Cetirizine protected guinea pigs from potentially lethal doses of histamine (ED 50 = 0.33 mg/kg). Cetirizine 0.1 mg/kg p.o. protected all animals for 12 hours and 80% for a 24-hour period.
NP-3	Guinea Pigs/ Male	Antagonism of histamine induced lethality	N/A	Cetirizine (2.5 mg/kg) Hydroxyzine (2.5 mg/kg)	i.v./p.o./acute i.v./acute	1 hour	Guinea pigs treated with cetirizine 2.5 mg/kg either i.v. or p.o. were protected from 300 and 400 times the lethal dose of histamine, respectively.
2. Protection Against Anaphylactic Bronchospasm							
NP-6	Sprague-Dawley Rats/ Male	Protection against antigen (iv)-induced bronchospasm	150	Cetirizine (10-100) Mepyramine (2.5-250) Hydroxyzine (1-10) Clemastine (10-100) Methysergide (0.001-0.1) Placebo	i.v./acute	Immediate	Cetirizine demonstrated some activity in blocking antigen-induced bronchospasm (primarily a serotonin mediated effect) but the ED 50 (10-100 mcmod/kg) could not be determined.
NP-5	Hartley Guinea Pigs/ Male	Protection against antigen (iv)-induced bronchospasm	220	Cetirizine (0.006-1.98 mg/kg) Mepyramine (0.006-0.06 mg/kg) Clemastine (0.006-0.36 mg/kg) Terfenadine (0.15-0.71 mg/kg) Hydroxyzine (0.006-0.36 mg/kg) Placebo	p.o./acute	1 Hour	Cetirizine (ED 50 = 0.3 mg/kg) significantly inhibited antigen-induced (primarily histamine-mediated) bronchospasm in the guinea pig. Activity was similar to hydroxyzine (ED 50 = 0.1 mg/kg), superior to clemastine and terfenadine (ED 50 = 0.8 mg/kg for both) and less potent than mepyramine (ED 50 = 0.02 mg/kg).

^a All doses are expressed as mcmod/kg unless otherwise specified.

^b All studies were sponsored by UCB with the exception of NP-20 which was a Pfizer sponsored study.

^c acute - Single dose

N/A - Information not available in report.

NDA Report No.	Animal Species/Sex	Study Design	Number of Animals	Treatment/Dose (mcmol/kg)	Route of Administration/ Duration of Treatment	Time of Testing After Last Dose	Results
NP-6	Hartley Guinea Pig/ Male, Female	Protection against antigen (aerosol) induced bronchospasm	5 per group	Cetirizine (0.01-10) Mepyramine (1-100) Clemastine (1-100) Placebo	p.o./acute	1 Hour	Cetirizine significantly protected guinea pigs from asthgas (given by aerosol) induced bronchospasm and was more potent than clemastine and mepyramine.
NP-7	Hartley Guinea Pig/ Male, Female	Protection against histamine, acetylcholine, serotonin induced by bronchospasm	6 per group	Cetirizine (0.03-100) Clemastine (0.32, 1, 3, 2) Mepyramine (0.003-10) Terfenadine (1.0) Placebo (1, 2)	i.v./acute i.d.o./acute i.v./acute i.d.o./acute i.d.o./acute	2 Mins	Cetirizine significantly inhibited histamine-induced bronchospasm (ED 50 = 7.2 mcmol/kg) in guinea pigs. Cetirizine had some effect (ED 50 = 7.3 mcmol/kg) on serotonin-induced bronchospasm and no effect (ED 50 greater than 100 mcmol/kg) on acetylcholine-induced bronchospasm.
2. Effect on Histamine/Allergen Induced Cutaneous Reactions							
NP-8	NIH3T3 Mice/ female	Protection against histamine induced cutaneous reactions	7-12 per group	Cetirizine (0.010-1) Hydroxyzine (0.1-10) Placebo	p.o./acute	2 Hours	Cetirizine significantly inhibited histamine-induced cutaneous reactions in mice (ED 50 = 0.006 mg/kg) 0.10 mcmol/kg) and was 30 times more potent than hydroxyzine.
NP-9	Sprague-Dawley Rat/ Female	Protection against histamine and serotonin induced cutaneous reactions	5 per group	Cetirizine N/A Mepyramine Clemastine Placebo	p.o./acute and i.v.	Immediate (i.v.) 15 mins (p.o.)	Cetirizine significantly blocked histamine induced cutaneous reaction in rats following p.o. (ED 50 = 0.2 mcmol/kg) and i.v. (ED 50 = 1.1 mcmol/kg) administration and was 2.5 and 30 times less potent against serotonin induced cutaneous reactions following oral and i.v. administration, respectively.
NP-10	Hartley Guinea Pig/ Male, Female	Protection against histamine induced cutaneous reactions	5 per group	Cetirizine N/A Mepyramine Clemastine Hydroxyzine Terfenadine Placebo	i.v./acute and p.o.	1 Hour	Cetirizine effectively inhibited histamine-induced cutaneous reactions in guinea pigs after p.o. (ED 50 = 0.6 mcmol/kg) and i.v. (ED 50 = 0.18 mcmol/kg) administration.
NP-11	Beagle Dog/ Female	Histamine and Ascaris induced cutaneous reactions	N/A	Cetirizine (0.01, 0.1, 1.0 mg/kg) Atemizole (0.23) Clemastine (0.28) Hydroxyzine (0.27) Terfenadine (2.2)	p.o./acute	0.5-26 Hrs	In dogs, cetirizine demonstrated significant suppression of histamine and Ascaris induced skin reactions. The duration of activity following 0.1 and 1.0 mg/kg was 0.5 and 26 hours, respectively.

i.d.o - intradermally.
N/A - Information not available in report.

Table 1. Antihistaminic Activity (continued)

NDA Report No.	Animal Species/Dose	Study Design	Number of Animals	Treatment/Dose (mg/kg)	Route of Administration/Duration of Treatment	Time of Testing After Last Dose	Results
ND-12	Dog	Histamine, Acariz, DPT, House Dust induced cutaneous reactions	7	Cetirizine (0.32) Cetirizine (0.107 mg/kg)	i.v./acute	0-20 hrs	Cetirizine (0.107 mg/kg) significantly inhibited histamine, Acariz and house dust induced cutaneous reactions in dogs at 0 hours post dose.
ND-13	Shrews (Meadow) 7M, 1F	Histamine, 0.1/0, Substance P, VIP induced cutaneous reactions	8	Cetirizine 10 mg/kg Clemastine 300 mg/kg Cetirizine 10 mg/kg Clemastine 300 mg/kg	p.o./acute	2 hrs	Cetirizine significantly inhibited cutaneous reactions induced by histamine, 0.1/0, substance P, and VIP in dogs, whereas clemastine was weakly effective. Cetirizine plus clemastine was less active than cetirizine alone.
ND-14	Shrews (Dogs) 6M, 1F	Effects on Histamine and Serotonin induced changes in blood pressure	5	Cetirizine 0.12-1.19 mg/kg Hydroxyzine 0.12-3.2 mg/kg Mepyramine 0.1-1.0 mg/kg	i.v./acute	5, 10 mins	Cetirizine had a significant effect on histamine induced hypertension but had no effect on serotonin induced hypertension.

3. Effects on Histamine - Induced Blood Pressure Changes

Effects on Histamine and Serotonin induced changes in blood pressure

II. TOXICOLOGY STUDIES:
ACUTE/SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY STUDIES:

ITEM 2: APPLICATION SUMMARY

V. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY SUMMARY

B. NONCLINICAL TOXICOLOGY

Table 1. Principal Findings

NDA Report No.	Type of Study	Species	Duration	Route of Administration	Dose Levels mg/kg/day	Principal Findings
T-1	Acute	Mouse Rat, Dog	Single Dose	PO; IV		Oral LD ₅₀ values about 700 mg/kg in mice, and 800 mg/kg in rats. Max. non-lethal oral dose in dogs was 320 mg/kg. I.V. LD ₅₀ values about 300 mg/kg in mice, and 70 mg/kg in rats. Max. non-lethal I.V. dose in dogs was 70 mg/kg. Clinical signs were CNS-related.
T-2	Subchronic	Mouse	15 Day	Oral (Diet/Gavage)	0, 5, 10, 20, 40, 80, 160	Increased liver weights and hepatic hypertrophy induced by both routes of administration. Hepatic steatosis at 160 mg/kg by gavage dosing; NOEL = 80 mg/kg (gavage); greater than 203 (male) and 371 (female) mg/kg (diet).
T-3	Subchronic	Mouse	4 Week	Oral (Diet)	0, 1, 3, 9, 27, 81	Hepatic changes in males only: Pharmacologic (increased liver weights; hypertrophy, and microsomal enzyme induction) Toxicologic (steatosis and serum enzyme modifications) - NOEL = 9 mg/kg Elevated serum triglyceride levels (81 mg/kg) and microsomal enzyme induction (9 mg/kg and higher) in female mice.
T-4 T-5	Subchronic Electron Microscopy - Addendum to NDA Report T-4	Mouse	4 Week	Oral (Diet)	0, 40, 160	Additional hepatic changes included elevated hepatic cholesterol, triglyceride and total lipid, and SER proliferation. Reversibility of all cetirizine-induced hepatic changes at both dose levels after 13 weeks of recovery.

ITEM 2: APPLICATION SUMMARY

V. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY SUMMARY

B. NONCLINICAL TOXICOLOGY

Table 1. Principal Findings (Cont'd)

NDA Report No.	Type of Study	Species	Duration	Route of Administration	Dose Levels mg/kg/day	Principal Findings
T-6	Subchronic	Rat	15 Day	Oral (Diet/Gavage)	0, 5, 10, 20, 40, 80, 160	Hepatic changes (increased liver weights; hypertrophy, and steatosis) induced by both routes of administration. NOEL for hepatic steatosis was 80 mg/kg in male and 20 mg/kg in female rats by gavage dosing and 25 mg/kg in male and 11 mg/kg in female rats by diet dosing.
T-7 T-8	Subchronic Liver Histopathology Review - Addendum to NDA Report T-7	Rat	1 Month	Oral (Gavage)	0, 25, 75, 225	Hepatic changes (increased liver weights; hypertrophy, and steatosis) at 75 and 225 mg/kg were more pronounced in male rats. NOEL for hepatic steatosis was 25 mg/kg for male and 75 mg/kg for female rats.
T-9	Subchronic	Rat	4 Week	Oral (Diet)	0, 2, 6, 18, 54, 160	Hepatic changes (increased liver weights; hypertrophy; steatosis, and microsomal enzyme induction) were more pronounced in male rats. NOEL=18 mg/kg.
T-10 T-11	Subchronic Electron Microscopy - Addendum to NDA Report T-10	Rat	4 Week	Oral (Diet)	0, 40, 160	Additional hepatic changes included elevated hepatic cholesterol, triglyceride and total lipids, and SER proliferation. Reversibility of all ceterizine-induced hepatic changes at both dose levels after 4 and 13 weeks of recovery.
T-12 T-13	Subchronic Electron Microscopy - Addendum to NDA Report T-12	Rat	6 Month	Oral (Gavage)	0, 8, 25, 75	Dose-related incidence of hepatic changes (increased liver weights; hypertrophy, and steatosis). SER proliferation at 75 mg/kg (only level examined). NOEL for hepatotoxicity was 8 mg/kg.

ITEM 2: APPLICATION SUMMARY

V. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY SUMMARY

B. NONCLINICAL TOXICOLOGY

Table 1. Principal Findings (Cont'd)

NDA Report No.	Type of Study	Species	Duration	Route of Administration	Dose Levels mg/kg/day	Principal Findings
T-14	Subchronic	Dog	1 Month	Oral (Capsule)	0, 15, 45, 135	At 135 mg/kg: toxic clinical signs; body weight losses and reduced food intake in two females not associated with any other changes. NOEL=45 mg/kg.
T-15	Subchronic	Dog	6 Month	Oral (Capsule)	0, 8, 25, 75	No target organ toxicity. At 25 and 75 mg/kg: increased incidence of vomiting; decreased body weight gains in females; one male dog died and a second male dog sacrificed. NOEL=8 mg/kg.
T-16	Subchronic-Pilot	Monkey	14 Day	Oral (Gavage)	50, 100, 200	At 50 and 100 mg/kg: vomiting/salivation and body weight losses. At 200 mg/kg: toxic clinical signs and marked body weight losses. NOEL less than 50 mg/kg.
T-17	Subchronic	Monkey	4 Week	Oral (Gavage)	0, 17, 50, 150	At 50 and 150 mg/kg: toxic clinical signs and marked body weight losses not associated with any other changes. One debilitated female at 150 mg/kg was sacrificed moribund due to marked reduction in food intake and body weight loss. NOEL=17 mg/kg.
T-18	Chronic	Dog	1 Year	Oral (Capsule)	0, 4, 15, 60	No target organ toxicity. Cetirizine induced a dose-related incidence of vomiting. NOEL=60 mg/kg.
T-19	Chronic	Monkey	1 Year	Oral (Gavage)	0, 5, 15, 45	No target organ toxicity. Cetirizine induced a dose-related incidence of salivation. NOEL=45 mg/kg.

CARCINOGENICITY, REPRODUCTION AND GENETIC TOXICOLOGY STUDIES:

ITEM 2: APPLICATION SUMMARY

V. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY SUMMARY

B. NONCLINICAL TOXICOLOGY

Table 1. Principal Findings (Cont'd)

<u>NDAs Report No.</u>	<u>Type of Study</u>	<u>Species</u>	<u>Duration</u>	<u>Route of Administration</u>	<u>Dose Levels mg/kg/day</u>	<u>Principal Findings</u>
T-20	Carcinogenicity	Mouse	2 Year	Oral (Diet)	0, 0, 1, 4, 16	Not carcinogenic. Increased incidence of spontaneously occurring benign liver cell tumors only in males at 16 mg/kg.
T-21	Carcinogenicity	Rat	2 Year	Oral (Diet)	0, 0, 3, 8, 20	Not carcinogenic.
T-22	Segment I	Mouse	Males: 8 weeks prior to mating, through mating, gestation and lactation. Females: 2 weeks prior to mating, through mating to termination either on day 17.5 of gestation or day 21 post partum.	Oral	0, 4, 16, 64	At 64 mg/kg: decreased maternal body weight gain; slightly lower pregnancy rate; lower fetal and litter weights; lower total litter size at birth, and delayed skeletal development and associated commonly occurring malformations. NOEL=16 mg/kg.
T-23	Segment II	Mouse	Days 6 to 15 of gestation	Oral	0, 6, 24, 96	Cetirizine was not teratogenic. Maternal and embryo-feto toxicity at 96 mg/kg. NOEL=24 mg/kg.
T-24	Segment II	Rat	Days 6 to 15 of gestation	Oral	0, 8, 25, 75, 225	Cetirizine was not teratogenic. Maternal toxicity at 75 mg/kg and higher; embryo-feto toxicity at 25 mg/kg and higher. NOEL=8 mg/kg.

ITEM 2: APPLICATION SUMMARY

V. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY SUMMARY
B. NONCLINICAL TOXICOLOGY

Table 1. Principal Findings (Cont'd)

NDA Report No.	Type of Study	Species	Duration	Route of Administration	Dose Levels mg/kg/day	Principal Findings
T-25	Segment II	Rabbit	Days 6 to 18 of gestation	Oral	0, 15, 45, 135	Cetirizine was not teratogenic. Maternal and embryo-feto toxicity at 45 mg/kg and higher. NOEL=15 mg/kg.
T-26	Segment III	Mouse	Day 15 of gestation throughout lactation	Oral	0, 6, 24, 96	At 96 mg/kg reduced maternal body weight gains and lower pup weights throughout lactation. NOEL=24 mg/kg.
T-27	Historical Data	Rat	-	-	-	-
T-28	Historical Data	Rat	-	-	-	-
T-29	Genetic	AMES Test			0-5000 mcg/plate	No mutagenic activity.
T-30	Genetic	Chromosomal Aberrations Assay - Human Peripheral Lymphocytes			20, 100, 500 mcg/ml	No mutagenic activity.
T-31	Genetic	Mouse Lymphoma TK Locus Assay			100-460 mcg/ml	No mutagenic activity.
T-32	Genetic	Micronucleus Test-Mouse			10, 70, 350 mg/kg/day	No mutagenic activity.

1 NOEL=No Effect Level

III. ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION STUDIES:

CETIRIZINE NDA

ATTACHMENT A. ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION (ADME) STUDY SUMMARY

NDA Report No.	Type of Study	Species	Duration	Route of Administration	Dose Levels	Principal Findings
NPK-1	PK	Mouse	Single Dose	IV, Oral	10 mg/kg	Rapid and extensive absorption, urinary excretion of cetirizine = 34% of dose.
NPK-2	Disposition	Mouse	Single Dose	IV, Oral	10 mg/kg	Males metabolized more cetirizine than females. One metabolite is F026.
NPK-3	PK	Mouse Rat	14 Days 14 Days	Oral (Diet) Oral (Diet)	3, 9, 27 mg/kg/day 6, 18, 54 mg/kg/day	Oral cetirizine well absorbed in mice and rats; saturation of metabolism in rats.
NPK-4	Monitoring	Mouse	1 Week	Oral (Diet)	1, 3, 9, 27, 81 mg/kg/day	Non-linear urinary excretion of drug.
NPK-5	PK	Rat	Single Dose	IV, Oral	10 mg/kg	Rapid absorption, extensive metabolism, greater in male rat than female.
NPK-6	Disposition	Rat	Single Dose	IV, Oral	1, 8, 25, 75 mg/kg	Non-linear pharmacokinetics, male rats metabolize drug more extensively than females.
NPK-7	Antipyrine Elimination	Rat	7 Days	Oral	75 mg/kg/day	Antipyrine metabolism increased with cetirizine treatment.
NPK-8	PK	Rat	Single Dose	Oral	1, 10, 100 mg/kg	Extensive oral absorption, excretion mainly in bile, metabolism is a saturable process.

CETIRIZINE NDA

ATTACHMENT A. ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION (ADME) STUDY SUMMARY

NDA Report No.	Type of Study	Species	Duration	Route of Administration	Dose Levels	Principal Findings
NPK-9	Monitoring	Rat	1 Month	Oral	25, 75, 225 mg/kg	Male metabolize drug to a greater extent than females. Non-linear pharmacokinetics.
NPK-10	Excretion	Rat	28 Days	Oral (Diet)	2, 6, 18, 54, 168 mg/kg/day	Females excreted more unchanged drug than males.
NPK-11	Monitoring	Rat	6 Months	Oral	3, 25, 75 mg/kg/day	Non-linear kinetics, males metabolize drug more extensively than females.
NPK-12	PK	Rabbit	Single Dose	IV, Oral	1, 15, 45, 135 mg/kg	Linear dose response. Extensive and rapid distribution into tissues.
NPK-13	PK	Dog	Single Dose	IV, Oral	1, 10 mg/kg	No sex-related differences in kinetics, rapid and extensive absorption, half-life 8-10 hours.
NPK-14	Disposition	Dog	Single Dose 9 Days	Oral (Diet)	0.64 mg/kg/day	Rapid and extensive absorption and tissue distribution. No sex-related difference in kinetics; steady-state reached in 4 days.
NPK-15	Metabolism	Dog	Single Dose	Oral	10 mg/kg	Rapid and extensive absorption, low first-pass metabolism. About 30% of drug metabolized.
NPK-16	Excretion	Dog	Single Dose	IV	10 mg/kg	3.2% of dose excreted into milk.
NPK-17	Monitoring	Dog	1 Month	Oral	15, 45, 135 mg/kg/day	Linear dose response (trough values) at entire dose range. Up to 32% of drug excreted unchanged in urine. Small amounts of P026 found, mainly in bile.

CETIRIZINE NDA

ATTACHMENT A. ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION (ADME) STUDY SUMMARY

NDA Report No.	Type of Study	Species	Duration	Route of Administration	Dose Levels	Principal Findings
NPK-18	Monitoring	Dog	6 Month	Oral	8, 25, 75 mg/kg/day	Linear dose response, steady-state reached by day 9. Up to 45% of daily dose excreted in urine as unchanged drug. PO26 minor component in plasma and urine.
NPK-19	Monitoring	Dog	52 Week	Oral	4, 15, 60 mg/kg/day	No sex-related differences in kinetics, dose-proportionality.
NPK-20	PK	Baboon	Single Dose	IV, Oral	1, 10 mg/kg	Rapid absorption, C _{max} and AUC linearly proportional to dose. No sex-related differences in kinetics.
NPK-21	PK	Monkey	Single Dose	IV, Oral	1, 10 mg/kg	Rapid absorption, C _{max} and AUC linearly proportional to dose. No sex-related differences in kinetics.
NPK-22	Monitoring	Monkey	14 Day	Oral	50, 100, 200 mg/kg/day	No consistent pattern to data.
NPK-23	Monitoring	Monkey	28 Day	Oral	17, 50, 150 mg/kg/day	Concentrations linearly proportional to dose. Excretion mainly via bile.
NPK-24	Monitoring	Monkey	52 Week	Oral	5, 15, 45 mg/kg/day	Concentrations linearly proportional to dose. No sex-related differences in kinetics.
NPK-25 2	Assay Development	-	-	-	-	GLC assay in plasma, detection range 4-32 mcg/ml.

CETIRIZINE NDA

ATTACHMENT A. ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION (ADME) STUDY SUMMARY

NDA Report No.	Type of Study	Species	Duration	Route of Administration	Dose Levels	Principal Findings
NPK-26	Assay Development	-	-	-	-	GLC assay in urine, detection range 10 to 300 mcg/ml.
NPK-27	Assay Development	-	-	-	-	HPLC assay in urine, detection range 5 to 75 mcg/ml.
NPK-28	Stability	Human	Greater than or equal to 1 year	-	2, 10, 20, 400, 800 ng/ml	Plasma and urine samples spiked with cetirizine stable for at least 1 year.

I. PHARMACOLOGY:

Primary activity: as an antihistamine or H1 receptor antagonist.

(A) In vivo studies: (Note: the ED₅₀ values on pages 2 38-2 39 are different from those listed under individual studies, e.g. NP-2, NP-4, NP-8, NP-10 on pages 5 31-5 139. The following summary is based on the results from individual studies. The applicant is to be requested to clarify the discrepancies)

Test/animal model	ED50 mg/kg	Dose mg/kg	Duration/remarks
(1) Lethality by			
(a) histamine guinea pig	0.35 (po)	0.1 (po)	protection: 100%-12 hrs 80%-24 hrs
		2.5 (iv)	800X LD50 hist
		2.5 (po-1hr)	400X LD50
		hydroxyzine:2.5 (iv)	800X LD50
(b) Compound 48/80: rat		1.4 (po)	80% protection
		hydroxyzine:44 (po)	40% "
(2) Bronchoconstriction by			
(a) Passive-immun. guinea pig	0.3(po) 0.3(po):hydroxyzine 0.8(po):terfenadine & clemastine 0.02(po):mepyramine		
rat	4.6(iv) 9.2(iv):mepyramine 1.4(iv):hydroxyzine NE:clemastine		
guinea pig			some protection at cetirizine:4.6 mg/kg(po) mepyramine:46 mg/kg (po) clemastine:46 mg/kg (po)
(b) guinea pig histamine	0.09 mg/kg(iv) 0.46 mg/kg(po)		iv: clemastine & mepyramine better than cetir. po: 3 drugs comparable

(continued)

(continued)

Test/model	ED ₅₀	Dose	Remarks
serotonin Ach	3.4 mg/kg(iv) greater than 46 mg/kg (iv)		
(3) Cutaneous Rnx by (a) histamine mice	0.046 (po) 0.76 (po): hydroxyzine		
rat	1.9 (po) 0.49(iv)		po & iv: cetirz. duration 6 hrs & better than clemastine & mepyramine.
guinea pig	0.8 (iv) 1.8 (po)		better than terfenadine, mepyramine, hydroxyzine; less than clemastine. cetirz best of the five.
dog		1 (po)	75% inh, 2-24 hrs, better than terfenadine, astemizole, clemastine. = hydroxyzine.
monkey(Rhesus)		10 (po)	76% inh.@ 2 hrs.
(b) Ascaris dog		1 (po) 0.15 (iv)	same as antihistamine 50% inh, 4-24 hrs.
(c) 48/80, VIP Substance P monkey		10 (po)	60-80% inh.@ 2 hrs
(4) Hypotension by histamine dog		0.12-1.19(iv)	reversed
serotonin dog		0.12-1.19(iv)	NE

(B) In vitro studies: (Vol 2.4)

Species	Tissue	Results (EC ₅₀ umol/l)
(1) Guinea pig	ileum	
(2) Guinea pig	Trachea	<u>histamine:</u> cetirz: 2 (or 9 ug/ml) hydroxz: 3 clemast: 10 mepyram: 0.05 <u>carbachol:</u> cetirz: 320-1000
(3) Human	bronchi	0.9 (or 0.4 ug/ml)
(4) Guinea pig	atrium	NE (100 ug/ml) (H ₂ receptor act.)
(5) Human	basophils	470 (or 217 ug/ml) (inhibition of histm-release)

Neuropharmacology:

Behavior studies:

Species	Test	Results
Mouse	Irwin (general behaviors)	46 mg/kg (ip): NE
		~~92 mg/kg (ip): sedation~~
		138 mg/kg (ip): lethal
		462 mg/kg (po): stimulation
		1384 mg/kg (po): lethal
Rat	Irwin	46 mg/kg (ip): NE
		92 mg/kg (ip): dec act. & mus tone lethal
		138 mg/kg (po): NE
		462 mg/kg (po): LD50
		hydroxyzine: 90 mg/kg (ip): convulsion
Rat	exploratory act in new environment	4.6 mg/kg (ip): NE 15 mg/kg (ip): <u>hypoactivity</u> 15-46 mg/kg (po): NE
Rat	retention of learning in passive avoidance test	15 mg/kg (po): NE
Dog	conditioning response	45 mg/kg: NE on selective atten. percept-motor coordination

Other neuropharmacological effects:

Activity	Species	Drug-ind	Effects	Dose(mg/kg)	Effects
(1) Anticonvulsant (NP-33)	mice	pentylene-tetrazol	seizure	15-46(ip)	NE
(NP-34)	mice	audiogenic	seizure	46 (ip) 45-46 (ip):hydroxy- zine & clemastine protected.	NE
(2) Neuroleptic (NP-35)	mice	apomorphine	climbing	15-46(ip)	inhibit
(NP-37)	rats	amphetamine	stereotype	46 (ip)	NE
(3) Interactions pentob (NP-32)	mice	pentobarbital	right-reflex	46(po,ip)	potent.
alcohol(NP-38)	rats	alcohol	open field	15 (po)	NE
(4) Ataxia (NP-36)	rats		Rotat-rod	45(ip)	NE
(5) EEG (NP-39)	rabbits		duration-arousal recording	1.5-46(iv)	dec.
			duration-sleep recording	1.5-46(iv)	inc.
			arousal rnx to sound	1.5-46(iv)	NE

Cardiovascular effects
In vivo studies:

Species		Dose (mg/kg)	HR	BP	Others
Rat	anesthetized	14.8 (iv) 26 (iv) 46 (iv)	NE NE lethal	NE -25%	
Dog	anesthetized (chloralose)	4.6 (iv) 14.8 (id) 46.1 (id) 67.7 (iv)cumul: 675 (id)cumul:	inc inc inc lethal lethal	inc. slig. dec	ECG/resp dep
Dog	conscious	1.2 (iv) 3.8 (iv) 11.9 (iv)	minor inc slig	minor +10% (dias) +10% (dias)	
Dog	anesthetized	11.9 (iv) 11.9 (iv)	NE on Ach- or Vagus-stim hypotension. NE on norepinephrine-hyperten. inh on carotid occlu-hypertens. NE on isoproterenol-hypotens & tachycardia.		
Dog	anesthetized	3.2 (iv)	NE on permanent-coronary-ligation induced arrhythmia.		

In vitro studies

Species	Issue/model	Drug-induced	Effects
Rat	aorta-contraction	norepinephrine KCl	150 mg/l : NE phentolamine: inh. 46 mg/l: NE
Guinea pig	right atrium left atrium	spontaneous electric-stim.	46 mg/l: NE on freq. 46 mg/l: NE on contractil.
Rat	working heart	none	46 mg/l: cardiotoxic on all parameters. 0.46 mg/ml: NE

Other effects:

Activity	Species	Drug-induced Effects	Dose(mg/kg)	Effects
(1) Anticholinergic (NP-30)	mice	light-pupillary diameter	138(po) 46(ip)	NE NE
(NP-31)	mice	oxotremorine-salivation -tremor	46(ip) 46(ip)	NE NE
(2) Anesthetic (NP-42)	guinea pig	corneal reflex	14.6 g/l	NE
(3) Analgesic (NP-40)	mice	acetic acid-writhing	ED ₅₀ =84(po)	
(NP-41)	rats	tail-flick latency	92(sc) 138(sc)	NE inhib.
		hydroxyzine	45(sc)	inhib.
(4) Antiinflam- matory(NP-55)	rats	carrageenan-edema	46(iv)	NE
		indomethacin	1.2(iv)	inhib.
(5) Delayed hyper- sensitivity(NP-54)	mice	sheep red cell-local inflamm.	3.2(sc)	NE
		dexamethasone	3.3(sc)	inhib.
(6) Immediate anaphylactic (NP-19)	human	basophil-anti IgE histamine rel.	EC ₅₀ 0.47mm/l	
		theophylline	EC ₅₀ 0.085mm/l	
(7) Ulcer (NP-56)	rats	stress(immob & immers.)	50(po)	NE

II. TOXICOLOGY

Acute Toxicity Studies (mouse, rat, dog):
Summary table: Page 24.

Subacute/Subchronic/Chronic Toxicity Studies:
Summary tables
Mouse: page 25.
Rat: page 26-27.
Dog: page 28.
Monkey: page 29.

Individual studies:
Mouse (1)-(3): pages 30 to 37
Rat (1)-(5): pages 38 to 50
Dog (1)-(3): pages 51 to 56
Monkey (1)-(3): pages 57 to 61

Carcinogenicity studies:
Mouse: page 62 to 63
Rat: page 64 to 68

II. Toxicology:

Acute Toxicity studies: performed by (1)

Rodents performed Feb-July, 1961; dogs in Feb. 1961 & March, 1963.
Observations for 14 days.

Route	Mice NMI, own breed 7 wks. 22-23gm		Rats Wistar 7 wks. 112-127 gm		Dog Beagle 20-54 months 8.3-14.2 kg	
	p.o.	i.v.	p.o.	i.v.	p.o.	i.v.
No./dosage	20 (10 M + 10 F)		20 (10 M + 10 F)		2 (1 m)	2 (1M-1F)
Dosage ranges (mg/kg)	100, 237, 562 & 1333	240, 270, 320 & 370	237-3162	42-100	40, 90, 160 & 320* *in 2 div	70 & 125 doses because of vomiting. Did not prev vom.
Observations	See below					
No death at (mg/kg)	237 (M) 100 (F)	240 (M) 240 (F)	237 (M) 237 (F)	none (M) 42 (F)	320 (M-F)	70
Death from (mg/kg)	562 (M) 237 (F)	320 (M) 270 (F)	562 (M) 562 (F)	42 (M) 56 (F)	none	125
LD_{50} (mg/kg) (95% conf.)	M: 600 (375-1391) F: 732 (432-9114)	336 (301-476) 301 (264-366)	M: 703 (305-1175), 66 (58-96) F: 565 (593-1353), 70 (61-82)			ED

Signs: Calm, cyanosis-all mice in h i hr. Dyspnea & death. Survivors recovered in 24 hrs Female mice lost 27% wt. at 240 mg/kg.

ins. motor act. unsteady gait-all mice immediately. Convulsions death. in 24 hrs Female mice lost 27% wt. at 240 mg/kg.

same as mice

i.v. death following cardiac arrest.

No effect at 40 mg/kg po. No heart rate. 80 mg/kg p.o. nervousness-160. Food and weight-all normal.

Necropsy: unremarkable in all animals.

I.v.:
nervousness, calm unsteady gait, salivation or tremor at 70 mg/kg. No ECG changes. Recovered in 24hrs

Death at 125 mg/kg nervousness, muscle hypertonicity, atax. ur. no, fall on side head backwards, strong extension of its legs and died.

15-Day (T-2)

4-Week (T-3)

4-Week (T-4)

Species	Mouse	
Strain	CR CD-1	CR CD-1
Age/sex		
by:	Huntingdon	Huntingdon
M + #gr	32 (16M + 16F) + main 20 (10M + 10F) + urine	24 (12M + 12F): ma 24 (12M + 12F): 4-w 24 (12M + 12F): 13-w
Route	P.O. (diet) daily - 4 wk	P.O. (diet) daily -
Drug in	diet	diet
Dosage levels (mg/kg/day)	0, 1, 3, 9, 27, 81	0, 40, 160 Dosing: 12/16/85 - 1/2/86 Recovery: 1/12/86 - 9/15/86
Death at	0 (1F), 9 (2M), 27 (1M)	0 (1M), 40 (1M +)
Cause	Total 4 from urine group, not drug-related.	Total 3, not drug-r
Signs		
Necropsy		
Body wt.	NE	NE except HD-M
Food consumption		during 13-wk recovery
	Gavage: dec. wt & food 20 - (160M) + 160(M) feed: food inc 80 - 160 (M + F)	
Signs	None	None
Blood analysis	Hgb: inc F (9-81) SGPT/OCT: inc. M (27-81) Triglycerides: dec M (81); inc. F (27-81)	SGPT/OCT: 160 (M +) Cholesterol: dec ⁴⁰ 160 (M); Total lipids: 160 (M + F) 40 (M)
Urinalysis	positive ketone in most samples.	Triglyceride: inc. 160 (M) 40 (M)
Organ wt.	Liver (absol/rel.): inc 40 (M: gavage) 80 (M: feeding) 160 (F: both routes)	Liver (absol/rel.): inc. 4 160 (M + F)
Relative "no-effect" dose	1 (M) 9 (F)	Not est. (M) 40 (F)
Approx. "effect" dose	3 (M): liver 27 (F): Hgb/trigly	40 (M): liver 160 (F): liver
Target organs	Liver cell hypertrophy	Liver cell hypertrophy
Pathology		
Gross-	G: unremarkable	G: enlarged liver 160 (M +) 40 (M)
* Micro-		
(1) Periportal hepatocyte	10-160 (M + F) Hypertrophy: both routes	Micro: (1) 160 & 40 (M + F) (2) fat: 160 & 40 (M).
(2) Periportal vasculature	some	

(B) Rat Studies:

SUMMARY OF SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY STUDIES: rats (Vol 2.10-2.16)

Duration 15-Day(T-6) 1-month(T-7) 4-week(T-9) 4-Week(T-10) 6-month(T-13)

Performed by

2/10-2/25/83 5/18-6/18/81 11/8-/12/8/83

2/22-9/2/82
3-mo interim sac.

T-10: 11/11-12/8/85
Recov. 12/7/85-3/11/86
Recov sac. @ Wk 4 & 13

	12(6M+ 6F)	20(10M + 10F)	20(10M + 10F)main 12(6M + 6F)satellite	t:40(20M + 20F) i:10(5M + 5F)
(M+F)/group			total: 32(16M + 16F)	50(25M + 25F)

t(terminal)
i(interim)@3-mo
Satellite:drug monitoring

T-10:
t: 20(10M + 10F)
Wk 4 : 20(10M + 10F)
Wk 13: 20(10M + 10F)
total: 60(30M + 30F)

	(a)gavage (b)diet	gavage	diet	diet	gavage
Daily for	15 days	1 month	4 weeks	4 weeks	6 months

Drug in water for gavage and in diet for feeding studies.

Doses mg/kg/day	0,5,10,20, 40,80,160	0,25,75,225.	0,2,6,18, 54,160	0,40,160.	0,8,25,75

Deaths	20(1F) intub.err.	total:6 225(3M+2F) 75 (1M) poor condition, distended GI	2(1F)	total:34(22M +12F) intubation error: C(3)+L(3)+M(10)+H(10) accident: M(1) unknown: L(2)+M(2)+H(3)

T-10: total 3
160(1F), 40(1M)
C(1F)

Wt./food	NE	Both reduced in M only. wt. Food -7% -9% -13% -9% -22% -22%	Wt.160(M) Food 160(F)	Wt.160(M)	NE

Signs	None	Noisy resp.(225) Day 1 only.	None	None	Quiet/nervous (75)

Duration	15-Day(T-6)	1-month(T-7)	4-week(T-9)	4-Week(T-10)	6-month(T-13)
Blood	ND	T-7: dec Hgb/Hct/RBC:225 (M) inc SGPT/AP/GLO/BUN: 225 (M + F) inc chols: 225-(M)		T-10: inc total lipid/trigly:40-160(M) inc Cholesterol:225(M)	T-13: dec Hct/RBC:75(M+F) inc SGPT/SGOT/SDH:25-75 dec trigl: 25-75
Organ wt.	T-6	T-7	T-9	T-10	T-13
Inc. liver	40-160	75-225(M+F)	54-160(M)	160 (M+F)	3-mo:25-75(M+F) 6-mo:75(M+F)
			Inc spleen:54-160(M)		Inc kidney:25-75(M+F) Inc adren/thyro:75(M)
Pathology					
Gross					
Enlarged liver	20(F) 40(M)	no	160(M+F)	no	no
Enlarged spleen	no	no	6-160(M)	no	no
Cellularity/spleen (inc.)			18-160(M)		
Histopathology					
Liver:					
hepatocytic hypertrophy	PA:40(M+F)		CL:54-160(M+F)	CL:160(M+F)	PA:8-75(M) 75(F)
		T-7: CL/ML:75-225(M+F)			
vacuolation	20(M+F)	225(M)	54-160(M+F)	40(M)	25-75(M) 75(F)
fat deposition	20	75-225(M)	54-160(M+F)	40(M)	25-75(M) 75(F)
necrosis		225(M)			
"no-effect"dose (mg/kg/day)	5 (M+F)	25 (M+F)	18 (M+F)	not est. (M) 40(F)	not est. (M) 8(F)
"Affect dose" (mg/kg/day)	10(spots/liver) 20(steatosis)	75	54	40(M) 160(F)	8(M) 25(F)
Target organ*	liver	liver	liver/spleen	liver	liver

see Recovery studies: reversible.

CL: centrilobular. ML: midzonal. PA: periacinar.

(C) Dog studies

chronic

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SUMMARY OF SUBACUTE/SUBCHRONIC TOXICITY STUDIES: Dogs (by #)

one-month (T-14) 6-month (T-15) 1-yr. (T-18)

Species	Dog		
Strain	Beagle		
Weight	12-15 months	7-9 months	9.2-10.6 kg, 10-15
M + F/Gr	6 (3M + 3F)	10 (5M + 5F)	10 (5M + 5F)
Route	P.O. (capsule)	P.O. (capsule)	P.O. (capsule)
Duration	Daily - one month Apr. 14 - May 14 1951	Daily - 6 months Interim sacrifice at 3-months Jan. 13 - July 13 1952	Daily for 512 weeks June 25 1954 - June 25 1955
Drug in	gelatin capsule	4 (2M + 2F) gelatin capsule	gelatin capsule
Dosage level (mg/kg/day)	0, 15, 45, 135	0, 8, 25, 75	0, 4, 15, 60
Death	None	2M (75) on Day 87 #182	None
Reason Cause		Respiratory difficulty + Tracheitis	
Signs	Vomiting: 15-135 Salivation/tremor/ataxia red food: 135 Body wt./Food: 135	Vomiting: 8-75 Behavior: jittery at 75 Body wt: dec. F (25-75) Food: dec. F (25-75)	Vomiting: 15-60 Body wt: dec. 15-60 ECG/BP: 60
Blood analysis	AP: inc. at 135	Cholesterol/triglyceride: dec. at 75 RBC/AP: inc. at 75	Hem. RBC, Hgb, APTT: 15-6
Relative "no-effect" dosage	45 (except vomiting)	8	4
Approx. "effect" dosage	135 (signs/wt.)	25-75 (signs/wt. decrease)	15 (vomiting, wt. ²⁰⁰⁰ decrease)
Pathology/ Target organs	Unremarkable Kidney & adrenal: wt. inc. at 135 ECG: Unremarkable	Unremarkable ECG: Unremarkable Urinalysis: dec sp. gr.	Unremarkable Hepatic enzymes: no effects

(D) Monkey studies

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Chronic

SUMMARY OF SUBACUTE/SUBCHRONIC/TOXICITY STUDIES: ^{by} Monkeys of Huntington

	14-Day (T-16)	4-week Monkey (T-17)	one-year (T-19)
Species		Monkey	
Strain	Cynomolgus		
Weight			2-3 kg, 2-4 yrs
M + F/gr	2 (1M + 1F)	6 (3M + 3F)	10 (5M + 5F)
Route	P.O. (gavage)	P.O. (gavage)	P.O. (gavage)
Duration	daily - 14 days	daily - 4 weeks	daily - 50 weeks
Drug	~~50-200~~ in water (5%)	in water (5%)	in water no soln (5%)
Dosage level (mg/kg/day)	50, 100, 200	0, 17, 50, 150	0, 5, 15, 45
Death	None	one F (150) sacrificed on Day 22.	None
Dose			
Cause			
Signs	Salivation/vomiting: 50-200 Quiet behavior/piloerection/ tremor/loose muscles face: 200	Vomiting/huddled posture/ poor coat/tremor/hypothermia: 50-150	Salivation: at 45 Body wt./food: NE
Blood analysis	Body wt.: losses 50-200 Food: dec. at 200 Dec. RBC: 50-200	Body wt.: losses 50-150 Food: only the sacrific F Inc Triglycerides @ 150	Unremarkable
Relative "no-effect" dosage	not established	17	~~15~~ ~~(no effect)~~
Approx. "effect" dosage	50 (signs + wt.)	50 (wt./signs)	45 (salivation only)
Pathology/ Target organs	Liver: fat deposition at 200 Lung: congestion at 200	Unremarkable microsomal enzymes: no sig. effect.	None

(A) Mouse Studies: (1)-(3)

(1) Subacute toxicity study: Range finding oral toxicity in mice (15 days). (T-2)

Performed by

Animals: OF1 SPF mice, 6 weeks old, 23-25 gm.

No. of animals/dosage: 12 (6M + 6F)/dosage:gavage
12 (6M + 6F)/dosage:feeding.

Route and duration of administration:

(1) Gavage: compound in dist. water, orally 7 days/week for 15 days

(2) Feeding: compound in dietary mixture, orally 7 days/week for 15 days

Dosage levels: mg/kg/day

(1) Control:	0
(2)	5
(3)	10
(4)	20
(5)	40
(6)	80
(7)	160

Results:

Mortality: one male of 40 mg/kg (gavage) died after 5 doses. Cause of death: aggression between mice, according to sponsor.

Clinical signs: no signs.

Body weight and food consumption:

Gavage: Slight decreases of weight gains in 20, 40 and 160 mg/kg males and 160 mg/kg females. Food consumption showed decreases in some treated groups.

Feeding: no effect on weight gains; food consumption showed increases in 80 and 160 mg/kg. Food consumption was higher in feeding group than gavage group resulting in higher dose levels in feeding group.

Organ weight:

Liver: increased absolute and relative weights in males (at 40, 80 and 160 mg/kg gavage), in females (at 160 mg/kg gavage and feeding) and in males (at 80 and 160 mg/kg feeding).

Pathology

Gross pathology: unremarkable

Histopathology:

Liver: periacinar hepatocytic hypertrophy from 10-20 mg/kg. The "no-effect" levels were 5 mg/kg (males and females gavage), 6.3 mg/kg* (males feeding) and 9.7 mg/kg* (females, feeding).
*determined by food consumption.

(2) Toxicity to Mice by Continuous Dietary Administration for 4 weeks (T-3)

Performed by:

Animals:

Charles River CD-1 mice of Swiss origin
Manston, Kent, U.K.

No. of animals/dosage: 32 (16M + 16F)
Main study: 20 (10M + 10F)
Satellite study: 12 (6M + 6F), for urinary excretion and liver drug-metabolizing enzymes studies.

Route and duration of administration:

Orally through dietary mixture daily for 4 weeks.

Dosage levels /day

- (1) Control: cont. diet
- (2) 1
- (3) 3
- (4) 9
- (5) 27
- (6) 81
- (7) Health check 10(5M + 5F): no pathological finding or signs at the beginning of study.

Results:

Mortality: Total 4, all from satellite study.

Two M of 9 mg/kg and 1 F of control groups died during week 1. These deaths: not considered drug-related. One M of 27 mg/kg found dead in week 2 showed ulceration and swelling of perigenital region, and dark staining of contents of small intestines.

Clinical signs: hair loss/cutaneous scab formation and ulceration occurred incidentally in male mice.

Body weight and food consumption:

Body weight gain: slightly lower at 81 mg/kg (3-4% lower than control)

Food consumption: no significant effect; only high-F showed 5% less food consumption than control group mostly during Week 4.

Blood analysis:

Hematology:

Hgb: inc. in F of 9, 27 and 81 mg/kg groups. F of 27 mg/kg also had increases of Hct, RBC and WBC.

Chemistry:

(1) SGOT, SGPT* and OCT*(ornithine carbamoyltransferase) inc. in M mice of 81 mg/kg; inc. SGPT* in M mice of 27 mg/kg.

(2) Triglycerides: inc. in F mice of 27 and 81 mg/kg groups; dec. in M mice of 81 mg/kg group.

(3) BUN* and glucose: inc. in M mice of 81 mg/kg group.

*statistically significant.

Urinalysis:

Many mice failed to produce urine (or enough urine) during collection period. No adverse effects apparent, though positive ketones were found in most samples.

Ophthalmology: examined at Week 4. No adverse effect noted.

Organ weight: absolute wt.

Liver: significant inc. in M mice of 81 mg/kg; other dosed M groups showed some inc. over control without dose-related effect.

Pathology:

Gross pathology:

Liver: enlargement in 4/16M of 81 mg/kg

Histopathology:

Liver: (1) Minimal to moderate centrilobular hepatocyte enlargement in M mice of 3, 9, 27 and 81 mg/kg groups (dose-related effect). Some dosed male mice showed minimal centrilobular vacuolation, but no dose-related effect was observed.

(2) Minimal to moderate lipid deposition: M mice of 9, 27 and 81 mg/kg groups showed dose-related effect; F mice of all groups including control showed randomized incidence (graded as minimal) without apparent dose-related effects.

Assay of drug-metabolizing enzymes: See T-22 study.

- (1) Increased cytochrome P450 and aniline hydroxylase: both M and F of 81 mg/kg.
- (2) Increased ethylmorphine N-demethylase: in M mice of 27 and 81 mg/kg, and in F mice of 9, 27 and 81 mg/kg groups.
- (3) Increased p-nitroanisole O-demethylase: in M mice of 27 and 81 mg/kg (not statistically significant though).

Urinary Excretion of UCB P071: on Day 2, 9 and 28 during 7-hr period.

- (1) Urinary excretion of unchanged drug: not detected in M mice of 27 mg/kg or F mice of 9 mg/kg.
- (2) Urinary excretion increased with times only in F mice of 27 mg/kg group; at 81 mg/kg levels, urinary excretions were similar in M and F mice and did not increase with time.
- (3) The urinary excretion generally accounted for less than 5% of doses at all time points in both M and F mice.

Subacute/Subchronic Toxicity Studies:

(3) A study to determine the reversibility of hepatic changes in mice (T-4)

Performed by:

Treatment: 12/16/85-1/12/86

Withdrawal: 1/13/86-4/15/86 for 4 and 13 weeks

Animals:

Charles River CD-1 mice. 5-6 weeks old

No./of animals/dosage: 72 (36M + 36F)/dosage

24 (12M + 12F): Main study

24 (12M + 12F): 4-week recovery period.

24 (12M + 12F): 13-week recovery period.

Route and mode of administration:

orally through dietary mix for 4 weeks.

Duration of treatment:

four weeks, followed by recovery periods of 4 weeks and 13 weeks.

Dosage groups: (mg/kg/day)

(1) Control: 0

(2) Low dosage group: 40

(3) High dosage group: 160

Results:

Signs: None attributable to treatment

Mortality: total 3 deaths (1 control M, 1 low M and 1 low F), not drug-related.

Body weight: no effect during the dosing period; slight reduction in wt. gain during recovery periods in high-dose males only.

Food consumption: no effect during the dosing period; slight reduction during recovery periods in low-dose males and high-dose females.

Achieved intake of test material: within target ranges.

Liver studies:

Parameters	Low		High	
	<u>Treatment</u>	<u>Withdrawal</u> 4-wk 13-wk	<u>Treatment</u>	<u>Withdrawal</u> 4-wk 13-wk
<u>Chemistry:</u>				
Inc. SGPT & OCT			M & F	recovered (4 wk)
Inc. SGOT			F	recovered (4 wk)
Inc. trig & cholest.	M	recovered (4 wk)	M	recovered (4 wk)
<u>Lipid analysis:</u>				
Inc total lipid & triglycerides	M		M & F	
Inc. Cholest.			M	recovered (4 wk)
<u>Enzyme assay:</u>				
microm protein	M		M & F	recovered (4 wk)
Cyto P-450	M		M & F	recovered (4 wk)
ani. hydro	M & F		M & F	recovered (4 wk)
<u>Organ wt</u>				
inc. slig. in all mice, recovered at 13-wk excp high M				
<u>Gross pathology:</u>				
Enlarged	M		M & F	recv. (13-wk)
<u>Histopathology</u>				
Enlarged centri lob. hepatocytes	M & F		M & F	recv. (13-wk)
+ fat deposition	M		M	recv. (13-wk)

Note: T-4 Study

(1) Enzyme induction was observed in both 4-week studies. The induction was reversible following 4-week recovery period.

(2) Increased SGPT/SGOT/OCT* and inc. cholesterol, total lipids and triglycerides were reversible following 4-week recovery period.

(3) Gross and histopathological changes (hypertrophy and fat deposition) of liver were reversible only after 13-week recovery period.

*ornithine carbamoyltransferase

A study to determine the reversibility of hepatic changes in mice electron microscopy of liver (T-5)

Extension of Study T-4 , only mice from control and high groups sacrificed at end of 4-week treatment and 4-week of withdrawal were examined.

Summary of results was copied as follows:

After 4 weeks of treatment period

Increased amount of smooth endoplasmic reticulum was seen in hepatocytes in mice from groups receiving 160 or 40 mg/kg/day;

occasional concentric membranous bodies were seen in hepatocytes from 1 male and 1 female mouse from the group treated with 160 mg/kg/day;

a higher incidence of mice with minimally increased microbodies in hepatocytes were seen in males treated with 160 mg/kg/day;

increased lipid in hepatocytes in mice treated with 160 or 40 mg/kg/day.

After 4 weeks of treatment followed by 4 weeks withdrawal period

Marginally higher incidence of mice with minimal increase in amount of smooth endoplasmic reticulum in hepatocytes confined to females from high dose group;

other changes seen at termination revealed recovery.

(B) Rat Studies: (1)-(5)

(1) Subacute toxicity study: Range finding oral toxicity in rats (15 days). (T-6).

Performed by: ; males: Feb. 19, 1983; females: Feb. 10, 1983

Animals: Sprague-Dawley SPF rats, 5-6 weeks old, 138-147 gm

No. of animals/dosage: 12 (6M + 6F)/dosage: gavage or feeding each.

Route and duration of administration: *Orally 7 days/week for 15 days

*(1) gavage: compound in dist. water

(2) feeding: compound in dietary mixture

Dosage levels: mg/kg/day

(1) Control:	0
(2)	5
(3)	10
(4)	20
(5)	40
(6)	80
(7)	160

Results:

Mortality: one female (20 mg/kg) died on day 12. Autopsy revealed bloody liquid in the trachea and in thoracic cavity. The cause of death was probably tracheal intubation.

Clinical signs: No signs observed.

Body weight and food consumption:

Body weight: no effects.

Food consumption: no effects.

Organ weight:

Liver: dose-related increases of absolute and relative weights from 40-160 mg/kg. Male rats of both gavage and feeding were affected more than female rats.

Pathology:

Gross pathology:

Swollen liver: 1 female (gavage: 20 mg/kg) and in males (gavage: 80 mg/kg; feeding: 40mg/kg). White or yellow spots or nodules on the livers were observed in some of the dosed females (gavage and feeding; 10 mg/kg) and in males (only gavage: 40 mg/kg).

Histopathology:

Treatment related lesions occurred in liver. Periacinar hepatocytic hypertrophy: more frequent and severe in male rats. Gavage and feeding: from 40 mg/kg. Periacinar hepatocytic large vacuolation (steatosis): more frequent in female rats. Gavage: control, low to high female. feeding: from 20 mg/kg.

(2) Subacute toxicology studies: One month oral (gavage) toxicity study in rats. (T-7)

Performed by _____, May 18, 1981-June 18, 1981. (GLP: not totally in compliance).

Animals: Sprague-Dawley SPF rats, 127-131 gm, 7 weeks old.

No. of animals/dosage: 20 (10 M and 10 F)/dosage.

Route and duration of administration: orally by gavage, 7 days/week for 1 month.

Dosage: drug in dist. water

- (1) Control: vehicle
- (2) Low dosage: 25 mg/kg/day
- (3) Mid dosage: 75 mg/kg/day
- (4) High dosage: 225 mg/kg/day

Mortality: total 6: 1 M (mid dose); due to intubation accident on Day 29.

3 M and 2 F (high dose): on day 11-16. All lost weight. Some had blood on the muzzle, respiratory difficulty and flatulence before death. Autopsy revealed flatulence in 2 M and distended stomach/intestines with yellowish liquid in 1 F.

NDA 19-835
Pfizer Pharmaceuticals
New York, NY 10017

Review # 1

Date of Submission: June 30, 1988

Date of Review: April 11, 1989

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Initial Submission of June 30, 1988
Original Summary

Drug:

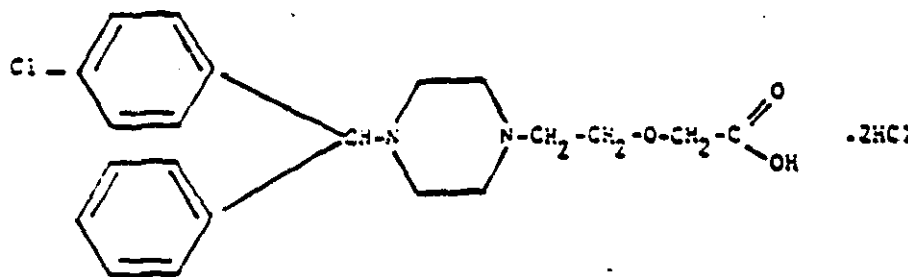
Trade name: Not established

Code name: UCBP071

Generic name: cetirizine HCl

Chemical name, empirical formula, molecular weight and structure:

2-[2-[4-[(4-chlorophenyl) phenylmethyl]-1-piperazinyl] ethoxy] acetic acid, dihydrochloride.



Molecular Formula: $C_{21}H_{25}N_2O_3Cl \cdot 2HCl$

Molecular Weight: 461.8

Dosage form: Tablets at 5, 10
Category: Antihistamine

Proposed indication:

Seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria.

Proposed dosage:

The recommended daily dose is 5 to 10 mg given as a single dose with or without food. If sufficient response is not obtained, the maximum daily dose is 20 mg.

Compositions:

	mg/tablet	
Components	5 mg	10 mg

Related drugs/INDs/NDAs/MFs:

IND
NDA

Pertinent memos/correspondence:

End of phase II meeting: IND of June 16, 1986

Preclinical studies and testing laboratories:

(1)
(2)

(3)

From page 4-15, summary tables are copied from NDA submission.
The tables included brief summaries of studies and principal findings.

- I. PHARMACOLOGY STUDIES (p. 4-6)
- II. TOXICOLOGY STUDIES (p. 7-9)
 - (A) ACUTE TOXICITY STUDIES (P. 7)
 - (B) SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY STUDIES (p. 7-9)
 - (C) CARCINOGENICITY STUDIES (p. 10)
 - (D) REPRODUCTION STUDIES (p. 10-11)
 - (E) GENETIC TOXICOLOGY STUDIES (p. 11)
- III. ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION STUDIES (p. 12-15)

From page 16 to 88, the summaries of I-III were prepared by this reviewer from individual study reports.

- I. PHARMACOLOGY STUDIES (p. 16-22)
- II. TOXICOLOGY STUDIES (p. 23-88)
 - (A) ACUTE TOXICITY STUDIES (P.24)
 - (B) SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY STUDIES (p.25-60)
 - (C) CARCINOGENICITY STUDIES (p.61-67)
 - (D) REPRODUCTION STUDIES (p.68-87)
 - (E) GENETIC TOXICOLOGY STUDIES (p.88)
- III. ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION (p.89-100) copied from NDA submission.

CETIRIZINE HCl
ITEM 3. Absorbable Pharmacology and Toxicology
1. Pharmacology
B. Summary Table

I. PHARMACOLOGY STUDIES:

Table 1. Antihistaminic Activity in Vivo

NDA Report No.	Animal Species/Sex	Study Design	Number of Animals	Treatment/Dose (mcg/ml/kg)	Route of Administration/Excision of Tissue	Time of Testing After Last Dose	Results
1. General Antihistaminic Activity							
NP-1 ^a	Sprague-Dawley Rats/ Male	Antagonism of 48/70-induced lethality	10 per group	Cetirizine (0.014, 0.14, 1.4 mg/kg) Hydroxyzine (0.04, 0.4, 4.0 mg/kg) Placebo	p.o./excise	2 Hrs	Cetirizine inhibited 48/70-induced lethality in rats (ED 50 = 0.014-0.14 mg/kg) and was more potent than hydroxyzine (ED 50 greater than 40 mg/kg)
NP-2	Hartley Guinea Pigs/ Male/Female	Antagonism of histamine induced lethality	3-10 per group	Cetirizine (0.01-0.17 mg/kg) Placebo	p.o./excise	1-16 Hrs	Cetirizine protected guinea pigs from potentially lethal doses of histamine (ED 50 = 0.5 mg/kg). Cetirizine 0.1 mg/kg p.o. protected all animals for 12 hours and 80% for a 24-hour period.
NP-3	Guinea Pig/ Male	Antagonism of histamine induced lethality	N/A	Cetirizine (2.5 mg/kg) Hydroxyzine (2.5 mg/kg)	i.v./p.o./excise i.v./excise	1 Hour	Guinea pigs treated with cetirizine 2.5 mg/kg either i.v. or p.o. were protected from 200 and 500 times the lethal dose of histamine, respectively.
2. Protection Against Anaphylactic Bronchospasm							
NP-4	Sprague-Dawley Rats/ Male	Protection against antigen (iv)-induced bronchospasm	10	Cetirizine (10-100) Mepyramine (7.5-250) Hydroxyzine (1-10) Clemastine (10-100) Methysergide (0.001-0.1) Placebo	i.v./excise	Immediate	Cetirizine demonstrated some activity in blocking antigen-induced bronchospasm (primarily a serotonin mediated effect) but the ED 50 (10-100 mcg/ml/kg) could not be determined.
NP-5	Hartley Guinea Pig/ Male	Protection against antigen (iv)-induced bronchospasm	20	Cetirizine (0.06-1.48 mg/kg) Mepyramine (0.004-0.24 mg/kg) Clemastine (0.004-0.24 mg/kg) Terfenadine (0.11-9.71 mg/kg) Hydroxyzine (0.004-0.48 mg/kg) Placebo	p.o./excise	1 Hour	Cetirizine (ED 50 = 0.3 mg/kg) significantly inhibited antigen-induced bronchospasm (mainly histamine-mediated) bronchospasm in the guinea pig. Activity was similar to hydroxyzine (ED 50 = 0.5 mg/kg), superior to clemastine and terfenadine (ED 50 = 0.8 mg/kg for both) and less potent than mepyramine (ED 50 = 0.02 mg/kg).

^a All doses are expressed as mcg/ml/kg unless otherwise specified.

^b All studies were sponsored by UCB with the exception of NP-10 which was a Pfizer sponsored study.

^c acute - single dose

N/A - Information not available in report.

NDA Report No.	Animal Species/Sex	Study Design	Number of Animals	Treatments/Dose (mcmol/kg)	Route of Administration/Duration of Treatment	Time of Testing After Last Dose	Results
NP-6	Hartley Guinea Pig/ Male, Female	Protection against antigen-induced bronchospasm	5 per Group	Cetirizine (0.01-10) Mepyramine (1-100) Clemastine (1-100) Placebo	p.o./acute	1 Hour	Cetirizine significantly protected guinea pigs from antigen (given by aerosol) induced bronchospasm and was more potent than clemastine and mepyramine.
NP-7	Hartley Guinea Pig/ Male, Female	Protection against histamine, acetylcholine, serotonin induced by bronchospasm	6 per Group	Cetirizine (0.03-100) (0.32,1,3.2) Clemastine (0.003-100) (3.2) Mepyramine (0.003-10) Terfenadine (1.0) (3.2) Placebo	i.v./acute i.o./acute i.o./acute i.o./acute i.o./acute	2 Min	Cetirizine significantly inhibited histamine-induced bronchospasm (ED 50 = 0.2 mcmol/kg) in guinea pigs. Cetirizine had some effect (ED 50 = 7.1 mcmol/kg) on serotonin-induced bronchospasm and no effect (ED 50 greater than 100 mcmol/kg) on acetylcholine-induced bronchospasm.
2. Effect on Histamines/Allergen Induced Cutaneous Reactions							
NP-8	MWBI Mice/female	Protection against histamine induced cutaneous reactions	7-12 per group	Cetirizine (0.010-1) Hydroxyzine (0.1-10) Placebo	p.o./acute	2 Hours	Cetirizine significantly inhibited histamine-induced cutaneous reactions in mice (ED 50 = 0.06 mcg/kg; 0.10 mcmol/kg) and was 30 times more potent than hydroxyzine.
NP-9	Sprague-Dawley Rats/ Female	Protection against histamine and serotonin induced cutaneous reactions	5 per Group	Cetirizine N/A Mepyramine Clemastine Placebo	p.o./acute and i.v.	Immediate (i.v.) 15 mins (p.o.)	Cetirizine significantly blocked histamine induced cutaneous reactions in rats following p.o. (ED 50 = 0.2 mcmol/kg) and i.v. (ED 50 = 1.1 mcmol/kg) administration and was 2.3 and 30 times less potent against serotonin induced cutaneous reactions following oral and i.v. administration, respectively.
NP-10	Hartley Guinea Pig/ Male, Female	Protection against histamine induced cutaneous reactions	5 per Group	Cetirizine N/A Mepyramine Clemastine Hydroxyzine Terfenadine Placebo	i.v./acute and p.o.	1 Hour	Cetirizine effectively inhibited histamine-induced cutaneous reactions in guinea pigs after p.o. (ED 50 = 0.4 mcmol/kg) and i.v. (ED 50 = 0.18 mcmol/kg) administration.
NP-11	Beagle Dogs/Female	Histamine and Acanth induced cutaneous reactions	N/A	Cetirizine (0.01,0.1,1.0 mg/kg) Asterizole (0.22) Clemastine (0.28) Hydroxyzine (0.22) Terfenadine (2.2)	p.o./acute	0.5-26 hrs	In dogs, cetirizine demonstrated significant suppression of histamine and Acanth induced skin reactions. The duration of activity following 0.1 and 1.0 mg/kg was 0-8 and 26 hours, respectively.

i.o. - Intradermally.
N/A - Information not available in report.

Table 1. Antihistaminic Activity (continued)

NDA Report No.	Animal Species/Sex	Study Design	Number of Animals	Treatment/Dose (mcg/kg)	Route of Administration/Duration of Treatment	Time of Testing After Last Dose	Results
NP-12 E-62/		Histamine, Acarbit, DPT, House Dust induced cutaneous reactions	7	Cetirizine (0.17) Cetirizine (0.107 mg/kg)	iv/acute	4-28 hrs	Cetirizine (0.107 mg/kg) significantly inhibited histamine, Acarbit and house dust induced cutaneous reactions in dogs at 4 hours post dose.
NP-13 Sherwin Meehan/7M, 1F		Histamine, 10/10, Substance P, VIP induced cutaneous reactions	8	Cetirizine 10 mg/kg Clemastine 300 mg/kg Cetirizine 10 mg/kg + Clemastine 300 mg/kg	p.o/acute	2 hrs	Cetirizine significantly inhibited cutaneous reactions induced by histamine, 10/10, substance P, and VIP in dogs, whereas clemastine was weakly effective. Cetirizine plus clemastine was less active than cetirizine alone.
NP-10 Morgan Dugli 6M, 1F		Effects on Histamine and Serotonin induced Changes in Blood Pressure	3	Cetirizine 0.12-1.19 mg/kg Hydroxyzine 0.32-3.2 mg/kg Mepyramine 0.1-1.0 mg/kg	iv/ single, cumulative doses	3, 10 mins	Cetirizine had a significant effect on histamine induced hypotension but had no effect on serotonin induced hypertension.

9. Effect on Histamine - Induced Blood Pressure Changes

II. TOXICOLOGY STUDIES:
ACUTE/SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY STUDIES:

ITEM 2: APPLICATION SUMMARY

V. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY SUMMARY
B. NONCLINICAL TOXICOLOGY

Table 1. Principal Findings

NDA Report No.	Type of Study	Species	Duration	Route of Administration	Dose Levels mg/kg/day	Principal Findings
T-1	Acute	Mouse Rat, Dog	Single Dose	PO; IV		Oral LD ₅₀ values about 700 mg/kg in mice, and 800 mg/kg in rats. Max. non-lethal oral dose in dogs was 320 mg/kg. I.V. LD ₅₀ values about 300 mg/kg in mice, and 70 mg/kg in rats. Max. non-lethal I.V. dose in dogs was 70 mg/kg. Clinical signs were CNS-related.
T-2	Subchronic	Mouse	13 Day	Oral (Diet/Gavage)	0, 5, 10, 20, 40, 80, 160	Increased liver weights and hepatic hypertrophy, induced by both routes of administration. Hepatic steatosis at 160 mg/kg by gavage dosing; NOEL 1.80 mg/kg (gavage); greater than 20 (male) and 37 (female) mg/kg (diet).
T-3	Subchronic	Mouse	6 Week	Oral (Diet)	0, 1, 3, 9, 27, 81	Hepatic changes in males only: Pharmacologic (increased liver weights; hypertrophy, and microsomal enzyme induction) Toxicologic (steatosis and serum enzyme modifications) - NOEL = 9 mg/kg Elevated serum triglyceride levels (81 mg/kg) and microsomal enzyme induction (9 mg/kg and higher) in female mice.
T-4 T-5	Subchronic Electron Microscopy - Addendum to NDA Report T-4	Mouse	6 Week	Oral (Diet)	0, 40, 160	Additional hepatic changes included elevated hepatic cholesterol, triglyceride and total lipid, and SER proliferation. Reversibility of all cetirizine-induced hepatic changes at both dose levels after 13 weeks of recovery.

ITEM 2: APPLICATION SUMMARY

V. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY SUMMARY

B. NONCLINICAL TOXICOLOGY

Table 1. Principal Findings (Cont'd)

NDA Report No.	Type of Study	Species	Duration	Route of Administration	Dose Levels mg/kg/day	Principal Findings
T-6	Subchronic	Rat	15 Day	Oral (Diet/Gavage)	0, 5, 10, 20, 40, 80, 160	Hepatic changes (increased liver weights; hypertrophy, and steatosis) induced by both routes of administration. NOEL for hepatic steatosis was 80 mg/kg in male and 20 mg/kg in female rats by gavage dosing and 25 mg/kg in male and 11 mg/kg in female rats by diet dosing.
T-7 T-8	Subchronic Liver Histopathology Review - Addendum to NDA Report T-7	Rat	1 Month	Oral (Gavage)	0, 25, 75, 225	Hepatic changes (increased liver weights; hypertrophy, and steatosis) at 75 and 225 mg/kg were more pronounced in male rats. NOEL for hepatic steatosis was 25 mg/kg for male and 75 mg/kg for female rats.
T-9	Subchronic	Rat	4 Week	Oral (Diet)	0, 2, 6, 18, 54, 160	Hepatic changes (increased liver weights; hypertrophy; steatosis, and microsomal enzyme induction) were more pronounced in male rats. NOEL-18 mg/kg.
T-10 T-11	Subchronic Electron Microscopy - Addendum to NDA Report T-10	Rat	4 Week	Oral (Diet)	0, 40, 160	Additional hepatic changes included elevated hepatic cholesterol, triglyceride and total lipids, and SER proliferation. Reversibility of all cetirizine-induced hepatic changes at both dose levels after 4 and 13 weeks of recovery.
T-12 T-13	Subchronic Electron Microscopy - Addendum to NDA Report T-12	Rat	6 Month	Oral (Gavage)	0, 8, 25, 75	Dose-related incidence of hepatic changes (increased liver weights; hypertrophy, and steatosis). SER proliferation at 75 mg/kg (only level examined). NOEL for hepatotoxicity was 8 mg/kg.

ITEM 2: APPLICATION SUMMARY

V. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY SUMMARY

B. NONCLINICAL TOXICOLOGY

Table 1. Principal Findings (Cont'd)

NDA Report No.	Type of Study	Species	Duration	Route of Administration	Dose Levels mg/kg/day	Principal Findings
T-10	Subchronic	Dog	1 Month	Oral (Capsule)	0, 15, 45, 135	At 135 mg/kg: toxic clinical signs; body weight losses and reduced food intake in two females not associated with any other changes. NOEL=45 mg/kg.
T-15	Subchronic	Dog	6 Month	Oral (Capsule)	0, 8, 25, 75	No target organ toxicity. At 25 and 75 mg/kg: increased incidence of vomiting; decreased body weight gains in females; one male dog died and a second male dog sacrificed. NOEL=8 mg/kg.
T-16	Subchronic-Pilot	Monkey	10 Day	Oral (Gavage)	50, 100, 200	At 50 and 100 mg/kg: vomiting/salivation and body weight losses. At 200 mg/kg: toxic clinical signs and marked body weight losses. NOEL less than 50 mg/kg.
T-17	Subchronic	Monkey	9 Week	Oral (Gavage)	0, 17, 50, 150	At 50 and 150 mg/kg: toxic clinical signs and marked body weight losses not associated with any other changes. One debilitated female at 150 mg/kg was sacrificed moribund due to marked reduction in food intake and body weight loss. NOEL=17 mg/kg.
T-18	Chronic	Dog	1 Year	Oral (Capsule)	0, 6, 15, 60	No target organ toxicity. Cetirizine induced a dose-related incidence of vomiting. NOEL=60 mg/kg.
T-19	Chronic	Monkey	1 Year	Oral (Gavage)	0, 5, 15, 45	No target organ toxicity. Cetirizine induced a dose-related incidence of salivation. NOEL=45 mg/kg.

CARCINOGENICITY, REPRODUCTION AND GENETIC TOXICOLOGY STUDIES:

ITEM 2: APPLICATION SUMMARY

V. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY SUMMARY

B. NONCLINICAL TOXICOLOGY

Table 1. Principal Findings (Cont'd)

<u>NTX Report No.</u>	<u>Type of Study</u>	<u>Species</u>	<u>Duration</u>	<u>Route of Administration</u>	<u>Dose Levels mg/kg/day</u>	<u>Principal Findings</u>
T-20	Carcinogenicity	Mouse	2 Year	Oral (Diet)	0, 0, 1, 4, 16	Not carcinogenic. Increased incidence of spontaneously occurring benign liver cell tumors only in males at 16 mg/kg.
T-21	Carcinogenicity	Rat	2 Year	Oral (Diet)	0, 0, 3, 8, 20	Not carcinogenic.
T-22	Segment I	Mouse	Males: 8 weeks prior to mating, through mating, gestation and lactation. Females: 2 weeks prior to mating, through mating to termination either on day 17.5 of gestation or day 21 post partum.	Oral	0, 4, 16, 64	At 64 mg/kg: decreased maternal body weight gain; slightly lower pregnancy rate; lower fetal and litter weights; lower total litter size at birth, and delayed skeletal development and associated commonly occurring malformations. NOEL=16 mg/kg.
T-23	Segment II	Mouse	Days 6 to 15 of gestation	Oral	0, 6, 24, 96	Cetirizine was not teratogenic. Maternal and embryo-feto toxicity at 96 mg/kg. NOEL=24 mg/kg.
T-24	Segment II	Rat	Days 6 to 15 of gestation	Oral	0, 8, 25, 75, 225	Cetirizine was not teratogenic. Maternal toxicity at 75 mg/kg and higher; embryo-feto toxicity at 25 mg/kg and higher. NOEL=8 mg/kg.

ITEM 2: APPLICATION SUMMARY

V. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY SUMMARY

B. NONCLINICAL TOXICOLOGY

Table 1. Principal Findings (Cont'd)

NDA Report No.	Type of Study	Species	Duration	Route of Administration	Dose Levels mg/kg/day	Principal Findings
T-25	Segment II	Rabbit	Days 6 to 18 of gestation	Oral	0, 15, 45, 135	Cetirizine was not teratogenic. Maternal and embryo-feto toxicity at 45 mg/kg and higher. NOEL=15 mg/kg.
T-26	Segment III	Mouse	Day 15 of gestation throughout lactation	Oral	0, 6, 24, 96	At 96 mg/kg reduced maternal body weight gains and lower pup weights throughout lactation. NOEL=24 mg/kg.
T-27	Historical Data	Rat	-	-	-	-
T-28	Historical Data	Rat	-	-	-	-
T-29	Genetic	AMES Test			8-3000 mcg/plate	No mutagenic activity.
T-30	Genetic	Chromosomal Aberrations Assay - Human Peripheral Lymphocytes			20, 100, 500 mcg/ml	No mutagenic activity.
T-31	Genetic	Mouse Lymphoma TK Locus Assay			100-460 mcg/ml	No mutagenic activity.
T-32	Genetic	Micronucleus Test-Mouse			14, 70, 350 mg/kg/day	No mutagenic activity.

† NOEL=No Effect Level

III. ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION STUDIES:

CETIRIZINE NDA

ATTACHMENT A. ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION (ADME) STUDY SUMMARY

<u>NDA Report No.</u>	<u>Type of Study</u>	<u>Species</u>	<u>Duration</u>	<u>Route of Administration</u>	<u>Dose Levels</u>	<u>Principal Findings</u>
NPK-1	PK	Mouse	Single Dose	IV, Oral	10 mg/kg	Rapid and extensive absorption, urinary excretion of cetirizine = 34% of dose.
NPK-2	Disposition	Mouse	Single Dose	IV, Oral	10 mg/kg	Males metabolized more cetirizine than females. One metabolite is P026.
NPK-3	PK	Mouse Rat	14 Days 14 Days	Oral (Diet) Oral (Diet)	3, 9, 27 mg/kg/day 6, 18, 54 mg/kg/day	Oral cetirizine well absorbed in mice and rats; saturation of metabolism in rats.
NPK-4	Monitoring	Mouse	4 Week	Oral (Diet)	1, 3, 9, 27, 81 mg/kg/day	Non-linear urinary excretion of drug.
NPK-5	PK	Rat	Single Dose	IV, Oral	10 mg/kg	Rapid absorption, extensive metabolism, greater in male rat than female.
NPK-6	Disposition	Rat	Single Dose	IV, Oral	1, 8, 25, 75 mg/kg	Non-linear pharmacokinetics, male rats metabolize drug more extensively than females.
NPK-7	Antipyrine Elimination	Rat	7 Days	Oral	75 mg/kg/day	Antipyrine metabolism increased with cetirizine treatment.
NPK-8	PK	Rat	Single Dose	Oral	1, 10, 100 mg/kg	Extensive oral absorption, excretion mainly in bile, metabolism is a saturable process.

CETIRIZINE NDA

ATTACHMENT A. ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION (ADME) STUDY SUMMARY

NDA Report No.	Type of Study	Species	Duration	Route of Administration	Dose Levels	Principal Findings
NPK-9	Monitoring	Rat	1 Month	Oral	25, 75, 225 mg/kg	Male metabolize drug to a greater extent than females. Non-linear pharmacokinetics.
NPK-10	Excretion	Rat	28 Days	Oral (Diet)	2, 6, 18, 54, 160 mg/kg/day	Females excreted more unchanged drug than males.
NPK-11	Monitoring	Rat	6 Months	Oral	8, 25, 75 mg/kg/day	Non-linear kinetics, males metabolize drug more extensively than females.
NPK-12	PK	Rabbit	Single Dose	IV, Oral	1, 15, 45, 135 mg/kg	Linear dose response. Extensive and rapid distribution into tissues.
NPK-13	PK	Dog	Single Dose	IV, Oral	1, 10 mg/kg	No sex-related differences in kinetics, rapid and extensive absorption, half-life 8-10 hours.
NPK-14	Disposition	Dog	Single Dose 9 Days	Oral (Diet)	0.64 mg/kg/day	Rapid and extensive absorption and tissue distribution. No sex-related difference in kinetics; steady-state reached in 8 days.
NPK-15	Metabolism	Dog	Single Dose	Oral	10 mg/kg	Rapid and extensive absorption, low first-pass metabolism. About 30% of drug metabolized.
NPK-16	Excretion	Dog	Single Dose	IV	10 mg/kg	3.2% of dose excreted into milk.
NPK-17	Monitoring	Dog	1 Month	Oral	15, 45, 135 mg/kg/day	Linear dose response (trough values) at entire dose range. Up to 32% of drug excreted unchanged in urine. Small amounts of 14O26 found, mainly in bile.

CETIRIZINE NDA

ATTACHMENT A. ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION (ADME) STUDY SUMMARY

NDA Report No.	Type of Study	Species	Duration	Route of Administration	Dose Levels	Principal Findings
NPK-18	Monitoring	Dog	6 Month	Oral	8, 25, 75 mg/kg/day	Linear dose response, steady-state reached by day 9. Up to 65% of daily dose excreted in urine as unchanged drug. PO26 minor component in plasma and urine.
NPK-19	Monitoring	Dog	52 Week	Oral	4, 15, 60 mg/kg/day	No sex-related differences in kinetics, dose-proportionality.
NPK-20	PK	Baboon	Single Dose	IV, Oral	1, 10 mg/kg	Rapid absorption, C _{max} and AUC linearly proportional to dose. No sex-related differences in kinetics.
NPK-21	PK	Monkey	Single Dose	IV, Oral	1, 10 mg/kg	Rapid absorption, C _{max} and AUC linearly proportional to dose. No sex-related differences in kinetics.
NPK-22	Monitoring	Monkey	14 Day	Oral	50, 100, 200 mg/kg/day	No consistent pattern to data.
NPK-23	Monitoring	Monkey	28 Day	Oral	17, 50, 150 mg/kg/day	Concentrations linearly proportional to dose. Excretion mainly via bile.
NPK-24	Monitoring	Monkey	52 Week	Oral	5, 15, 45 mg/kg/day	Concentrations linearly proportional to dose. No sex-related differences in kinetics.
NPK-25 25	Assay Development	-	-	-	-	GLC assay in plasma, detection range 6-32 mcg/ml.

CETIRIZINE NDA

ATTACHMENT A. ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION (ADME) STUDY SUMMARY

NDA Report No.	Type of Study	Species	Duration	Route of Administration	Dose Levels	Principal Findings
NIK-26	Assay Development	-	-	-	-	GLC assay in urine, detection range 10 to 300 mcg/ml.
NIK-27	Assay Development	-	-	-	-	HPLC assay in urine, detection range 5 to 75 mcg/ml.
NIK-28	Stability	Human	Greater than or equal to 1 year	-	2, 10, 20, 400, 800 ng/ml	Plasma and urine samples spiked with cetirizine stable for at least 1 year.

I. PHARMACOLOGY:

Primary activity: as an antihistamine or H1 receptor antagonist.

(A) In vivo studies: (Note: the ED₅₀ values on pages 2 38-2 39 are different from those listed under individual studies, e.g. NP-2, NP-4, NP-8, NP-10 on pages 5 31-5 139. - The following summary is based on the results from individual studies. The applicant is to be requested to clarify the discrepancies)

Test/animal model	ED ₅₀ mg/kg	Dose mg/kg	Duration/remarks
(1) Lethality by (a) histamine guinea pig	0.35 (po)	0.1 (po)	protection: 100%-12 hrs 80%-24 hrs
		2.5 (iv)	800X LD50 hist
		2.5 (po-1hr)	400X LD50
		hydroxyzine:2.5 (iv)	800X LD50
(b) Compound 48/80: rat		1.4 (po)	80% protection
		hydroxyzine:44 (po)	40% "
(2) Bronchoconstriction by (a) Passive-immun. guinea pig	0.3(po)		
	0.3(po):hydroxyzine		
	0.8(po):terfenadine & clemastine		
	0.02(po):mepyramine		
rat	4.6(iv)		
	9.2(iv):mepyramine		
	1.4(iv):hydroxyzine		
	NE:clemastine		
guinea pig			some protection at cetirizine:4.6 mg/kg(po) mepyramine:46 mg/kg (po) clemastine:46 mg/kg (po)
(b) guinea pig histamine	0.09 mg/kg(iv)		iv: clemastine & mepyra- mine better than cetir.
	0.46 mg/kg(po)		po: 3 drugs comparable

(continued)

(continued)

Test/model	ED50	Dose	Remarks
serotonin Ach	3.4 mg/kg(iv) greater than 46 mg/kg (iv)		
(3) Cutaneous Rnx by (a) histamine mice	0.046 (po) 0.76 (po): hydroxyzine		
rat	1.9 (po) 0.49(iv)		po & iv: cetirz. duration 6 hrs & better than clemastine & mepyramine.
guinea pig	0.8 (iv) 1.8 (po)		better than terfenadine, mepyramine, hydroxyzine; less than clemastine. cetirz best of the five.
dog		1 (po)	75% inh. 2-24 hrs, better than terfenadine, astemizole, clemastine. = hydroxyzine.
monkey(Rhesus)		10 (po)	76% inh. @ 2 hrs.
(b) Ascaris dog		1 (po) 0.15 (iv)	same as antihistamine 50% inh. 4-24 hrs.
(c) 48/80, VIP Substance P monkey		10 (po)	60-80% inh. @ 2 hrs
(4) Hypotension by histamine dog		0.12-1.19(iv)	reversed
serotonin dog		0.12-1.19(iv)	NE

(B) In vitro studies: (Vol 2.4)

Species	Tissue	Results (EC ₅₀ umol/l)
(1) Guinea pig	ileum	
(2) Guinea pig	Trachea	<u>histamine:</u> cetirz: 2 (or 9 ug/ml) hydroxz: 3 clemast: 10 mepyram: 0.05 <u>carbachol:</u> cetirz: 320-1000
(3) Human	bronchi	0.9 (or 0.4 ug/ml)
(4) Guinea pig	atrium	NE (100 ug/ml) (H ₂ receptor act.)
(5) Human	basophils	470 (or 217 ug/ml) (inhibition of histm-release)

Neuropharmacology:
Behavior studies:

Species	Test	Results
Mouse	Irwin (general behaviors)	46 mg/kg (ip): NE
		~~92 mg/kg (ip): sedation~~
		138 mg/kg (ip): lethal
		462 mg/kg (po): stimulation
		1384 mg/kg (po): lethal
Rat	Irwin	46 mg/kg (ip): NE
		92 mg/kg (ip): dec act. & mus tone lethal
		138 mg/kg (po): NE
		462 mg/kg (po): LD50
		hydroxyzine: 90 mg/kg (ip): convulsion
Rat	exploratory act in new environment	4.6 mg/kg (ip): NE 15 mg/kg (ip): <u>hypoactivity</u> 15-46 mg/kg (po): NE
Rat	retention of learning in passive avoidance test	15 mg/kg (po): NE
Dog	conditioning response	45 mg/kg: NE on selective atten. percept-motor coordination

Other neuropharmacological effects:

Activity	Species	Drug-Ind	Effects	Dose(mg/kg) Effects
(1) Anticonvulsant (NP-33)	mice	pentylene-tetrazol	seizure	15-46(ip) NE
(NP-34)	mice	audiogenic	seizure	46 (ip) NE 45-46 (ip):hydroxy- zine & clemastine protected.
(2) Neuroleptic (NP-35)	mice	apomorphine	climbing	15-46(ip) inhibit
(NP-37)	rats	amphetamine	stereotype	46 (ip) NE
(3) Interactions pentob (NP-32)	mice	pentobarbital	right-reflex	46(po,ip) potent.
alcohol(NP-38)	rats	alcohol	open field	15 (po) NE
(4) Ataxia (NP-36)	rats		Rotat-rod	45(ip) NE
(5) EEG (NP-39)	rabbits		duration-arousal recording	1.5-46(iv) dec.
			duration-sleep recording	1.5-46(iv) inc.
			arousal rxn to sound	1.5-46(iv) NE

Cardiovascular effects
In vivo studies:

Species		Dose (mg/kg)	HR	BP	Others
Rat	anesthetized	14.8 (iv) 26 (iv) 46 (iv)	NE NE lethal	NE -25%	
Dog	anesthetized (chloralose)	4.6 (iv) 14.8 (id) 46.1 (id) 67.7 (iv)cumul: 675 (id)cumul:	inc inc inc lethal lethal	inc. slig. dec	ECG/resp dep
Dog	conscious	1.2 (iv) 3.8 (iv) 11.9 (iv)	minor inc slig	minor +10% (dias) +10% (dias)	
Dog	anesthetized	11.9 (iv) 11.9 (iv)	NE on Ach- or Vagus-stim hypotension. NE on norepinephrine-hyperten. inh on carotid occlu-hypertens. NE on isoproterenol-hypotens & tachycardia.		
Dog	anesthetized	3.2 (iv)	NE on permanent-coronary-ligation induced arrhythmia.		

In vitro studies

Species	tissue/model	Drug-induced	Effects
Rat	aorta-contraction	norepinephrine KCl	150 mg/l : NE phentolamine: inh. 46 mg/l: NE
Guinea pig	right atrium left atrium	spontaneous electric-stim.	46 mg/l: NE on freq. 46 mg/l: NE on contractil.
Rat	working heart	none	46 mg/l: cardiotoxic on all parameters. 0.46 mg/ml: NE

Other effects:

Activity	Species	Drug-induced Effects	Dose(mg/kg)	Effects
(1) Anticholinergic (NP-30)	mice	light-pupillary diameter	138(po) 46(ip)	NE NE
(NP-31)	mice	oxotremorine-salivation -tremor	46(ip) 46(ip)	NE NE
(2) Anesthetic (NP-42)	guinea pig	corneal reflex	14.6 g/l	NE
(3) Analgesic (NP-40)	mice	acetic acid-writhing	ED ₅₀ =84(po)	
(NP-41)	rats	tail-flick latency	92(sc) 138(sc)	NE inhib.
		hydroxyzine	45(sc)	inhib.
(4) Antiinflam- matory(NP-55)	rats	carrageenan-edema	46(iv)	NE
		indomethacin	1.2(iv)	inhib.
(5) Delayed hyper- sensitivity(NP-54)	mice	sheep red cell-local inflamm.	3.2(sc)	NE
		dexamethasone	3.3(sc)	inhib.
(6) Immediate anaphylactic (NP-19)	human	basophil-anti IgE histamine rel.	EC ₅₀ 0.47mm/l	
		theophylline	EC ₅₀ 0.085mm/l	
(7) Ulcer (NP-56)	rats	stress(immob & immers.)	50(po)	NE

II. TOXICOLOGY

Acute Toxicity Studies (mouse, rat, dog):
Summary table: Page 24.

Subacute/Subchronic/Chronic Toxicity Studies:

Summary tables
Mouse: page 25.
Rat: page 26-27.
Dog: page 28.
Monkey: page 29.

Individual studies:

Mouse (1)-(3): pages 30 to 37
Rat (1)-(5): pages 38 to 50
Dog (1)-(3): pages 51 to 56
Monkey (1)-(3): pages 57 to 61

Carcinogenicity studies:

Mouse: page 62 to 63
Rat: page 64 to 68

II. Toxicology:

Acute Toxicity studies: performed by (1)

Rodents performed Feb-July, 1961; Dogs in Feb. 1961 & March, 1963.
Observations for 14 days.

Route	Mice B6C1, var. breed 7 wks. 22-23g		Rats Wistar 7 wks. 112-121 gm		Dog Beagle 20-5+ months 6.5-14.2 kg	
	p.o.	i.v.	p.o.	i.v.	p.o.	i.v.
No./dosage	20 (10 M + 10 F)		20 (10 M + 10 F)		2 (1 m)	2 (1M-1F)
Dosage ranges (mg/kg)	100, 237, 562 & 1333	240, 270, 320 & 370	237-3162	42-120	40, 50, 160 & 320*	70 & 125* *in 2 div doses because of vomiting. Did not prev vom.
Observations	See below					
No death at (mg/kg)	237 (M) 100 (F)	240 (M) 240 (F)	237 (M) 237 (F)	none (M) 42 (F)	320 (M+F)	70
Death from (mg/kg)	562 (M) 237 (F)	320 (M) 270 (F)	562 (M) 562 (F)	42 (M) 56 (F)	none	125
LD_{50} (mg/kg) (97% conf.)	M: 600 (375-1391) F: 752 (432-5114)	336 (301-476) 301 (261-366)	M: 703 (305-1173), 66 (58-96) F: 965 (553-1353), 70 (61-82)	ND		

Signs: Calm, cyanosis-all mice in 1 hr. Dyspnea & death. Survivors recovered in 24 hrs. Female mice lost 25% wt. at 240 mg/kg.

inc. motor act. unsteady gait-all mice immediately. Convulsions death. Female mice lost 25% wt. at 240 mg/kg.

same as i.v. death following cardiac arrest.

No effect at 40 mg/kg po. (no heart rate-80 mg/kg p.o. nervousness-160. Food and weight-all normal.

i.v.:
Nervousness, calm unsteady gait, salivation or tremor at 70 mg/kg. No ECG changes. Recovered in 24hrs

Death at 125 mg/kg nervousness, muscle hypertonicity, lost sr.me, fall on side head backwards, strong extension of its legs and died.

Necropsy: unremarkable in all animals.

15-Day (T-2)

4-week (T-3)

4-week (T-4)

Species strain age/wc.	OFI SPF	Mouse CR CD-1	CR CD-1
by:	D.C. Br / Life Sci [†]	Huntingdon	Huntingdon
M + 5785	(a) 12 (6M + 6F) (b) 12 (6M + 6F)	32 (16M + 16F) : main 20 (10M + 10F) : urine	24 (12M + 12F) : ma 24 (12M + 12F) : 4-w 24 (12M + 12F) : 13-w
Route	(a) gavage, daily - 15d (b) diet (feeding)	P.O. (diet) daily - 4 wk	P.O. (diet) daily -
Drug in	(a) in water (b) in diet	diet	diet
Dosage levels (mg/kg/day)	0, 5, 10, 20, 40, 80, 160	0, 1, 3, 9, 27, 81	0, 40, 160 Dosing: 12/16/85 - 1/2/86 Recovery: 1/19/86 - 4/15/86
Death at Cause Signs Necropsy	40 gavage (1M) not drug-related	0 (1F), 9 (2M), 27 (1M) Total 4 from urine group, not drug-related.	0 (1M), 40 (1M +) Total 3, not drug-r
Body wt. Food consumption	Gavage: dec. wt & food 20 - 160 (M) + 160 (M) feed: food inc 80 - 160 (M + F)	NE	NE except HD-M during 13-week recovery
Signs	None	Hair loss / scab / ulceration of skin: M	None
Blood analysis	ND	Hgb: inc F (9-81) SGPT/OCT: inc. M (27-81) Triglycerides: dec M (81); inc. F (27-81)	SGPT/OCT: 160 (M +) Cholesterol: dec ⁴⁰ 160 (M); Total lipids: 160 (M + F) 40 (M)
Urinalysis	ND (16)	positive ketone: most samples.	Triglyceride: inc. 160 (M) 40 (F)
Organ wt.	Liver (absol/rel.): inc 40 (M: gavage) 80 (M: feeding) 160 (F: both routes)	Liver: inc M (81)	Liver (absol/rel.): inc. 4 160 (M + F)
Relative "no-effect" dose	5 (gavage + diet)	1 (M) 9 (F)	Not est. (M) 40 (F)
Approx. "effect" dose	10 (gavage + diet)	3 (M): liver 27 (F): Hgb/trigly	40 (M): liver 160 (F): liver
Target organs Pathology	Liver cells: hypertrophy	Liver cell hypertrophy	
Gross-	G: unremarkable	G: enlarged liver M (81)	G: enlarged liver 160 (M +) 40 (M)
* Micro-		Micro: (1): M (3-81) (2): M (9-81)	Micro: (1) 160 & 40 (M + F) (2) fat: 160 & 40 (M).
(1) Peri-acinar hepatocyte	10-160 (M + F) Hypertrophy: both routes		
(2) Portal triad vasculature	some		

(B) Rat Studies:

SUMMARY OF SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY STUDIES: rats (Vol 2.10-2.16)

Duration 15-Day(T-6) 1-month(T-7) 4-week(T-9) 4-Week(T-10) 6-month(T-13)

Performed by

2/10-2/25/83 5/18-6/18/81 11/8-/12/8/83 2/22-9/2/82
3-mo interim sac.

T-10: 11/11-12/8/85
Recov.12/7/85-3/11/86
Recov sac. @ Wk 4 & 13

	12(6M+ 6F)	20(10M + 10F)	20(10M + 10F)main 12(6M + 6F)satellite	t:40(20M + 20F) i:10(5M + 5F)
(M+F)/group			total: 32(16M + 16F)	50(25M + 25F)

t(terminal)
i(interim)@3-mo
Satellite:drug monitoring

T-10:
t: 20(10M + 10F)
Wk 4 : 20(10M + 10F)
WK 13: 20(10M + 10F)
total: 60(30M + 30F)

	(a)gavage (b)diet	gavage	diet	diet	gavage
Daily for	15 days	1 month	4 weeks	4 weeks	6 months

Drug in water for gavage and in diet for feeding studies.

Doses:					
mg/kg/day	0,5,10,20, 40,80,160	0,25,75,225.	0,2,6,18, 54,160	0,40,160.	0,8,25,75

Deaths	20(1F) intub.err.	total:6 225(3M+2F) 75 (1M) poor condition, distended GI	2(1F)	total:34(22M +12F) intubation error: C(3)+L(3)+M(10)+H(10) accident: M(1) unknown: L(2)+M(2)+H(3)

T-10: total 3
160(1F), 40(1M)
C(1F)

Wt./food	NE	Both reduced in M only. wt. Food	Wt.160(M) Food 160(F)	Wt.160(M)	NE
		-7% -9%			
		-13% -9%			
		-22% -22%			

Signs	None	Noisy resp.(225) Day 1 only.	None	None	Quiet/nervous (75)

Duration	15-Day(T-6)	1-month(T-7)	4-week(T-9)	4-Week(T-10)	6-month(T-13)
Blood	ND	T-7: dec Hgb/Hct/RBC:225 (M) inc SGPT/AP/GLO/BUN: 225 (M + F) inc chols: 225-(M)			T-13: dec Hct/RBC:75(M+F) inc SGPT/SGOT/SDH:25-75 dec trigl: 25-75
		T-9: inc Hgb/Hct/RBC:160(M) inc WBC/lymph:54-160(M)		T-10: inc total lipid/trigly:40-160(M) inc Cholesterol:225(M)	
Organ wt.	T-6	T-7	T-9	T-10	T-13
Inc. liver	40-160	75-225(M+F)	54-160(M)	160 (M+F)	3-mo:25-75(M+F) 6-mo:75(M+F)
			Inc spleen:54-160(M)		Inc kidney:25-75(M+F) Inc adren/thyro:75(M)
Pathology					
Gross					
Enlarged liver	20(F) 40(M)	no	160(M+F)	no	no
Enlarged spleen	no	no	6-160(M)	no	no
Cellularity/spleen (inc.)			18-160(M)		
Histopathology					
Liver:					
hepatocytic hypertrophy	PA:40(M+F)		CL:54-160(M+F)	CL:160(M+F)	PA:8-75(M) 75(F)
		T-7: CL/ML:75-225(M+F)			
vacuolation	20(M+F)	225(M)	54-160(M+F)	40(M)	25-75(M) 75(F)
fat deposition	20	75-225(M)	54-160(M+F)	40(M)	25-75(M) 75(F)
necrosis		225(M)			
"no-effect"dose (mg/kg/day)	5 (M+F)	25 (M+F)	18 (M+F)	not est.(M) 40(F)	not est.(M) 8(F)
"Affect dose" (mg/kg/day)	10(spots/liver) 20(steatosis)	75	54	40(M) 160(F)	8(M) 25(F)
Target organ*	liver	liver	liver/spleen	liver	liver

see Recovery studies: reversible.
CL: centrilobular. ML: midzonal. PA: periacinar.

(L) Dog studies

Chronic

NDA 19-835
Page 28

SUMMARY OF SUBACUTE/SUBCHRONIC TOXICITY STUDIES: Dogs (by #)

one-month (T-14) 6-month (T-15) 1-yr (T-18)

Species	Dog		
Strain	Beagle		
Weight	12-15 months	7-9 months	9.2-10.6 kg, 10-15
M + F/♂	6 (3M + 3F)	10 (5M + 5F)	10 (5M + 5F)
Route	Apr. 14 - May 14 1981 P.O. (capsule)	Jan. 13 - July 13 1982 P.O. (capsule)	June 28 1984 - June 28 1985 P.O. (capsule)
Duration	daily - one month	daily - 6 months interim report at 3-months	daily for 52 weeks
Drug in	gelatin capsule	4 (2M + 2F) gelatin capsule	gelatin capsule
Dosage level (mg/kg/day)	0, 15, 45, 135	0, 8, 25, 75	0, 4, 15, 60
Death	None	2M (75) on Days 87 & 182	None
Dose Cause		Respiratory difficulty & Tracheitis	
Signs	Vomiting: 15-135 Salivation/tremor/ataxia red food: 135 Body wt./Food: 135	Vomiting: 8-75 Behavior: jittery at 75 Body wt: dec. F (25-75) Food: dec. F (25-75)	Vomiting: 15-60 Body wt: dec. 15-60 ECG/BP: 60
Blood analysis	AP: inc. at 135	Cholesterol/triglycerides: dec. at 75 RBC/Al: inc. at 75	Inc. RBC, Hgb, APTT: 15-6
Relative "no-effect" dosage	45 (except 100)	8	4
Approx. "effect" dosage	135 (signs/wt.)	25-75 (signs/wt. dosage)	15 (vomiting, wt. in 2 wks)
Pathology/Target organs	Unremarkable Kidney & adrenal: wt. inc. at 135 ECG: Unremarkable	Unremarkable ECG: Unremarkable Urinalysis: dec sp. gr.	Unremarkable Hepatic enzymes: no effects

D) Monkey studies

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Chronic

SUMMARY OF SUBACUTE/SUBCHRONIC/TOXICITY STUDIES: ^{by} Monkeys of Huntington

	14-Day (T-16)	4-week Monkey (T-17)	one-year (T-19)
Species		Monkey	
Strain	Cynomolgus		
Weight			2-3 kg, 2-4 gm
N + F/G	2 (1M + 1F)	6 (3M + 3F)	10 (5M + 5F)
Route	M. 6 1954 - Apr. 3 1954 P.O. (gavage)	Mar. 7 1954 P.O. (gavage)	Oct 4 1954 - Oct 10 1955 P.O. (gavage)
Duration	daily - 14 days	daily - 4 weeks	daily - 50 weeks
Drug	~~50-200~~ in water (5%)	in water (5%)	in water or sola (5%)
Dosage level (mg/kg/day)	50, 100, 200	0, 17, 50, 150	0, 5, 15, 45
Death	None	one F (150) sacrificed on Day 22.	None
Dose			
Cause			
Signs	Salivation/vomiting: 50-200 Quiet behavior/piloerection/ tremor/loose muscles face: 200	Vomiting/huddled posture/ poor coat/tremor/hypothermia: 50-150	Salivation: at 45 Body wt./food: NE
Blood analysis	Body wt.: losses 50-200 Food: dec. at 200 Dec. RBC: 50-200	Body wt.: losses 50-150 Food: only the sacrifice Inc. Triglycerides @ 150	Unremarkable
Relative "no-effect" dosage	not established	17	15 ~~45~~ (salivation only)
Approx. "effect" dosage	50 (signs + wt.)	50 (wt./signs)	45 (salivation only)
Pathology/Target organs	Liver: fat deposition at 200 Lung: congestion at 200	Unremarkable microscopic changes: no sig. effect.	None

(A) Mouse Studies: (1)-(3)

(1) Subacute toxicity study: Range finding oral toxicity in mice (15 days). (T-2)

Performed by

Animals: OF1 SPF mice, 6 weeks old, 23-25 gm.

No. of animals/dosage: 12 (6M + 6F)/dosage:gavage
12 (6M + 6F)/dosage:feeding.

Route and duration of administration:

(1) Gavage: compound in dist. water, orally 7 days/week for 15 days

(2) Feeding: compound in dietary mixture, orally 7 days/week for 15 days

Dosage levels: mg/kg/day

(1) Control:	0
(2)	5
(3)	10
(4)	20
(5)	40
(6)	80
(7)	160

Results:

Mortality: one male of 40 mg/kg (gavage) died after 5 doses. Cause of death: aggression between mice, according to sponsor.

Clinical signs: no signs.

Body weight and food consumption:

Gavage: Slight decreases of weight gains in 20, 40 and 160 mg/kg males and 160 mg/kg females. Food consumption showed decreases in some treated groups.

Feeding: no effect on weight gains; food consumption showed increases in 80 and 160 mg/kg. Food consumption was higher in feeding group than gavage group resulting in higher dose levels in feeding group.

Organ weight:

Liver: increased absolute and relative weights in males (at 40, 80 and 160 mg/kg gavage), in females (at 160 mg/kg gavage and feeding) and in males (at 80 and 160 mg/kg feeding).

Pathology

Gross pathology: unremarkable

Histopathology:

Liver: periportal hepatocytic hypertrophy from 10-20 mg/kg. The "no-effect" levels were 5 mg/kg (males and females gavage), 6.3 mg/kg* (males feeding) and 9.7 mg/kg* (females, feeding).
*determined by food consumption.

(2) Toxicity to Mice by Continuous Dietary Administration for 4 weeks (T-3)

Performed by:

Animals:

Charles River CD-1 mice of Swiss origin
Manston, Kent, U.K.

No. of animals/dosage: 32 (16M + 16F)
Main study: 20 (10M + 10F)
Satellite study: 12 (6M + 6F), for urinary excretion and liver drug-metabolizing enzymes studies.

Route and duration of administration:
Orally through dietary mixture daily for 4 weeks.

Dosage levels: mg/kg/day

- (1) Control: control diet
- (2) 1
- (3) 3
- (4) 9
- (5) 27
- (6) 81
- (7) Health check 10(5M + 5F): no pathological finding or signs at the beginning of study.

Results:

Mortality: Total 4, all from satellite study.

Two M of 9 mg/kg and 1 F of control groups died during week 1. These deaths: not considered drug-related. One M of 27 mg/kg found dead in week 2 showed ulceration and swelling of perigenital region, and dark staining of contents of small intestines.

Clinical signs: hair loss/cutaneous scab formation and ulceration occurred incidentally in male mice.

Body weight and food consumption:

Body weight gain: slightly lower at 81 mg/kg (3-4% lower than control)

Food consumption: no significant effect; only high-F showed 5% less food consumption than control group mostly during Week 4.

Blood analysis:

Hematology:

Hgb: inc. in F of 9, 27 and 81 mg/kg groups. F of 27 mg/kg also had increases of Hct, RBC and WBC.

Chemistry:

(1) SGOT, SGPT* and OCT*(ornithine carbamoyltransferase) inc. in M mice of 81 mg/kg; inc. SGPT* in M mice of 27 mg/kg.

(2) Triglycerides: inc. in F mice of 27 and 81 mg/kg groups; dec. in M mice of 81 mg/kg group.

(3) BUN* and glucose: inc. in M mice of 81 mg/kg group.

*statistically significant.

Urinalysis:

Many mice failed to produce urine (or enough urine) during collection period. No adverse effects apparent, though positive ketones were found in most samples.

Ophthalmology: examined at Week 4. No adverse effect noted.

Organ weight: absolute wt.

Liver: significant inc. in M mice of 81 mg/kg; other dosed M groups showed some inc. over control without dose-related effect.

Pathology:

Gross pathology:

Liver: enlargement in 4/16M of 81 mg/kg

Histopathology:

Liver: (1) Minimal to moderate centrilobular hepatocyte enlargement in M mice of 3, 9, 27 and 81 mg/kg groups (dose-related effect). Some dosed male mice showed minimal centrilobular vacuolation, but no dose-related effect was observed.

(2) Minimal to moderate lipid deposition: M mice of 9, 27 and 81 mg/kg groups showed dose-related effect; F mice of all groups including control showed randomized incidence (graded as minimal) without apparent dose-related effects.

Assay of drug-metabolizing enzymes: See T-22 study.

- (1) Increased cytochrome P450 and aniline hydroxylase: both M and F of 81 mg/kg.
- (2) Increased ethylmorphine N-demethylase: in M mice of 27 and 81 mg/kg, and in F mice of 9, 27 and 81 mg/kg groups.
- (3) Increased p-nitroanisole O-demethylase: in M mice of 27 and 81 mg/kg (not statistically significant though).

Urinary Excretion of UCB P071: on Day 2, 9 and 28 during 7-hr period.

- (1) Urinary excretion of unchanged drug: not detected in M mice of 27 mg/kg or F mice of 9 mg/kg.
- (2) Urinary excretion increased with times only in F mice of 27 mg/kg group; at 81 mg/kg levels, urinary excretions were similar in M and F mice and did not increase with time.
- (3) The urinary excretion generally accounted for less than 5% of doses at all time points in both M and F mice.

Subacute/Subchronic Toxicity Studies:

(3) A study to determine the reversibility of hepatic changes in mice (T-4)

Performed by:

Treatment: 12/16/85-1/12/86

Withdrawal: 1/13/86-4/15/86 for 4 and 13 weeks

Animals:

Charles River CD-1 mice. 5-6 weeks old

No./of animals/dosage: 72 (36M + 36F)/dosage

24 (12M + 12F): Main study

24 (12M + 12F): 4-week recovery period.

24 (12M + 12F): 13-week recovery period.

Route and mode of administration:

orally through dietary mix for 4 weeks.

Duration of treatment:

four weeks, followed by recovery periods of 4 weeks and 13 weeks.

Dosage groups: (mg/kg/day)

(1) Control: 0

(2) Low dosage group: 40

(3) High dosage group: 160

Results:

Signs: None attributable to treatment

Mortality: total 3 deaths (1 control M, 1 low M and 1 low F), not drug-related.

Body weight: no effect during the dosing period; slight reduction in wt. gain during recovery periods in high-dose males only.

Food consumption: no effect during the dosing period; slight reduction during recovery periods in low-dose males and high-dose females.

Achieved intake of test material: within target ranges.

Liver studies:

Parameters	Low		High	
	Treatment	Withdrawal 4-wk 13-wk	Treatment	Withdrawal 4-wk 13-wk
<u>Chemistry:</u>				
Inc. SGPT & OCT			M & F	recovered (4 wk)
Inc. SGOT			F	recovered (4 wk)
Inc. trig & cholest.	M	recovered (4 wk)	M	recovered (4 wk)
<u>Lipid analysis:</u>				
Inc total lipid & triglycerides	M		M & F	
Inc. Cholest.			F	recovered (4 wk)
<u>Enzyme assay:</u>				
microm protein	M		M & F	recovered (4 wk)
Cyto P-450	M		M & F	recovered (4 wk)
ani. hydro	M & F		M & F	recovered (4 wk)
<u>Organ wt</u>				
Inc. slig. in all mice, recovered at 13-wk excp high M				
<u>Gross pathology:</u>				
Enlarged	M		M & F	recv. (13-wk)
<u>Histopathology</u>				
Enlarged centri lob. hepatocytes + fat deposition	M & F		M & F	recv. (13-wk)
	M		M	recv. (13-wk)

Note: T-4 Study

- (1) Enzyme induction was observed in both 4-week studies. The induction was reversible following 4-week recovery period.
- (2) Increased SGPT/SGOT/OCT* and inc. cholesterol, total lipids and triglycerides were reversible following 4-week recovery period.
- (3) Gross and histopathological changes (hypertrophy and fat deposition) of liver were reversible only after 13-week recovery period.

*ornithine carbamoyltransferase

A study to determine the reversibility of hepatic changes in mice electron microscopy of liver (T-5)

Extension of Study T-4 , only mice from control and high groups sacrificed at end of 4-week treatment and 4-week of withdrawal were examined.

Summary of results was copied as follows:

After 4 weeks of treatment period

Increased amount of smooth endoplasmic reticulum was seen in hepatocytes in mice from groups receiving 160 or 40 mg/kg/day;

occasional concentric membranous bodies were seen in hepatocytes from 1 male and 1 female mouse from the group treated with 160 mg/kg/day;

a higher incidence of mice with minimally increased microbodies in hepatocytes were seen in males treated with 160 mg/kg/day;

increased lipid in hepatocytes in mice treated with 160 or 40 mg/kg/day.

After 4 weeks of treatment followed by 4 weeks withdrawal period

Marginally higher incidence of mice with minimal increase in amount of smooth endoplasmic reticulum in hepatocytes confined to females from high dose group;

other changes seen at termination revealed recovery.

(B) Rat Studies: (1)-(5)

(1) Subacute toxicity study: Range finding oral toxicity in rats (15 days), (T-6).

Performed by: ; males: Feb. 19, 1983; females: Feb. 10, 1983

Animals: Sprague-Dawley SPF rats, 5-6 weeks old, 138-147 gm

No. of animals/dosage: 12 (6M + 6F)/dosage: gavage or feeding each.

Route and duration of administration: *Orally 7 days/week for 15 days

*(1) gavage: compound in dist. water

(2) feeding: compound in dietary mixture

Dosage levels: mg/kg/day

(1) Control:	0
(2)	5
(3)	10
(4)	20
(5)	40
(6)	80
(7)	160

Results:

Mortality: one female (20 mg/kg) died on day 12. Autopsy revealed bloody liquid in the trachea and in thoracic cavity. The cause of death was probably tracheal intubation.

Clinical signs: No signs observed.

Body weight and food consumption:

Body weight: no effects.

Food consumption: no effects.

Organ weight:

Liver: dose-related increases of absolute and relative weights from 40-160 mg/kg. Male rats of both gavage and feeding were affected more than female rats.

Pathology:

Gross pathology:

Swollen liver: 1 female (gavage: 20 mg/kg) and in males (gavage: 20 mg/kg; feeding: 40mg/kg). White or yellow spots or nodules on the livers were observed in some of the dosed females (gavage and feeding; 10 mg/kg) and in males (only gavage: 40 mg/kg).

Histopathology:

Treatment related lesions occurred in liver. Periacinar hepatocytic hypertrophy: more frequent and severe in male rats. Gavage and feeding: from 40 mg/kg. Periacinar hepatocytic large vacuolation (steatosis): more frequent in female rats. Gavage: control, low to high female. feeding: from 20 mg/kg.

(2) Subacute toxicology studies: One month oral (gavage) toxicity study in rats. (I-7)

Performed by _____, May 18, 1981-June 18, 1981. (GLP: not totally in compliance).

Animals: Sprague-Dawley SPF rats, 127-131 gm, 7 weeks old.

No. of animals/dosage: 20 (10 M and 10 F)/dosage.

Route and duration of administration: orally by gavage, 7 days/week for 1 month.

Dosage: drug in dist. water

- (1) Control: vehicle
- (2) Low dosage: 25 mg/kg/day
- (3) Mid dosage: 75 mg/kg/day
- (4) High dosage: 225 mg/kg/day

Mortality: total 6: 1 M (mid dose); due to intubation accident on Day 29.

3 M and 2 F (high dose): on day 11-16. All lost weight. Some had blood on the muzzle, respiratory difficulty and flatulence before death. Autopsy revealed flatulence in 2 M and distended stomach/intestines with yellowish liquid in 1 F.

Clinical signs: Noisy respiration was noted in high-dose group on Day 1. After 2 weeks no differences among 4 groups.

Body weight and food consumption:

No significant effects were observed in F. For male rats, the changes were as follows:

	BW	FC
L:	-7%	-9%
M:	-13%	-9%
H:	-22%	-22%

Blood analysis:

Hematology: F: no significant changes. In high-M rats, slight decreases of RBC, Hct, Hgb and MCV (5-10%) increases of MCHC (6%) and platelets (17%).

Chemistry:
(in the high dose group)

inc. ALAT (SGPT): 47-52%
AP: 20-30%
globulins (alpha and beta): 16-32%
albumin/globulin ratio: 10-14%
BUN: 15%

Urinalysis: in high-M, increased epithelial cells and decreased phosphates in the centrifuged deposit.

Ophthalmology: not performed.

Drug monitoring: urinary unchanged drug higher in F than M (mostly in free form). After 1 month no accumulation of unchanged drug or induction of metabolism was apparent.

Organ weight:

Liver: dose related increases of absolute and relative weights in the M and H groups.

Pathology:

Gross pathology: no significant findings.

Histopathology: in the mid (3M) and the high dose (10M) male rats, increased fat desposition and hepatocyte necrosis in the centrilobular and midlobular areas (degenerative and necrotic lesions of the liver parenchyma in the midzonal and central areas of the lobules).

Histopathological review of livers from preliminary study of P071 toxicity to rats in repeated oral administration for one month (T-8).

The study (T-7) was performed by the sponsor, the liver slides were reviewed again by The results were as follows:

P071 one-month rat gavage study
Re-evaluation of H & E stained and DKO stained sections of liver:
Summary of treatment-related changes

	25		75		225	
	mg/kg/day		mg/kg/day		mg/kg/day	
	d	7	d	7	d	7
<u>H & E stained liver sections</u>						
Hypertrophy						
Centrilobular						
Slight	0	0	4	2	0	0
Minimal	0	0	1	1	0	0
Moderate	0	0	0	0	1	2
Centrilobular/Midzonal						
Minimal	0	0	0	0	1	1
Moderate	0	0	0	0	0	0
Vacuolation						
Centrilobular						
Minimal	0	0	0	0	0	0
Moderate	0	0	0	0	0	1
Midzonal						
Minimal	0	0	1	0	0	0
Moderate	0	0	0	0	1	0
Centrilobular necrosis (one lobe)						
	0	0	0	0	1	0
<u>DKO stained liver sections</u>						
Midzonal						
Trace	0	0	1	0	1	0
Minimal	0	0	0	0	4	0
Moderate	0	0	0	0	0	0
Midzonal (trace)/Periportal (minimal)						
	0	0	1	0	0	1
Centrilobular (minimal)/Midzonal (moderate)						
	0	0	0	0	1	0
Periportal (minimal)/Midzonal (moderate)						
	0	0	0	0	1	0

(3) Toxicity to Rats by Continuous Dietary Administration for 4 weeks (T-~~12~~⁹).

Performed by:

Main Study: 11/8/83 - 12/6-8/83; Satellite study: 11/8/83-12/6-21/83.

Animals: Charles River CD rats of Sprague-Dawley strain (Portage, MI, U.S.A.)

No. of animals/dosage: 30 (15 M+ 15 F); 20(10M+ 10F) for main study and 10(5M+5F) for satellite study. (Urine and drug metabolizing enzymes)

Route and duration of administration: orally through dietary mixture for 4 weeks.

Dosage levels:

- (1) Control diet
- (2) 2 mg/kg/day
- (3) 6 mg/kg/day
- (4) 18 mg/kg/day
- (5) 54 mg/kg/day
- (6) 160 mg/kg/day

Results:

Mortality:

One F from satellite group of 2 mg/kg died during week 3 of acute cystitis with necrosis of urinary bladder and epithelial hyperplasia of urethra.

Clinical signs:

No signs of ill health, behavioral changes or reaction to treatment was noted.

Body weight and food consumption:

Body weight gains: lower for 160-M and F only
Food: lower for 160-M and F only

Blood analysis:
Hematology:

160-M: increased erythrocytic parameters (Hct, Hgb, RBC and MCHC); Inc. WBC, neutrophils and lymphocytes.

160-F: Inc. neutrophils and monocytes.

Chemistry: Statistical changes were still within normal ranges.

Na+: slight dec. in dosed M and F.

Glucose: slight inc. at 54- and 160-F.

Urinalysis: Not performed.

Organ weight: (Absolute weight) statistically significant changes were observed in only, inc. liver and spleen (54 and 160), thyroid (160), gonad (18, 54 and 160). Dec. adrenal (160)

Pathology:

Gross pathology:

- (1) Liver: enlargement in 4/16M and 1/16F of 160 mg/kg group.
- (2) Spleen: enlargement in 2/16 M of 6 mg/kg, 2/16 M of 18 mg/kg and 1/16 M of 160 mg/kg.
- (3) Stomach: Nodules in antrum randomly (1-5 rats) in each group, no dose-or drug-related frequencies noted.

Histopathology:

- (1) Liver: Centrilobular hepatocyte enlargement and mid-zonal/centrilobular fat deposition at 54 and 160 mg/kg levels.
- (2) Spleen: Minimally increased cellularity of red pulp in 1 1/16 M of 160 mg/kg, 4/16 M of 54 mg/kg and 1/16 M, of 18 mg/kg groups.

Assay of Drug Metabolizing Enzymes

The levels of hepatic cytochrome P₄₅₀ and drug metabolizing enzymes (aniline hydroxylase, ethyl morphine-N-demethylase and p-nitroanisole-o-demethylase) were assayed in the microsomal fraction hepatocytes following 4 weeks of treatment.

- (1) The relative "no-effect" dose was 18 mg/kg level.
- (2) Male rats showed increases of all enzymes from 54 mg/kg.
- (3) Female rats showed increases of O-demethylase and protein synthe from 54 mg/kg.

Urinary Excretion of P071:

Urinary excretion was measured during a 12-hour period on Days 1, 8, 28.

- (1) Urinary excretions were below detection limit at 18 mg/kg on all days.
- (2) The urinary excretions, ^(u)were greater in females than in males on days and increased with the times in both M and F.
- (3) The urinary excretions, ^{of u)}generally, less than 5% of the doses for M

(4) A study to determine the reversibility of hepatic changes in rats (T-10)

Performed by:

Treatment: Nov. 11, 1985-Dec. 8, 1985
Withdrawal: Dec. 9, 1985-Mar. 11, 1986

Animals:

Sprague-Dawley rats, 5-6 weeks old, Charles River, Portage, Michigan

No. of animals/dosage: 60 (30 M + 30 F): 20 (10 M + 10 F) each
sacrificed at end of 4-week treatment, 4- and
13-week withdrawal

Route and duration of administration:

Orally through dietary mix daily for 4 weeks

Dosage levels:

- (1) Control: control diet
- (2) Low dosage: 40 mg/kg/day
- (3) High dosage: 160 mg/kg/day

Results:

Mortality: 3 (control: 1 F, Low: 1 M, High: 1F).

Clinical signs: unremarkable

Body weight and food consumption:

Lower weight gains in high-M only. Food/efficiency: unremarkable.

LIVER STUDIES:

Parameters	40		160 mg/kg/day	
	Dosing	Withdrawal	Dosing	Withdrawal
<u>Chemistry</u>	unremarkable in both groups			
<u>Lipid analysis</u>				
Inc. cholest.			M	recovered (4 wk)
Inc. tot. lipid	M	recov. (4 wk)	M	recovered (4 wk)
Inc. triglycer.	M	recov. (4 wk)		
<u>Enzymes</u>				
Micro. protein				
p-450	M + F	recov. (4 wk)	M + F	recovered (4 wk)
P-NOD*			M + F	recovered (4 wk)
<u>Organ wt</u>				
abs. (inc)	M	recov. (4 wk)	M	recovered (4 wk)
<u>Gross pathology</u>	unremarkable			
<u>Histopathology</u>				
Enlargement				
centrilobular				
hepatocytes	M	recov (4 wk)	M + F	recovered (4 wk)
+ fat depos.				
in midzone			M + F	recovered (4 wk)

*P-NOD: p-nitroanisole-O-demethylase

A study to determine the reversibility of hepatic changes in rats.
Electron microscopy of liver (T-11).

An extension of Study T-10, only rats from control and high dose groups sacrificed at the end of 4-week treatment and 4-week of withdrawal were examined.

In this electron microscopical examination of liver from rats treated with compound P071 for 4 weeks followed by 4 and 13 weeks withdrawal, the results may be summarized as follows:

minimally increased amounts of smooth endoplasmic reticulum in occasional hepatocytes from 10/10 male and 8/10 female rats treated with 160 mg/kg/day and 3/10 male rats treated with 40 mg/kg/day at termination;

occasional concentric membranous bodies in hepatocytes from 7/10 male rats treated with 160 mg/kg/day and 2/10 male rats treated with 40 mg/kg/day at termination;

increased lipid in hepatocytes from rats treated with 160 mg/kg/day at termination.

These changes were not seen in rats from the 160 mg/kg/day treatment group allowed a 4-week recovery period.

NOTE:

Study T-9: The satellite study was for drug monitoring of urine (days 1, 8 and 28).

- (1) Urinary excretion increased with dosing days.
- (2) Urinary excretion of unchanged drug accounting for 5% dose was higher in F than M.
- (3) Metabolites were not indentified.

Study T-10: only liver effects (enzymes, fat contents, light and electron microscopies) were studied.

- (1) All liver effects (increased total lipids, triglycerides and cholesterol, histopathological changes of hypertrophy, fat deposition, vacuolation and EM findings of increased smooth endoplasmic reticulum, lipid droplets, concentric membrane bodies) were reversible after 4-13 weeks recovery period (most parameters recovered in 4 weeks).
- (2) Enzyme induction occurred at 40-160 mg/kg (M + F) more in M. The induction was reversible after 4-13 weeks recovery period.

(5) Chronic Toxicology studies: Oral toxicity study in rats (repeated dosage for 6 months). (T-12)

Performed by : (1), February 22, 1982-August 23/September 2, 1982.

Animals: Sprague-Dawley rats, 7 weeks old. M: 131 gm and F: 97 gm

No. of animals/dosage: 50 (25 M and 25 F)/dosage. Interim sacrifice at 3-month: 10 (5M + 5F)/dosage.

Route and duration of administration: orally by gavage, 7 days/week for 6 months. Interim sacrifice at 3 months.

Dosage: in dist. water

- (1) Control: vehicle
- (2) Low dosage: 8 mg/kg/day
- (3) Mid dosage: 25
- (4) High dosage: 75

Results:

Mortality: total 34 (22 M and 12 F). 26 deaths (C:3, L:3, M: 10 and H: 10); intubation in the trachea; 1 death (M): accidental; 7 deaths (L:2, M:2 and H:3): undetermined cause.

Clinical signs: High dose group: quieter, but hyperactive when handled in this group and mid dose group.

Body weight and food consumption: no significant finding.

Blood analysis:

Hematology: slight decreases of RBC and PCV in high group.

Chemistry: marked inc. of SDH; slight inc. of ASAT (SGOT) and ALAT (SGPT) and slight dec. of triglycerides in mid and high groups (started at 6 weeks)

Urinalysis: no significant finding.

Drug monitoring: Urinary excretion of unchanged drug was higher in F than M, esp. in low group.

Absorption and urinary excretion of UCB PO71 in M and F did not appear to be affected following chronic dosings.

Organ weight:

Liver: both absolute and relative weights were increased in mid and high groups (at 3-month) and in high group (at 6-month).

Kidneys: slight increase (abs and rel) in high (M & F) and mid (M) group at 6 months.

Adrenals and thyroids: slight increase in high-M.

Pathology:

Gross pathology: no significant finding.

Histopathology:

A dose related increase in the frequency and severity of peri-acinar hepatocytic hypertrophy (male rats from low dose and female rats at high dose only) and slight to moderate peri-acinar hepatocytic large droplet fatty infiltration (male rats from mid dose and female rats at high dose only) were observed. More male rats were affected. EM study of livers of control and high dose, (3 M + 3 F) each group, revealed increased smooth endoplasmic reticulum and lipid droplets in all 3 male and 1 female rats of high dose group.

Interim sacrifice at 3-month:

Liver effects progressed from 3 months to 6 months while treatment continued.

Six-month toxicity study in rats with test substance P071.
Electron microscopy of selected hepatic tissues of control and group 4 treated rats(T-13)

An extension of Study T-12, the results were based on the observations from three rats of each sex from control and 75 mg/kg/day groups. The results are copied as follows:

In the limited numbers of animals observed, ultrastructural changes in the hepatic tissue of the rat were almost totally confined to the males with an evident increase in smooth endoplasmic reticulum in the periactinar region and a slight increase in the centriactinar region. There were elevated numbers of lipid droplets observed in both centriactinar and periactinar regions with some clumping of lipid droplets in the periactinar region which on occasion formed very large lipid droplets. Many lipid droplets of varying size had a 'vacuolar' appearance, a not uncommon effect caused by storage of tissues in formaldehyde.

The female treated rats had numbers of lipid droplets similar to the female controls, and with the exception of the periactinar region of 4F Oil which had a slight increase in smooth endoplasmic reticulum, no observable increases in smooth endoplasmic reticulum were found in the centriactinar or the periactinar region.

In both male and female treated rats all other hepatic ultrastructural features were regarded as similar to those observed in controls.

(1) Subchronic toxicity study: Toxicity to dogs in repeated oral administration for one month (T-14)

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Performed by: (1), April 14, 1981 - May 14, 1981.

Animals: Beagle dogs, 12-15 months old.

No. of animals/dosage: 6 (3M + 3F)/dosage.

Route and duration of administration: orally 7 days/week for 1 month.

Dosage levels: in gelatin capsules.

(1) Control:	0
(2) Low:	15 mg/kg/day
(3) Mid:	45
(4) High:	135

Results:

Mortality: none

Clinical signs:

- (1) Vomiting: drug- and dose-related increased incidences in all dose groups.
- (2) Impaired condition (body tremor, salivation, ataxia, reduced food consumption): in 2 high-dose females at end of treatment.

Body weight and food consumption:

Both showed decreases in high dose females (mostly due to 2 females).

Blood analysis:

Hematology: unremarkable

Chemistry: Increased AP in high dose M and F and increased α_2 globulins in high dose F.

Urinalysis: Significant decreases of specific gravity in high-dose M (-22%) and F (-34%); volume increased.

Ophthalmology: not performed.

Heart rate and EKG: no significant findings.

Organ weight: Relative weights of

kidneys: increased in high dose male and female dogs.

adrenals: increased in high dose male and female dogs

Pathology:

Gross pathology: unremarkable.

Microscopic pathology: unremarkable.

(2) Chronic toxicity study: Oral toxicity study in beagle dogs,
Repeated dosage for 6 months (7:15).

Performed by: ~~QD~~ January 13, 1982 - July 13, 1982

Histopathology:

Animals: Beagle dogs, 7-9 months old.

No. of animals/dosage: 10 (5M + 5F)/dosage.

Route and duration of administration: orally 7 days/week for 6 months.

Interim sacrifice at 3 months, (2 M + 2 F) from each group.

Dosage levels: in gelatin capsules.

- (1) Control: empty gelatin
- (2) Low: 8 mg/kg/day
- (3) Mid: 25
- (4) High: 75

Results:

Mortality: 2 males of high group. One died on Day 87 after displaying respiratory difficulties. Another male dog was sacrificed on Day 182. Autopsy revealed dense foam in trachea and an atrophy of mandibular salivary glands. Histopathological examination showed slight, diffuse acute tracheitis.

Clinical signs:

- (1) Vomiting: drug and dose-related increases of incidences.
- (2) Behavior changes: high dose dogs were quieter, but became nervous when touched.

Body weight and food consumption:

Body weight: reduced weight gains were observed in mid and high-dose F only. (Starting from week 2, dose and duration related decreases were observed).

Food consumption: in mid and high F only, correlating to reduced weight gains.

Blood analysis:

Hematology:

MCV: 10% decreases in high M and F.

RBC: 10% increases in high M and F.

Chemistry:

Cholesterol and triglycerides: tendency to decrease in high M.

Alk. phosphatase: slight increases in high M and F.

Urinalysis: tendency to slight decreases of specific gravity in high-dose group.

Ophthalmology: unremarkable.

Heart rate and EKG: no significant finding.

Organ weight: No significant changes were observed at 3-month, or at 6-month for male dogs. At 6 months, mid and high F showed increased relative weights of most organs (due to the suppressed weight gains at these levels).

Pathology:

Gross pathology: no significant findings at 3- or 6-months.

Histopathology: no significant findings at 3- and 6-months.

(3) One-year Oral Toxicity Study of Cetirizine P071) in Beagle Dogs
(IND Report Y-29, Report 208/851114/PFZ) (F-18)

Performed by:

June 28, 1984 - June 29, 1985

Animals:

Beagle Dogs, from Hacking and Churchill, Cambell Farm, Wt. 10.6 kg (M)
9.2 kg (F), age: 24-28 weeks

No. of Animals/dosage:

10 (5M + 5F)

Route of Administration:

Orally through gelatin capsules daily for 52 weeks.

Duration of Treatment:

Daily for 52 weeks.

Dosage groups: (mg/kg/day)

(1) Control:	empty gelatin capsule
(2) Low dosage group:	4
(3) Mid dosage group:	15
(4) High dosage group:	60

Results:

Signs:

Vomiting: dose-related within 1-hour of dosing in M and F, only
occasional in low-dose group.

Mortality: None

Body weight: M (mid & high): decreased weight gains during 52 weeks.

Food consumption: No significant finding.

Physical examinations: on pre-dose, weeks 12, 24, 38, and 50.

ECG: sig. increase QTC in HD-M only at week 50.

BP: some increase in dosed F during pre-dose and week 50

Ophthalmic examination: pre-dose, weeks 12, 24, 38, and 50.
Unremarkable.

Hematology/bone marrow/coagulation:

Changes (mostly inc) in RBC, Hgb, McHc and APTT in MD and HD female during weeks 12 and 24.

Bone marrow smears: normal in cellularity, morphology and cell distribution at sacrifice.

Blood chemistry: No significant finding.

Urinalysis: Unremarkable.

Organ weights: Unremarkable.

Gross pathology: Unremarkable.

Histopathology: Unremarkable.

ADME data: Week 52 data

* F > M

(1) Dose (mg/kg/day)	Tmax(hr)	Cmax(μ g/ml)	AUC(μ g.hr/ml)	Bile/plasma
4	1.5	5.5	65.0	17.8
15	1.3	29.7	325.7	26.1
60	2.4	101.5*	1456.1	30.1

(2) Steady state reached in 1 week

(3) No accumulation was apparent.

(4) Except at HD where F > M in peak plasma levels, no sex difference in pharmacokinetics were observed.

Hepatic drug metabolizing capacity: no sacrifice.

Parameters: microsomal protein, cytochrome P-450, aniline hydroxylase, ethylmorphine-N-demethylase, acetylcholinesterase: no significant effect.

(D) Monkey studies: (1) - (3)

(1) Preliminary Oral Toxicity Study in Cynomolgus Monkeys ~~(T-16)~~ (T-16)

Performed by:

Animals:

Wild-caught cynomolgus monkeys (*Macaca fascicularis*)

No. of animals/dosage: 2 (1 M+ 1 F), each pair was studied at a time.

Route and duration of administration:

Orally by gavage as a solution in distilled water, daily for 14 days.

Dosage levels: (4 ml/kg of 5% solution, except*)

(1) Control: distilled water

(2) Low dosage: 50 mg/kg/day

(3) Mid dosage: 100 mg/kg/day

(4) High dosage: 200 mg/kg/day *(vol. of 4 ml/kg - 1 day; 2.5% - 8 ml/kg - 13 days).

Results:

Mortality: none.

Clinical signs:

Salivation and vomiting from 50 mg/kg.

Quiet behavior/pilo-erection/ tremor/loose, mucus feces: 200 mg/kg.

Body weight and food consumption:

Body weight: losses from 50 mg/kg (F), 100 mg/kg (*M and F) and 200 mg/kg (*M and F). *more losses.

Food: decreased in both M and F of 200 mg/kg group.

Blood analysis:

Hematology:

RBC: dec. from 50 mg/kg on Day 11.

Pathology: liver findings of fat deposition in both monkeys of 200 mg/kg group; F monkey had pallid and mottled liver. Bot monkeys had congested lungs.

(2) 4-week Oral Toxicity Study in Cynomolgus Monkeys (T-25)¹⁷.

Performed by:

Animals:

Wild-caught monkeys (*Macaca fascicularis*).

No. of animals/dosage: 6 (3M+ 3F)

Route and duration of administration:

Orally by gavage of solution in distilled water daily for 4 weeks.

Dosage levels:

- (1) Control: vehicle
- (2) Low dosage: 17 mg/kg/day
- (3) Mid dosage: 50 mg/kg/day
- (4) High dosage: 150 mg/kg/day

Results:

Mortality:

One F from 150 mg/kg group sacrificed on Day 22.

Clinical signs:

Vomiting (shortly after dosing), huddled posture, poor condition of the coat, limb tremors, abdominal scratching motion and drop in body temperature: at 150 mg/kg level.

Body weight and food consumption.

Body weight: marked losses in high dose group and moderate losses in 2 F of 50 mg/kg group.

Food: only the sacrificed F showed dec. food consumption.

Blood analysis:
Hematology:

No significant trends.

Chemistry:

- (1) Dec. ornithine carboxyltransferase: at 50 and 150 mg/kg.
- (2) Dec. sorbitol dehydrogenase: at 17, 50 and 150 mg/kg.
- (3) Inc. triglycerides: at 150 mg/kg.

Urinalysis: marginally dec. specific gravity in 150 mg/kg group.

Ophthalmology: unremarkable.

Heart rate and ECG:

ECG: only the sacrificed F showed low HR with sinus arrhythmia.

Organ weight:

Kidneys and lungs: increases of absolute and relative wts. only in 150 mg/kg group.

Pathology:

Gross pathology: No significant finding.

Histopathology: No significant finding.

Assay of Drug Metabolizing enzymes: at end of 4 weeks.

- (1) Liver weight: both absolute and relative weights were lower in F of 150 mg/kg group.
- (2) Total microsomal protein: lower in the F of 150 mg/kg.
- (3) Three hepatic microsomal enzymes (ethylmorphine-N-demethylase, aniline hydroxylase and p-nitroanisole O-demethylase) showed increased activities in F monkeys of 50 and 150 mg/kg groups and in M monkeys of 17 and 150 mg/kg groups, but no statistical significance was established.

(3) One-Year Oral Toxicity Study of Cetirizine (UCB P071) in Cynomolgus Monkeys (IND Report T-30, HRC Report UCB 220-g/86186) (T-19).

Performed by:

October 4, 1984 - October 4, 1985

Animals:

Wild-Caught Cynomolgus Monkeys (*Macaca fascicularis*), from Shamrock Farms, Great Britain, wt. 2-3 kg, age: 2-4 yrs

No. of animals/dosage: 10 (5M + 5F)

Route and duration of administration:

Oral by gavage, as a solution in water daily for 52 weeks.

Dosage levels: (mg/kg/day)

- (1) Control: vehicle
- (2) Low dosage: .5
- (3) Mid dosage: 15
- (4) High dosage: 45

Results:

Mortality: None.

Clinical signs: Salivation: mainly at HD

Body weight and food consumption: No significant effect.

Blood analysis:

Hematology: No consistent/significant findings.
Bone Marrow smear: no effect.

Chemistry: No consistent changes.

Urinalysis: Inc. volume and dec. sp. gr. at HD

Ophthalmology: Unremarkable.

Heart rate and ECG: Unremarkable.

Organ weight: Testes: inc. abso & rel. wt. at HD

Pathology:

Gross pathology: Unremarkable.

Histopathology: Unremarkable.

ADME data:

* F M

Week 52 data

(1)Dose (mg/kg/day)	Tmax(hr)	Cmax(ug/ml)	AUC(ug.hr/ml)	Bile/plasma
5	0.9	3.3	9.9	
15	1.2	10.0	32.4	
45	1.5	31.9	134.4	

(2) Steady states reached in 1 week.

(3) No accumulation was apparent.

(4) No sex difference in pharmacokinetics were observed.

Hepatic drug metabolizing enzymes: at sacrifice.

Parameters: Microsomal protein, cytochrome P-450, aniline hydroxylase, p-nitroanisole-o-demethylase and ethylmorphine-N-demethylase: no significant effect.

Carcinogenicity Studies: 1-2.

1. Two-Year Dietary Mouse Carcinogenicity Study (T-20).

GLP statement: yes.

Performed by:

Animals: Charles River CD-1 mice, approximately 5-6 weeks old at the start of treatment, obtained from Charles River Breeding Lab., Margate, Kent, UK. M: 27 gm and F: 19 gm.

No of animals/dosage: 104 (52M + 52F).

Route, mode and duration of administration:

Orally through dietary mixture daily for 104 weeks or 2 years.

Dosage selection: based on 4-week dietary study that showed drug-related toxicological effects in livers. Lipid deposition and elevated liver enzymes at 27-81 mg/kg in male mice. Female mice showed elevated triglycerise at 27-81 mg/kg. Centrilobular hepatocyte hypertrophy (enlargement) in 3-81 mg/kg M mice was considered of no toxicological significance because it was related to enzyme adaptive changes.

Dosage levels (mg/kg/group): weekly analyses (body weight, food consumption and inclusion levels of test compound) revealed all within target ranges.

(1) Control: 0
(2) Control: 0
(3) Low dose group: 1
(4) Mid dose group: 4
(5) High dose group: 16

Health check group: 20 (10M + 10F) no lesions or infectious diseases found on 6/13/84 (sacrificed and macroscopic and histopathological examination).

Results:

Signs: no significant signs attributable to treatment.

Body weight:

Weight gains comparable among groups during study period.

Food consumption: comparable among groups during study period.

Blood Smears:

Taken from all surviving mice during weeks 52, 53, 57 and at termination showed no significant effect.

Mortality: no significant finding. Cause of death attributed to injuries from fighting among males during the first 13 weeks. Mortalities ranged 50-58% (M) and 29-54% (F). One of the contributing factors to female deaths was lymphosarcoma accounting for 4, 8, 3, 9 and 9 deaths in Groups 1-5, respectively in female mice. Distribution of deaths are as follows:

	Group and dosage (mg/kg/day)									
	1 st Control	2 nd Control	3 rd 1	4 th 4	5 th 16	1 st Control	2 nd Control	3 rd 1	4 th 4	5 th 16
Initial group size	52	52	52	52	52	52	52	52	52	52
No. sporadic deaths occurring weeks:										
1 - 26	0	1	3	2	1	0	1	0	0	0
27 - 52	2	2	9	2	5	1	3 ^A	1	3 ^B	0
53 - 78	6	14	9	5	4	5	7	4	6	6
79 - 104	18	13	13	19	18	18	17	10	12	15
105 - 108	0	0	0	0	0	0	0	0	0	1
Terminal sacrifice	26	22	22	24	24	28	24	27	31	30
% survival of mice at termination	50	42	42	46	46	54	46	52	58	58

^A Includes 2 mice, Nos. 339 and 340 (#443 and 444) sacrificed in week 44 after receiving inappropriate diets

Pathology:

Gross pathology: no significant finding, except high-dose males with higher incidences of liver mass than control. In addition, high-dose males that were dead or sacrificed during study period also having higher incidence of liver mass.

NUMBER OF MALE MICE WITH:

MALE EXAMINED: $\frac{1}{18}$ $\frac{1}{18}$ $\frac{1}{17}$ $\frac{1}{17}$ $\frac{1}{18}$ $\frac{1}{17}$ $\frac{1}{18}$ $\frac{1}{17}$ $\frac{1}{17}$

D: found dead or sacrificed; T: terminal sacrifice

LIVER	10	11	12	11	6	16	7	12	16	12
MASS OF LIVER	0	0	0	1	3	0	1	1	0	1
NO. OF AREAS	1	1	1	3	3	2	1	4	3	4
NO. OF AREAS OF AREAS	0	0	1	3	0	1	3	0	0	0
NO. OF CYSTS	0	0	0	0	0	1	1	1	0	4
NO. OF FIBROUS	0	1	0	0	0	0	0	1	0	0
NO. OF IRREGULAR SURFACE DEPRESSIONS	0	0	0	0	0	0	1	0	1	0
NO. OF PITS	4	7	1	4	8	4	6	3	9	3
NO. OF LABILE MARKINGS OBSERVED	0	0	0	1	0	0	0	0	0	0
NO. OF AREAS	1	0	0	1	1	0	1	0	0	0

Histopathology:

Neoplastic changes:

(1) Benign liver cell tumor: increased incidence of benign liver cell tumors was observed in high-dose male mice only. In addition, a greater number of them also was found bearing multiple benign liver cell tumors (see tables). Statistical analysis on liver cell tumors (benign and malignant combined) and on malignant liver cell tumors alone for male mice was

performed. The high-dose male mice had significantly more liver cell tumors than control (p=0.02). The test for trend over all groups was significant (p=0.01). The test for trend for the first 4 groups excluding the high-dose group, however, was not significant. No significance was found in the incidence of malignant liver tumor.

(1) Incidence of male mice with liver cell tumors

	Group				
	1	2	3	4	5
Benign	13	14	13	18	28
Malignant	7	8	7	8	8
Benign and/or malignant	18	18	19	26	37
Number of animals examined	82	82	82	82	82

(2) Incidence of male animals with benign liver cell tumors

	Group				
	1	2	3	4	5
Benign liver cell tumour (one)	12	10 ^a	9	8	12 ^a
Benign liver cell tumour (two)	0	2	4	4	9 ^a
Benign liver cell tumour (three)	1	2	1	2	3
Benign liver cell tumour (four)	0	0	1	1	1
Animals with any benign liver cell tumour	13	14	15	15	25
Percentage	25.0	26.9	28.0	28.0	40.1
Animals examined	82	82	82	82	82

NOTES: In comparison with the main tables:

- ^a Includes the animal with the infarcted liver cell tumour, but excludes the animal with the benign tumour in the G20 section
- ^b Includes the animal with the benign liver cell tumour in the G20 section
- ^c Includes the animal with the necrotic benign liver cell tumour

Historical control data from 9 studies from the performing lab. showed an incidence of 3.8%-25.9%. The concurrent control groups showed incidences of 25.0% and 26.9%, within historical control ranges.

Incidence of liver cell tumors in untreated control male mice

	Study								
	01E	02A	02B	02C	02D	02E	02F	03A	03B
Benign liver cell tumors	2	13	18	6	16	11	12	14	9
Percentage	2.0	12.3	14.4	5.5	16.2	11.2	22.1	26.9	17.3
No. of mice	82	106	124	82	86	82	82	82	82

(2) Lymphosarcoma in multiple organs: increased in 16 mg/kg female mice (35, 51, 30, 27 and 56 total incidences in groups 1-5, respectively).

Non-neoplastic changes:

Some macroscopic findings mostly at high dose: liver masses/cysts (M), fluid in abdomen/thoracic cavity, subcutis edema/hemorrhage, stomach (depression in corpus mucosa, dark/blood contents) and ovarian cysts (F). Histopathology did not reveal significant finding in treated mice.

2. Two-Year Dietary Rat Carcinogenicity Study (T-21).

GLP statement: yes.

Performed by:

Animals: CD-rats, Sprague-Dawley strain, 5-6 weeks old at the start of treatment, obtained from Charles River Breeding Lab., Portage, Michigan.

No. of animals/dosage: 100 (50M + 50F).

Route, mode and duration of administration: orally through dietary mixture, daily for 104 weeks or 2 years.

Dosage election: based on 4-week dietary study that showed drug-related toxicological effects in livers. Hepatotoxicity (enlargement of the centrilobular hepatocytes and vacuolation of midzonal hepatocytes with associated fat deposition) were observed at 54-160 mg/kg in both males and females. The relative "no-effect" level was 18 mg/kg.

Dosage levels (mg/kg/day): weekly analyses (body weight, food consumption and inclusion levels of test compound) revealed all within target ranges.

- (1) Control: 0
- (2) Control: 0
- (3) Low dose group: 3
- (4) Mid dose group: 8
- (5) High dose group: 20

Health check (Feb. 16, 1984) on 10 M and 10F revealed no lesions associated with infection except ro nodule of antrum mucosa in the sotmach of 2 M (Ectopic focus of non-glandular epithelium in the glandular region).

Signs: none related to treatment was reported. Sialodacryoadenitis was found in most rats of all groups during week 83 and 84 resulting in swelling of ventral cervical region, dryness of eyes, reduced food intake and body weight gains. The symptoms regressed and all animals recovered.

Mortality: no treatment related mortality (M:60-72%; F:52-64%) was evident. The distribution of deaths was follows:

Sex	Dose (mg/kg/day)					Total
	0	3	8	20	Control	
Initial group size	50	50	50	50	50	250
No. animals deaths	0	0	0	0	0	0
No. animals surviving	50	50	50	50	50	250
Survival (%)	100	100	100	100	100	100
Number of rats terminated	0	0	0	0	0	0
Number of rats terminated (%)	0	0	0	0	0	0

Body weight: no significant finding.

Food consumption: no significant finding.

Efficiency of food utilization: no significant finding except for mid F and high F with higher efficiency during month 4-6.

Blood smears: no significant finding at Week 52, 78 and 104.

Pathology: gross and histopathology were performed.

Neoplastic changes: thyroid follicular adenoma, pituitary tumors (carcinoma and adenoma) and liver malignant tumor were increased in some dosed groups.

(1) Thyroid follicular adenoma:

Number of thyroid follicular tumors in male rats

groups	1	2	3	4	5
Adenoma	1	3	1	2	4
Adenocarcinoma	2	1	3	2	1
Total	3	4	4	4	5
Number of rats examined	50	50	50	50	50

- This number includes a thyroid follicular cystadenoma

Incidence of thyroid follicular tumors in untreated male Sprague-Dawley rats (Historical control values)

Study Identity	A	B	C	D	E	F	G	I	J	K	L	M	N	O	P
Number of rats with:															
Adenoma	3	2	2	6	3	1	4	0	4	2	1	2	3	6	2
Adenocarcinoma	0	1	0	1	1	0	0	0	1	0	1	2	0	1	1
No. of rats examined:	99	50	100	50	98	49	100	100	99	50	49	99	50	100	50

Increased incidence was observed at 20 mg/kg male rats. The historical data showed thyroid follicular adenoma in male Sprague-Dawley rats ranged 0-12%. The statistical analysis by sponsor concluded as follows:

Male rats receiving 20 mg/kg/day ucb P071 showed significantly more benign follicular tumors than the pooled controls, $P = 0.047$ and the test for trend over Groups 1 to 5 was significant $P = 0.009$, but did not persist when the high dose group was excluded.

For combined benign and malignant follicular tumors the test for trend over Groups 1 to 5 was significant $P = 0.03$, although the pairwise comparison between the high dose group and the pooled controls was not significant.

The incidence of benign follicular tumors in male rats receiving 20 mg/kg/day ucb P071 of 6/50 is within the range of historical control values in this laboratory. In addition, there was no evidence of a treatment-related effect on non-neoplastic lesions in the thyroid gland. Bearing these facts in mind, the increased incidence of thyroid follicular tumors was considered of no biological significance.

(2) Pituitary tumors:

Pituitary carcinoma increased in 8 mg/kg female rats. Pituitary adenoma increased in 8 and 20 mg/kg female rats. When the carcinoma and adenoma are combined, the incidences were increased in 8 and 20 mg/kg female rats

Number of pituitary tumours in female rats

Groups	1	2	3	4	5
Adenoma	26	31	27	30	32
Carcinoma	2	1	1	7	3
Total	28	32	28	37	35
Number of rats examined	50	50	50	50	50

Incidence of pituitary tumours in
unselected female Sprague-Dawley rats
(Historical control values)

Study identity	A	B	C	D	E	F	G	I	J	K	L	M	N	O	P
Number of rats with:															
Adenoma	63	30	85	28	72	34	52	82	56	36	27	54	31	59	31
Carcinoma	8	1	8	2	11	1	4	7	3	8	2	7	1	4	4
No. of rats examined	100	49	98	49	100	50	99	100	98	50	49	101	48	100	50

The historical control data in female S-D rats revealed adenoma at 60-82% and carcinoma at 2-11%.

The statistical analysis by Sponsor concluded as follows:

For malignant pituitary tumors in females the 8 mg/kg/day group showed significantly more tumors than the controls, $P=0.01$. Since the 20 mg/kg/day group was not significantly different from the controls the test for a linear trend across Groups 1 to 5 was not significant, but the test for non-linearity was $P=0.04$.

Where benign or malignant pituitary tumors combined were analysed the 8 mg/kg/day group showed a higher incidence of tumors than controls, but again the test for trend was not significant.

The incidence of pituitary carcinoma in female rats receiving 8 mg/kg/day ucb P071 (7/50) is greater than the historical control data, however, in the absence of an increased incidence of this change at the high dose level this result, confined to the intermediate dose level, is considered unlikely to be of any toxicological importance.

Moreover the incidence of pituitary tumors in female rats receiving 8 mg/kg/day and 20 mg/kg/day ucb P071 of 37/50 and 35/50 is within the range of historical control values in this laboratory (see table) and as such this result is considered to be of no biological significance.

- (3) Liver malignant tumors:
Liver malignant tumors increased in 8 mg/kg male rats.

Group	Number of liver cell tumours in male rats				
	1	2	3	4	5
Benign	1	0	0	1	0
Malignant	0	1	0	3	2
Total tumours	1	1	0	4	2
No. of rats examined	50	50	50	50	50

The statistical analysis revealed no significant differences from controls.

- (4) Mammary gland:
Fibroadenoma with epithelial atypia (2, 2, 4, 4, and 5 for C, C, low, mid and high, respectively) appeared increase in the dosed groups.

Non-neoplastic changes:

(1) Stomach:

Ulceration in the non-glandular stomach was observed from 3 to 20 mg/kg in female rats (see Table). Minimal to marked hyperplasia and hyperkeratosis of the epithelium of the non-glandular region (18, 14, 18, 24 and 20 for males, and 13, 18, 21, 19 and 26 for females for C, C, low, mid and high groups, respectively) occurred in all groups, but showed treatment-related effects at 8 mg/kg (males) and at 20 mg/kg (females). Pale (5, 3, 7, 8 and 9, respectively) increased at 3-20 mg/kg (males). Depression (7, 7, 13, 14 and 12, respectively), or thickness (2, 4, 5, 7 and 7, respectively) of forestomach increased at 3-20 mg/kg (females). The "NOEL" was not established in both male and female rats.

Incidence of ulceration in the non-glandular stomach

Group	1	2	3	4	5
Ulceration non-glandular stomach	3	6	10	10	11
No. of rats examined	50	50	50	50	50

(2) Liver:

Masses (2, 0, 1, 4, 2 for males and 1, 0, 1, 0, 0 for females) showed increase only in 8 mg/kg male rats. For male rats, enlarged (10, 7, 6, 16 and 16) /swollen (12, 14, 11, 18 and 19) /darken (25, 29, 34, 37 and 26) liver and periportal fat deposition (17, 22, 20, 26 and 27) increased at 8-20 mg/kg. Centrilobular vacuolation (13, 7, 8, 15 and 21 for males, and 13, 10, 7, 10 and 17 for females) increased at 20 mg/kg. The "NOEL" appears to be at 3 mg/kg for both male and female rats.

(3) Kidneys:

Enlarged with minimal to marked progressive glomerulonephrosis (34, 36, 37, 41 and 42 for males, 21, 25, 31, 27 and 22 for females for C, C, low, mid and high groups, respectively) occurred in all groups, but showed some treatment- and dose-related effects in male and female rats.

(4) Thyroids:

Epithelial whorls were 3, 4, 2, 1 and 6 (male rats) and 3, 4, 1, 7 and 7 (female rats) for C, C, low, mid and high groups, respectively.

(5) Pituitary: Enlarged (27, 33, 33, 43 and 35 for C, C, low, mid and high groups, respectively) with microscopic finding of dilated/congested sinusoids (15, 22, 22, 29 and 24 for C, C, low, mid and high groups, respectively) in female rats at 8-20 mg/kg.

(6) Pancreas: masses (6, 5, 2, 12 and 8 for C, C, low, mid and high groups, respectively) in 8-20 mg/kg female rats.

(Cetirizine: 071)
SUMMARY OF REPRODUCTION STUDIES
(Oral by Gavage)

Segment	I	II	II	II	III
Species	mouse	rat	rabbit	mouse	mouse
Duration	(1) M: 8wks prior to mating, continued on until sacr. (2)F: 2 wks prior to mating, continued on until (a) Day 17.5 pregnancy (b) Day 21 postpartum	Day 6-15	Day 6-18	Day 6-15	Day 15 Day 21 postpartum
No.	(1) M: 20 (2) F: 40: Day 21, from each group for F ₁ & F ₂	25-26F	16-18F	30F	32F
Doses mg/gk/day	4 16 64*	8 25 75 225	15 45 135	6 24 *96	6 24 *96
*increased liver weight					
Adult data:					
Effect doses:	64	75-225	135	96	96
	(pregnancy/ mating perf)	(wt./sign/ death)	(wt./deaths)	(wt.)	(wt.)
					(96:nursing/ lactating performance)
No effect doses:	16	25	45	24	24

(continued)
(Cetirizine: 071)
SUMMARY OF REPRODUCTION STUDIES
(Oral by Gavage)

Litter data:	I (mouse)	II (rat)	II (rabbit)	II (mouse)	III (mouse)
Effect doses:	64 (embryocidal) 64(malformations (cleft palate) 16-64(skeletal variants/anomalies)	225(embryocidal) 25-225 (skeletal anomalies/variants)	135 (skeletal anomalies/ variants)	NE	96 (lower pup wt/ day 4-21 lower M/F @birth & weaning.
No-effect doses:	4	8	45	96	24
Significance:					
Embryocidal:	NE	225	NE	NE	NE
Teratogenicity:	64(?)		NE	NE	
Skeletal(anomaly variants)	16-64	25-225	135		
Pregnancy/mating	64				
Nursing/lactating:					96
F ₁ & F ₂ generations (no treatments)	No effects: development and reproductive functions Liver and kidney weight			(F ₁ only) No effect: development and liver and kidney wt.	

Reproduction Studies: 1-5

i. Segment I Reproduction Study:

Fertility and General Reproductive Performance of the Mouse (T-26).

Performed by:

March 24, 1984 - July 20, 1984

Animals:

Mice (CD-1 strain) from Charles River UK Ltd. Margate, Kent.
M (weeks old), F (9 weeks old).

Route and duration of administration: orally by gastric intubation

- (1) Dosed M: 8 weeks prior to mating and continued until sacrificing.
- (2) Dosed F: 2 weeks prior to mating and continued on until either sacrificed on Day 17.5 of pregnancy or after rearing young to Day 21 postpartum.

Dosage levels: (0.1 ml/10gm)

- (1) Control: distilled water
- (2) Low: 4 mg/kg
- (3) Mid: 16 mg/kg
- (4) High: 64 mg/kg

Results:

Maternal data:

Mortality: Total 3 (1 F of 16 mg/kg, 2 of 64 mg/kg)

Body weight and signs:

Body weight and food consumption were slightly lower at 64 mg/kg level, only food consumption attained statistical significance.

Signs: reported as unremarkable.

Pregnancy: pregnancy rate slightly lower only at 64 mg/kg level.

Mating performance: median precoital time was 3 days for all groups, but more mice of mid and high groups mated on or after 6 days. In addition, more mice of mid and high groups showed no positive mating.

Labor: not commented upon.

Necropsy: no significant finding. Liver: centrilobular hypertrophy at 64 mg/kg level.

Liver: relative weight was significantly increased only at 64 mg/kg level
F sacrificed on Day 17.5: relative liver wt. increased at 16 mg/kg level.

Length of gestation: *slightly* prolonged only in high group.

Litter data: On Day 21, 16 M and 16 F pups per group were retained for further study.

Litter Size: from dams allowed to litter.

Control, low and mid groups: had litter size of 10.1 - 10.3.
High group: 9.1 (statistically significant).

Survival:

Pup survivals at birth and through day 4-21 were not adversely affected by drug.

Sex ratio: 50% at birth and day 21.

Body weight: Pups weight: comparable at birth, not adversely affected from day 4-21.

Malformations:

Cleft palate: higher incidences (both in terms of litters and fetuses) at 64 mg/kg (control and low: 0, mid: 1 fetus, high: 4 fetuses).

Skeletal anomalies and variants:

unossified 5th metacarpals, total variant sternabrae (unossified, reduced, asymmetric/bipartite) affected cervical vertebrae, reduced metatarsals and occipitals were higher (in terms of litters and fetuses) at 16 and 64 mg/kg.

Visceral anomalies (dilatation of renal pelvis, abdominal hemorrhage ect.): lower among dosed groups.

Necropsy:

Macroscopic findings on weaned litters showed no significant effects.

Liver and kidneys weight: from 1 M and 1 F of weaned litters showed comparable relative weights.

F₁ Generation (No Treatment)

Pre weaning development: group mean age (days post coitum).
Surface righting: 23 days for all groups
Air righting: 28 days for all groups
Startle response: 30.5 days for all groups

Post-weaning development:

(a) Signs and mortality:

No signs in F₁ generation; one F from 64 mg/kg parents was sacrificed on Day 55 (age) - failed to show vaginal opening.

(b) Body weight: no significant effects noted.

(c) Vaginal opening: comparable opening age in all groups.

(d) Pupil reflex test: comparable among groups (tested at week 4).

(e) Behavioral tests: tested at 5 weeks of age.

(i) Actimat (testing activity):

(ii) Rotarod test (testing motor coordination and balance)

(iii) Passive avoidance (tested at 7 weeks of age for learning):
no effects seen.

(f) Mating performance and pregnancy rate:

(i) Mating performance (median pre-coital times and positive indication of mating): similar among groups.

(ii) Pregnancy rate: 100% in all groups.

(g) Gestation period: 18.6 days (18-19 days) in all groups.

(h) Terminal autopsy: no significant finding.

Liver and kidneys weights: relative weights were comparable among groups.

Litter data:

(a) Total litter loss: two dams showed total litter loss. One from 64 mg/kg parents and the other from 4 mg/kg parents.

(b) Litter size and pup mortality: comparable among groups.

(c) Litter and mean pup weight: comparable.

(d) Terminal autopsy: no significant finding. Liver and kidneys weight: relative weights of both organs taken from 1M and 1F from each litter were comparable among groups.

Subpoint = mouse

TABLE 5

Mating performance and pregnancy rate - F0 generation

Group	Dosage ucb P071 (mg/kg/day)	Number of females paired	Number of successful mating pairs on Day:								Total No.	Pregnancy rate (%)	Median pre-coital time ^a days	Observation at mating	
			1	2	3	4	5	6	>6	Vaginal plug				No. indica- tion of mating	
1	0	40	11	6	11 ^a	8	0	1	3	40	100	3.0	39	1	
2	4	40	6	11 ^a	13	5	1	0	4	40	100	3.0	39	1	
3	16	39	7	9 ^a	15 ^{aa}	6	0	1	1	39	100	3.0	36	3	
4	64	40	9	2	12 ^a	3	0	3	7 ^{aaa}	36	90	3.0	32	4	

^a Includes one (aa, two aaa, three) female(s) with no indication of mating on day of conception - day determined retrospectively assuming a 19 day gestation
^b Time by which half of the paired females had conceived

Segment I: mouse

TABLE 10

Group mean incidence of malformations and anomalies

Group	Dosage mg/kg/day (m/ky/day)	Number of litters	Number of foetuses									
			Malformations				Anomalies /					
			Examined	Affected		Mean l	Examined	Total No.	Mean l	Visceral (Wilson technique)		
				litters	foetuses					Examined	Total No.	Mean l
1	0	20	201	2	4	2.3	98	4	5.2	99	7	10.0
2	4	20	225	1	1	0.4	111	8	6.8	112	7	6.7
3	16	19	211	3	3	1.8	105	12	16.7	103	1	1.1
4	61	17	173	5	9	5.5	82	12	15.3	82	1	1.2

/ Foetuses with malformations excluded

→ Skeletal anomalies: statistical analysis non-significant at Kruskal-Wallis test ($P > 0.05$)

Background data

Data from control and inactive test groups from three mouse teratology studies using CD-1 mice performed at Huntington Research Centre 1981 - 84.

Number of litters examined 370
 Number of foetuses examined 3815
 Number of foetuses with malformations 34

Type of malformations observed

- Cleft palate 17
- Neural tube defects (e.g. craniorachischisis) 8
- Digital and limb defects 5
- Open eye 4
- Others 11

* Includes foetuses with multiple malformations

2. Reproduction Study: teratogenicity study in mouse (T-27)

Performed by :

August 23, 198 -September 5, 1984

Animals:

Mice (CrL: COBS CD-1 (ICR) BR strain) from Charles River
U.K. Margate, Kent. 20-27 gm

Route and duration of administration:

Orally by gastric intubation from Day 6-15 of pregnancy; sacrificed
on Day 17.5 of pregnancy.

No. of animals/group

30F/group:

Dosage levels: (0.1 ml/10 gm)

- (1) Control: distilled water
- (2) Low: 6 mg/kg/day
- (3) Mid: 24 mg/kg/day
- (4) High: 96 mg/kg/day

Results:

Mortality: None

Signs: Incidental signs of eye discharge, fur loss, noisy respiration.

Body weight and food:

Mean weight gains slightly higher at mid and high doses during the
later part of pregnancy.

Food consumption slightly lower in all dosed groups from Day 8-13.

Pregnancy Rate: comparable among groups.

Necropsy:

Liver: absolute and relative weights significantly increased at 96 mg/kg level.

Kidneys: weights decreased at 96 and 6 mg/kg

Resorption: no apparent drug-effect.

Implantations: Pre-and post-implantation losses showed no drug-related effect.

Litter data:

Litter Size: comparable among groups

Sex ratio: no significant difference

Body weight: comparable

Viscera: anomaly: No effect

External anomaly: no effect

Skeletal anomaly: no effect.

TABLE 7
Group mean incidence of malformations and anomalies

Group	Dosage ucb P071 (mg/kg/day)	Number of litters	Number of fetuses								
			Malformations			Anomalies [/]					
						Skeletal			Visceral (Wilson technique)		
			Examined	Total No.	Mean %	Examined	Total No.	Mean %	Examined	Total No.	Mean %
1	0	23	199	0	0.0	100	10	8.1	99	3	3.4
2	6	20	181	1	0.4	91	5	4.7	89	6	7.7
3	24	21	212	2	0.8	104	8	8.1	106	1	1.0
4	96	24	250	1	0.4	124	6	5.6	125	6	4.6

[/] Fetuses with malformations excluded

3. On oral teratological study in rats.

Performed by

November 4-December 9, 1981.

Animals: Sprague-Dawley rats (OFA, CD-IOPs caw), 10 weeks-old, weight 229 gm.

No. of animal/dosage: 25-26

Route and duration of administration: orally by gavage the compound (in dist. water) from Day 6-Day 15 of gestation.

Dosage level:

- (1) Control: water
- (2) Low: 8 mg/kg/day
- (3) Mid: 25
- (4) High: 75
- (5) Highest: 225

Results:

(A) Maternal data:

- (a) Mortality: 8 deaths (1 F from 75 mg/kg and 2 F from 225 mg/kg were considered accidental deaths due to tracheal intubation; 5 F from 225 mg/kg died of toxic effects of drug. Blood on the muzzle and respiratory difficulties, reduced body weight gains were observed before deaths). Autopsy revealed flatulence in most deaths.
- (b) Clinical signs:
 - Hair losses: in 8 and 75 mg/kg/day rats
 - Respiratory difficulties: in 75 and 225 mg/kg/day rats.
 - Arched back, nervousness and difficult to handle: 225 mg/kg/day rats.
- (c) Body weight and food consumption: weight gains and food consumption were suppressed only in 225 mg/kg/day rat.
- (d) Pregnancy rate: comparable among groups.
- (e) No macroscopic abnormalities were observed.

(B) Litter Data:

(a) Pre- and post-implantation losses:

Although not statistically significant, both pre- and post-implantation losses (%) were considerably higher at 225 mg/kg level, mainly due to 4 litters.

(b) Fetal weight:

Mean fetal weights were significantly lower in 8, 75 and 225 mg/kg groups, but may not be biologically significant because of the nominal values. More runts at 225 mg/kg.

(c) Malformations: Unremarkable

One fetus from 8 mg/kg group had major anomalies (absence of jaw with eyes and ears displaced). This fetus also had major visceral anomaly (left microphthalmia) and lower body weight. Another pup from 225 mg/kg had left microphthalmia and lower body weight.

(d) Visceral anomalies: Unremarkable.

Visceral minor anomalies (increased renal pelvic cavitation, uni- or bilateral with papilla present) were found in control and dose groups. Hypertrophy of one or both kidneys with or without hemorrhage/slightly external or medial displacement of kidney were observed in 3 fetuses of 8 mg/kg, 1 fetus of 25 mg/kg, 2 fetuses of 225 mg/kg.

(e) Skeletal anomalies/variants:

Skeletal minor anomalies (retarded ossification of isolated bones of the skull-parietal, interparietal or multiple-bone-, sternbrae-bipartite or irregular, thoracic or caudal vertebrae-reduced or unossified) were higher in 25, 75 and 225 mg/kg groups with no dose-related effect. Pronounced retardation of ossification were observed in 2 pups of 2 litters from 75 mg/kg groups and 7 pups of 1 litter from 225 mg/kg group.

Segment V - rat

TABLE VI

litter data - means per litter

Compound Dose (mg/kg/ day)	Mr of pregn. females	I graids	Mean	Nr of litters consid.	Corpora lutea	Implan- tations	Live foetus.	Dead foetus.	Early resorpt.	Late resorpt.	Mean total loss	Pre- implant loss	Post- implant loss	foetal weight (g)		Placental weight (g)	
														Mean litter (1)	Mean foetal (2)	Mean litter (1)	Mean foetal (2)
Control	26/26	100	A - B	26	18.4	14.4	13.4	0	0.92	0.08	1.00	19.55	6.94	51.33	3.82	7.29	0.54
PO11 B	23/25	92	A - B	23	19.0	14.5	13.7	0	0.65	0.09	0.74	21.31	4.98	51.20	3.73	7.28	0.53
PO11 25	23/25	92	A	23	17.4	12.5	11.6	0	0.65	0.22	0.87	24.43	11.19	44.78	3.86	6.55	0.54
PO11 75	22/26	84.62	A - B	21	16.7	13.0	12.1	0	0.68	0.18	0.86	21.13	7.15	53.20	3.89	7.33	0.54
PO11 225	25/26	96.15	A - B	17	17.4	14.3	13.7	0	0.48	0.14	0.62	16.40	4.37	44.59	3.72	6.63	0.55

Comparison of means : each group versus control by two-sample : Wilcoxon test (1)
Student t test (2)

Segment II : rat

Table VII

Group mean incidence of major and minor anomalies - Summary.

Doses	Nr of foetus and litters														
	Total nr of foetuses examined		Major malformations						Minor anomalies (x)						
			Wilson sl.			Skeletal ex.			Wilson sl.			skeletal variants			
	W. (i)	S. (ii)	Total malf. (1)	Nr litter (2)	Mean % (3)	Total malf. (1)	Nr litter (2)	Mean % (3)	Total anom. (1)	Nr litter (2) (b)	Mean % (3)(a)	Total anom. (1)	Nr litter (2) (b)	Mean % (3) (a)	
Control	176	173	0	0/26	0	0	0/26	0	18	12/26	10,1	12	10/26	6,8	
PO71 8 mg/kg	158	158	1	1/23	0,9	0	0/23	0	31	16/23 NS	19,6 NS	16	10/23 NS	9,6 NS	
PO71 15 mg/kg	136	131	0	0/22	0	0	0/22	0	17	12/22 NS	11,5 NS	17	11/22 NS	17,9 NS	
PO71 15 mg/kg	141	146	0	0/21	0	0	0/21	0	30	15/21 NS	20,7 0	22	13/21 NS	14,5 NS	
PO71 225 mg/kg	102	102	1	1/17	0,8	0	0/17	0	15	7/17 NS	14,4 NS	18	9/17 NS	17,2 NS	

(i) Wilson' technique = W

(ii) Skeletal examination = S

(1) Number of foetuses presenting malformations or anomalies.

(2) Number of litters affected versus number of litters examined.

(3) Mean of percentages of foetuses affected per litter per group.

(a) Comparison of means : each group versus control group by two-sample : Wilcoxon test.

(b) Comparison between treated group and control is made with a Chi² test.

(x) Foetuses showing major malformations excluded.

4. Oral teratological study in rabbits: (T-25)

Performed by March 9, 1982-April 20, 1982

Animals: New Zealand White rabbits, 6 months old, 3.5 kg.

No. of animals/group: 14-18 females

Route and duration of administration:

orally by gavage the compound (in dist. water) from Day 6-Day 18 of pregnancy.

Dosage levels: mg/kg/day

(1) Control:	water	(17 rabbits)
(2) Low	15 mg/kg	(16 rabbits)
(3) Mid	45	(16 rabbits)
(4) High	135	(18 rabbits)
(5) Positive control:	150 mg/kg/day thalidomide (as 0.5% of methylcellulose suspension).	(14 rabbits).

Results:

(A) Maternal data:

(a) Mortality: 3 (1 control and 2 high dose rabbits).

One control and one high dose females were sacrificed on Day 15-17 of pregnancy. Autopsy revealed tracheal intubation as cause of death. Another high dose rabbit was found dead on Day 9. Tracheal intubation was also the cause of death. These 3 rabbits were not included in calculations.

(b) clinical signs: none reported.

(c) Body weight and food consumption:

During the treatment, only high dose group showed suppressed weight gains (~23%) than control group. After the treatment period, all 3 dosed groups showed lower weight gains. Thalidomide showed an 80% lower weight gains during this period. Food consumption (by visual inspection only) showed decreases in some control and treated rabbits.

(d) Pregnancy rate: comparable among groups.

(e) No macroscopic abnormalities were observed in dams.

(B) Litter data:

(a) Pre- and post-implantation losses:

No significant findings were observed up to 135 mg/kg level, whereas significant post-implantation losses were seen in thalidomide group which had fewer live fetuses.

(b) Fetal weight: both fetal and placental weights were lower in thalidomide group only.

(c) Malformations: unremarkable (none in control group, 2 fetuses from 15 mg/kg, 2 fetuses from 45 mg/kg and 1 fetus from 135 mg/kg groups).

These anomalies included internal hydrocephaly, meningocele, microcephaly, failure of development of the frontal and parietal bones, kidneys smaller or missing descending tubules in medulla or hydronephrosis. In the thalidomide group, in addition to the aforementioned anomalies, missing digits, fibula reduced to a trace, absences of talus, malrotation of limbs, reduced caudal vertebrae and agenesis of kidneys were observed in 50% of litters.

(d) Visceral anomalies: Unremarkable.

(e) Skeletal anomalies/variants:

These included 4th and 5th sternbrae fused, reduced ossification in control, 15 and 45 mg/kg groups. At 135 mg/kg, in addition to the aforementioned skeletal anomalies, fontantella very enlarged, sternbrae irregular were also observed. Higher incidences of skeletal minor anomalies were observed at 135 mg/kg level and thalidomide group.

TABLE V

Litter data : mean per litter

Compound & doses mg/kg/day	Nr of pregnant females	% of pregnancy	Nr of litters	Mean	Corpora lutea	Implantations	Live foetus	Dead foetus	Early resorpt	Late resorpt	Mean total loss	Pre-implant loss	Post-implant loss	foetal weight			Placental weight		
														Mean by group of litter weight	Mean by group of individual foetal weight	Mean by group of the mean by litter of foetal weight	Mean by group of placental litter weight	Mean by group of the individual placental weight	Mean by group of the mean by litter of placental weight
Control	17/17	100	16	A-B	12.3	9.4	8.1 (1)	0	0.94 (1)	0.38 (1)	1.31 (1)	19.97	14.02 (1)	352.08 (1)	43.33 (2)	43.86 (1)	50.55 (1)	6.22 (2)	6.25 (1)
FD71 15	16/16	100	16	A-B	11.7	8.6	7.8 NS	0.06	0.44 NS	0.38 NS	0.81 NS	23.74	10.02 NS	342.08 NS	44.14 NS	45.30 NS	48.29 NS	6.23 NS	6.41 NS
FD71 45	15/16	93.8	15	A-B	11.7	8.3	8.0 NS	0	0.27 a	0.07 NS	0.33 aa	28.39	3.81 aa	336.34 NS	41.37 a	42.70 NS	45.95 NS	5.74 aa	5.86 NS
FD71 135	15/18	88.9	14	A-B	11.9	9.1	8.1 NS	0	0.57 NS	0.16 NS	0.93 NS	21.62	9.26 NS	343.61 NS	42.20 NS	43.46 NS	48.50 NS	5.96 NS	6.17 NS
Insulin 150	13/16	92.9	17	A-B	11.1	9.7	5.5 aa	0.08	2.54 NS	1.62 ?	4.15 aa	12.06 ?	44.87 aa	219.07 a	40.11 aa	40.27 a	30.63 ?	3.61 aa	5.69 NS

Regression analysis : analysis of variance for regression

Control versus treated	NS	a	NS	aa	NS	NS	NS	NS
Linearity	NS	NS	NS	NS	NS	NS	NS	NS
Around linearity	NS	NS	NS	?	a	NS	NS	NS

Comparison of means : each group versus control by two-sample Wilcoxon test (1)

Student t test(2)

TABLE VI

Group mean incidence of major malformations and minor anomalies - Summary

Compound and doses (mg/kg/day)	Number of foetuses and number of litters									
	Total number of foetuses examined	Major malformations			Minor anomalies (a)					
		Nr of foetuses with (2)	Mean % per litter (1)	Nr of litters with (2)	Gross autopsy			Skeletal examination		
					Nr of foetuses with (2)	Mean % per litter (1)	Nr of litter with (2)	Nr of foetuses with (2)	Mean % per litter (1)	Nr of litter with (2)
Control	130	0	0	0/16	0	0	0/16	5	3.6	3/16
ucb P071 15	124	(b) 2 NS	2.1 NS	1/16	0	0	0/16 NS	4	3.8 NS	3/16 NS
ucb P071 45	120	2 NS	1.7 NS	2/15 NS	1 NS	0.8 NS	1/15 NS	4 NS	2.9 NS	3/15 NS
ucb P071 135	114	1 NS	0.7 NS	1/14 NS	0	0	0/14 NS	14 ■	10.9 NS	7/14 ■
Thalidomide 150	71	(b) 34 ■■■	50.5 ■■	11/13 ■■	3 ■	4.10 NS	2/13 NS	20 ■■■	26.8 ■■	10/13 ■■

(a) Foetus showing major malformations excluded

(b) 1 dead foetus excluded (see table IV)

Comparison of means : each group versus control : - Wilcoxon test (1)
- (Chi)² test (2)

(5) Segment III Reproduction Study: Peri- and post-natal reproduction study
in mouse. (T-28)

Performed by:

September 15 - October 12, 1984

Animals: Mice (CrL.: COBS CD-1 (ICR) BR strain), from Charles River
U.K. Ltd. Margate, Kent.

Route and duration of administration:

Orally by gastric intubation from Day 15 of pregnancy to Day 21 postpartum.

No. of animals/group: 32 F/group

Dosage levels: (0.1 ml/10gm)

- (1) Control: distilled water
- (2) Low: 6 mg/kg/day
- (3) Mid: 24 mg/kg/day
- (4) High: 96 mg/kg/day

Results:

Maternal data:

Mortality: None

Body weight and signs:

Reduced body weight and food consumption were observed at 96 mg/kg level
during postpartum.

No unusual signs observed.

Necropsy:

Significant increase of liver weight (absolute and relative) at 96 mg/kg
level.

Pregnancy: comparable among groups (91%-97%)

Labor: Not commented on.

Nursing performance:

Judging from lower pup weight gain from Day 4 postpartum to weaning,
nursing performance was probably affected at 96 mg/kg.

Length of gestation: No significant effect.

Necropsy: Unremarkable

Liver: weight increase at 96 mg/kg.

Kidneys: no effect.

Litter data:

Litter size: Comparable among 4 groups

Survival: No significant difference among 4 groups.

Pre-weaning development: surface and air righting reflex were comparable among 4 groups. Startle response: Statistically delayed from 24 mg/kg level, but not of biological significance because of marginal differences.

Sex ratio:

Lower M/F ratio observed at 96 mg/kg level at birth and weaning.

Body weight:

From Day 4 postpartum to weaning on Day 21:
Significantly lower pup weight at 96 mg/kg level only.

Anomaly: None reported; cold pups were noted in 2 litters (24 mg/kg) and 3 litters (96 mg/kg) and none in control and low groups.

Liver and kidney weight (1 M and 1 F pups per litter for these organ weight data): no significant findings.

V. GENETIC TOXICOLOGY STUDIES

Summary of mutagenicity testings

: (1), (2) and (4)
(3)

Tests	(1) Ames	(2) Clastogenic Activity Assay	(3) Forward Mutation Assay	(4) Micronucleus test
Study No.	T-29	T-30	T-31	T-32
Date	March, 1982	March-May, 1982	1986	July-Sept. 1982
Strains/Cells	Salmonella typhimurium TA 1535, 1537, 1538 TA 98 and 100	Human peripheral lymphocytes	mouse lymphoma L5178Y cells	mice 10(5M +5F)
Positive control	yes	cyclophosphamide	yes	Chlorambucil 30 mg/kg/day
Solvent	water	water	water	water
Conc. or dosages	5, 50, 500 and 5,000 ug/plate (+ S-9 mix)	20, 100 500 ug/ml (+ S-9)	260-420 (-S-9) 150-300 (+S-9) (ug/ml)	14, 70 and 350 mg/kg day P.O. for 2 days
Cytotox. positive@	5000 ug/pl	500 ug/ml	420 (-S-9) 300 (+S-9)	
Results	No increase of revertants (+9-S)	no damage to chromosomal structure	no increase of mutant frequency	N/A no increase of micronuclei (+ S-9)
Remarks	Negative	Negative	Negative	Negative

V. ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION:Table 1. Pharmacokinetics of Cetirizine in Animals (10 mg/kg) and in Man (10 mg)¹

Parameter	Mouse		Rat		Rabbit		Dog	Monkey	Man
	M	F	M	F	M	F	(M&F)	(M&F)	(M)
C _{max} (mcg/ml)	11.6	11.3	1.6	4.2	13.6 ²	13.4 ²	18.6	8.3	0.7
T _{max} (hr)	0.7	0.7	0.5	0.5	0.7	0.7	3.0	1.3	1.0
AUC (hr.mcg/ml)	65.4	52.3	-	-	29.0 ²	35.0 ²	334.0	23.8	3.0
Half-Life (hr)	3.5	3.0	0.5 ⁴	0.7 ⁴	1.9	2.8	10.0	1.4 ⁴	8.0
Urinary Excretion of unchanged cetirizine (% dose) ⁵	24.1	29.8	1.5	9.6	60.7	65.8	34.2 ⁶	35.0	60.0
NDA Report No.	NPK-1		NPK-5		NPK-12		NPK-13	NPK-21	CPK-1.

¹ Mean data of 2-10 animals, or 35 human subjects in 2 single dose bioequivalence studies, expressed as the dihydrochloride salt.

² Adjusted to 10 mg/kg.

³ Calculated for 10 mg/kg (based on 50 kg man) C_{max} = 20 and AUC = 170.

⁴ Determined after IV administration.

⁵ 72 hours;

⁶ 96 hours.

⁷ Mean daily excretion of unchanged cetirizine from multiple dose study; no excretion data was collected in the bioequivalence studies.

TABLE I. PHARMACOKINETIC STUDY DATA SUMMARY IN ANIMAL SPECIES

SITES/ STRAIN	NDA REFERENCE (M)	DOSE (mg/kg)	ROUTE OF ADMINISTRATION	NUMBER OF ANIMALS	Cmax (mcg/ml)		Tmax (hr)		PARAMETERS T _{1/2} (hr)		AUC (mcg·hr/ml)		Bioavailability (%)
					M	F	M	F	M	F	M	F	
Dog/ Beagle	NPK-1	10	IV	10	11.4	11.3	0.67	0.67	2.8	3.1	61.7	57.3	106
		10	PO	216					3.5	3.0	65.6	52.3	
Rat/ Wistar	NPK-3	10	IV	7	17.0	26.9							36
		10	PO	60	1.6	0.2	0.3	0.3	0.3	0.7			
Cat/ New Zealand	NPK-12	1	PO	6	1.4	1.3	0.67	0.67	1.9	2.8	2.9	3.3	53
		1	IV	4					1.0	1.3	3.2	3.2	
		15	PO	6	16.0	10.3	1.0	1.0	2.4	2.2			
		65	PO	5	30.2	63.7	1.3	1.0	1.3	1.6			
		135	PO	6	169.4	167.8	3.0	1.3	3.3	3.0			
Dog/ Beagle	NPK-13	1	IV	8					8.6				103
		10	IV	8	2.7		2		7.7				
			IV	9	18.6		3		9.3				
			PO	4					10				
Dog/ Beagle	NPK-19	0.6	PO	9	1.67	1.93	1.34	2.38	8.2	7.9			273
		0.6 x 9 days	PO	3	1.80	1.58	1.08	1.50	11.5	10.3			
Dog/ Beagle	NPK-15	10	PO	3	29.6		1.3		9.9				273
			PO	2	0.5	0.3	2	0.3					
			IV	2	5.8	6.1	0.5	0.5	1.2	1.3	2.1	1.6	
			IV	2					1.7	1.4	68.0	33.7	
Monkey/ Cynomolgus	NPK-21	1	PO	2	0.8	0.9	1	2			2.9	2.8	26.6
		1	IV	2					1.0	1.5	3.3	2.8	
		10	PO	2	6.8	9.7	2	0.3			26.6	23.3	
		10	IV	2					1.3	1.5	46.3	31.1	

* Determined from urinary excretion of cetirizine.
 ** - Numbers in center of column indicate combined M&F results.
 *** Results of individual animal.
 **** - AUC (16 hr)
 ***** - AUC (48 hr)
 ***** - AUC (26 hr)
 ***** - AUC (12 hr)

TABLE 2. EXCRETION OF CETIRIZINE IN DIFFERENT ANIMAL SPECIES

Species/ Strain	NDA Report No.	Dose (mg/kg)	Route of Administration	Sampling Time (hr)	Total Amount Excreted (% dose Cetirizine)			
					Urine		Feces	
					Male	Female	Male	Female
Mouse/NMRI	NPK-1	10	IV	0-72	31.8	36.2		
		10	PO	0-72	24.1	29.8		
Mouse/OFF SPF	NPK-2	10	IV	0-96	41.5*	53.8*	66.3*	43.2*
		10	PO	0-96	36.5*	57.6*	59.8*	46.4*
Rat/Wistar	NPK-5	10	IV	0-72	4.1	20.8		
		10	PO	0-72	1.5	9.6		
Rat/ Sprague Dawley	NPK-6	1	IV	0-96	11.8*	21.6*	79.1*	76.6*
		5	PO	0-96	16.4*	25.8*	82.6*	71.6*
		25	PO	0-96	15.4*	41.1*	73.2*	53.0*
		75	PO	0-96	20.0*	52.8*	64.6*	43.2*
Rat/ Sprague Dawley	NPK-8	1	PO	0-8	4.4*		5.9*	
		10	PO	0-24	5.3*		64.8*	
		100	PO	0-48	23.8*		64.6*	
Rat/ Sprague Dawley	NPK-9	25	PO	0-24	1.5	17.9		
		75	PO	0-24	11.5	22.5		
		225	PO	0-24	17.4	23.5		
		25 x 1 month	PO	0-24	5.8	20.6		
		75 x 1 month	PO	0-24	20.8	22.0		
		225 x 1 month	PO	0-24	16.3	32.7		

TABLE 2. (Cont.) EXCRETION OF CETIRIZINE IN DIFFERENT ANIMAL SPECIES

Species/ Strain	NDA Report No.	Dose (mg/kg)	Route of Administration	Sampling Time (hr)	Total Amount Excreted (% dose Cetirizine)			
					Urine		Feces	
					Male	Female	Male	Female
Rat/ Sprague Dawley	NPK-11	8	PO	Day 1				
				0-24	0.6	5.6		
				0-24	6.9	10.5		
		25	PO	0-24	15.3	21.6		
				0-24				
				0-24				
		75	PO	Day 9				
				0-24	0.6	11.8		
				0-24	2.9	14.2		
	75	PO	0-24	14.2	14.1			
			0-24					
			0-24					
	8	PO	Day 43					
			0-24	0.4	8.9			
			0-24	6.8	15.0			
0-24			10.3	22.2				
0-24								
0-24								
25	PO	Day 180						
		0-24	1.4	12.7				
		0-24	9.8	19.5				
		0-24	19.4	19.8				
		0-24						
		0-24						
75	PO	0-72	60.7	65.8				
		0-72	46.7	64.7				
		0-72	49.1	69.3				
		0-72	62.4	76.4				
		0-72	51.2	71.0				
		0-72						
Rabbit/ New Zealand	NPK-12	1	PO					
		i	IV					
		15	PO					
		45	PO					
		135	PO					

TABLE 2. (Cont.) EXCRETION OF CETIRIZINE IN DIFFERENT ANIMAL SPECIES

Species/ Strain	NDA Report No.	Dose (mg/kg)	Route of Administration	Sampling Time (hr)	Total Amount Excreted (% dose Cetirizine)			
					Urine		Feces	
					Male	Female	Male	Female
Dog/Beagle	NPK-13	1	IV	0-96	25.7			
		1	PO	0-96	27.3			
		10	IV	0-96	31.9			
		10	PO	0-96	34.2			
Dog/Beagle	NPK-14	0.6 x 9 days	PO	Day 1	25.6*		6.6*	
				2	37.5*		30.4*	
				3	35.3*		45.2*	
				4	38.1*		31.3*	
				5	42.5*		53.0*	
				6	41.0*		55.8*	
				7	40.9*		41.7*	
				8	38.7*		68.0*	
Dog/Beagle	NPK-15	10	PO	0-120	40.1*		55.7*	
Dog/Beagle	NPK-17	15	PO	Day 22 0-24	23.5			
		45	PO	0-24	31.0			
		135	PO	0-24	32.3			

TABLE 2. (Cont.) EXCRETION OF CETIRIZINE IN DIFFERENT ANIMAL SPECIES

Species/ Strain	NDA Report No.	Dose (mg/kg)	Route of Administration	Sampling Time (hr)	Total Amount Excreted (% dose Cetirizine)									
					Urine		Feces							
					Male	Female	Male	Female						
Dog/Beagle	NPK-18	8	PO	Day 1 0-24	16.2									
					25	PO	0-24	19.8						
								75	PO	0-24	17.1			
		8	PO	Day 9 0-24							32.3			
					25	PO	0-24				27.4			
								75	PO	0-24	34.5			
		8	PO	Day 43 0-24							33.9			
					25	PO	0-24				34.8			
								75	PO	0-24	43.8			
		8	PO	Day 180 0-24							45.2			
					25	PO	0-24				37.0			
								75	PO	0-24	41.2			
		Baboon/Papio Spp.	NPK-20	1							PO	0-72	34.5	
					1	IV	0-72						26.9	
								10	PO	0-72			29.0	
10	IV												0-72	35.5
		1	PO	0-72							37.3			
					1	IV	0-72				39.3			
								10	PO	0-72	35.0			
10	IV										0-72	19.7		

TABLE 2. (Cont.) EXCRETION OF CETIRIZINE IN DIFFERENT ANIMAL SPECIES

Species/ Strain	NDA Report No.	Dose (mg/kg)	Route of Administration	Sampling Time (hr)	Total Amount Excreted (% dose Cetirizine)				
					Urine		Feces		
					Male	Female	Male	Female	
Monkey/Cynomolgus	NPK-23			Day 1					
		17	PO	0-24	28.9				
		50	PO	0-24	29.6				
		150	PO	0-24	31.5				
				Day 9					
		17	PO	0-24	38.2				
		50	PO	0-24	25.0				
		150	PO	0-24	32.4				
				Day 28					
		17	PO	0-24	29.5				
		50	PO	0-24	25.8				
		150	PO	0-24	37.6				
Monkey/Cynomolgus	NPK-24	5	PO	0-24	32.5				
		15	PO	0-24	26.1				
		45	PO	0-24	28.6				

* = Percentage of Dose of Radioactivity Excreted

TABLE 2. METABOLIC PROFILE OF CLITIZINE IN DEFICIENT ANIMALS

Species/ Strain	NDA Report # No.	Dose (mg/kg)	Route of Administration	Biological Fluid	Sampling Time (hr)	Clitizine (%)		Radioactivity (% of Dose)		Other									
						Male	Female	Male	Female										
Mouse/NRRI	NPK-1	10	IV	Urine	0-72	31.8	36.2	1.3	1.2										
											24.1	29.8	3.9	2.3					
Mouse/OF1 SPF	NPK-2	10	IV	Plasma	0-033	23.3	27.6	N.D.*	N.D.										
												0-083	16.7	12.9	N.D.	N.D.			
												0-167	14.0	17.2	N.D.	N.D.			
												0-3	10.8	13.3	0.11	N.D.			
												1	9.6	9.8	0.30	N.D.			
												2	5.3	6.3	0.37	0.15			
												4	6.2	2.7	0.59	0.63			
												6	3.7	1.9	0.49	0.29			
												8	2.5	1.7	0.66	0.50			
												16	0.20	N.D.	N.D.	N.D.			
												0-96	23.6	40.3	1.8	1.0			
0-96	19.6	46.5	1.5	1.1															
Rat/ Sprague Dawley	NPK-8	1	PO	Plasma*	1	57	5	3	N.D.		38								
												4	85	6	5				
												8	86	3	11				
												24	87	3	8				
												72	73	13	12				
												1	93	2	5				
												4	87	3	10				
												8	90	5	5				
												12	77	8	13				
												24	80	9	11				
												0-8	0.1	0.1	N.D.	6.2			
												10	PO	Urine	0-12	0.1	0.1	0.1	3.7
												100	PO	Urine	0-8	11.9	0.1	1.5	2.9
0-24	33.7	6.1	1.5																
0-48	23.0	0.3	6.0																
1	PO	Feces	0-8	0.4	0.4	1.6	3.7												
10	PO	Feces	0-12	3.0	3.7	33.6													
							0-24	13.9	3.4	35.9									
100	PO	Feces	0-12	2.9	6.3	23.4													
							0-24	6.6	6.8										
							0-48	13.7	5.8										

TABLE 3. (Cont.) METABOLIC PROFILE OF CETIRIZINE IN DIFFERENT ANIMALS

Species/ Strain	NDA Report No.	Dose (mg/kg)	Route of Administration	Biological Fluid	Sampling Time (hr)	Radioactivity (% of Dose)							
						Cetirizine		POZ6		Other			
						Male	Female	Male	Female	Male	Female		
Dog/Beagle	NPK-14	0.6	PO	Urine	Day 1	20.3		0.22					
					Day 2	32.8		0.43					
					Day 3	28.0		0.32					
					Day 4	23.1		0.43					
					Day 5	33.2		0.48					
					Day 6	30.6		0.40					
					Day 7	31.7		0.36					
					Day 8	30.0		0.52					
Dog/Beagle	NPK-15	10	PO	Urine	0-48	31.5		0		7.9			
				Feces	0-48	27.4		4.8		20.0			
Dog/Beagle	NPK-18	8	PO	Plasma	Day 1								
					1.5	22.9		0.13					
					4	26.6		0.21					
					8	12.1		0.30					
					24	4.9		0.24					
					25	PO	Plasma	1.5	64.5		0.06		
								4	69.2		0.28		
								8	37.9		0.64		
								24	18.4		0.62		
					75	PO	Plasma	1.5	105.5		0.52		
								4	127.1		0.79		
								8	83.9		1.34		
		24	52.1					2.18					
		8	PO	Plasma	Day 180								
					0	13.6		0.77					
					1.5	37.1		0.82					
					4	35.4		0.97					
					8	20.6		1.13					
					24	9.9		0.74					
					25	PO	Plasma	0	32.7		1.83		
								1.5	82.3		1.75		
		4	89.3					2.27					
		8	58.2					1.66					
		75	PO	Plasma	0	60.1		1.54					
1.5	32.7					1.83							
4	82.3					1.75							
8	58.2					1.66							
8	PO	Plasma	0	95.4		5.76							
			1.5	183.2		8.97							
			4	217.9		8.37							
			8	144.6		7.10							
75	PO	Plasma	0	90.0		4.94							
			1.5	183.2		8.97							
			4	217.9		8.37							
			8	144.6		7.10							

* ND = none detected * Data expressed as % sample radioactivity

TABLE 2. TISSUE DISTRIBUTION OF RADIOACTIVITY AFTER ADMINISTRATION OF INC-CETIRIZINE

SPECIES/ STRAIN	NDA REINVENT NO.	DOSE (mg/kg)	ROUTE OF ADMINISTRATION	SAMPLING TIME (hr)	PLASMA		LIVER		LUNG		KIDNEY		BRAIN					
					M	F	M	F	M	F	M	F	M	F				
Mouse/ OF1 SIF	NPK-2	10	IV	0.033	25.7	28.7	66.3	37.3										
				0.083	22.3	20.4	97.3	31.8										
				0.167	16.7	18.2	38.3	34.6										
				0.3	42.4	14.1	34.6	30.2										
				1	11.1	10.4	23.2	21.1										
				2	6.4	7.0	21.6	19.1										
				3	3.8	3.7	22.3	10.3										
				6	3.0	2.9	14.6	8.3										
				8	0.0	2.8	11.9	8.8										
				16	0.3	0.2	1.6	0.6										
				Rat/ Sprague Dawley	NPK-6	1	PO	1	0.033	0.133	0.779	1.882	0.081	0.167	0.237	0.803	0.003	4.012
								2	0.069	0.031	0.763	0.703	0.044	0.082	0.364	0.232	0.004	0.011
								4	0.096	0.030	0.987	0.333	0.031	0.674	0.317	0.232	0.009	0.317
								8	0.066	0.032	0.734	0.181	0.19	0.010	0.082	0.003	0.001	0.004
								24	0.028	0.019	0.083	0.040	0.009	0.240	0.034	0.001	0.001	0.003
								1	0.210	-	1.93	-	0.10	-	0.693	-	0.909	-
2	0.140	0.074	1.13					0.747	0.080	0.103	0.424	0.393	0.008	0.012				
4	0.161	0.077	0.99					0.494	0.096	0.069	0.421	0.324	0.007	0.004				
8	0.118	0.046	0.67					0.316	0.033	0.079	0.213	0.145	0.006	0.010				
24	0.073	0.028	0.26					0.081	0.034	0.931	0.143	0.093	0.004	0.004				
Rat/ Sprague Dawley	NPK-8	1	PO					1	0.03	4.43*			0.02*	0.36*				
								4	0.27	28.0*			0.43*	1.24*				
								8	0.04	0.9*			0.01*	0.09*				
								1	1.03	21.0*			0.14*	1.17*				
								4	0.21	1.7*			0.23*	0.43*				
								8	1.30	9.1*			0.23*	0.38*				
				12	0.26	0.6*			0.01*	0.03*								
				24	0.34	2.6*			0.03*	0.17*								
				Rat/ Sprague Dawley	NPK-3	100	PO	1	0.9	16.2*			0.74*	2.03*				
								4	20.0	8.3*			0.22*	1.02*				
								8	11.1	3.6*			0.23*	0.49*				
								12	2.9	1.7*			0.08*	0.15*				
								24	2.7	2.3*			0.10*	0.18*				
								48	0.8	0.7*			0.01*	0.03*				

TABLE 9. (Cont.) TISSUE DISTRIBUTION OF RADIOACTIVITY
AFTER ADMINISTRATION OF 14C-CETIRIZINE

SPECIES/ STAIN	NDA REPORT NO.	DOSE (mg/kg)	ROUTE OF ADMINISTRATION	SAMPLING TIME (hr)	PLASMA		LIVER		LUNG		KIDNEY		BLZ	
					M	F	M	F	M	F	M	F	M	F
Rabbit/ New Zealand	NFK 12	1	PO	0.67	1.06	0.12	0.63	6.00	0.01					
				3	0.36	1.01	0.33	1.93	0.02					
				6	0.37	0.85	0.36	1.93	0.03					
				26	0.03	0.34	0.04	0.66	0.01					
Dog/ Beagle	NFK-18	1 (pregnant)	PO	0.67	0.21	1.91	0.19	1.48	0.01	0.01	0.01	0.01	0.01	
				3	0.25	1.28	0.33	3.19	0.02	0.02	0.02	0.02		
				6	0.23	0.62	0.25	1.94	0.04	0.04	0.04	0.04		
				26	0.03	0.17	0.03	0.64	0.01	0.01	0.01	0.01		
	NFK-19	0.6	PO	2	2.37	2.71	1.06	1.51	0.27	0.27	0.27	0.27		
				6	1.70	0.73	0.21	0.37	0.27	0.27	0.27	0.27		
				26	0.26	0.33	0.33	0.27	0.26	0.26	0.26	0.26		
				48	0.13	2.37	1.33	2.12	0.54	0.54	0.54	0.54		
NFK-13	0.6 + 9 days	PO	2	1.96	4.18	1.86	2.04	0.54	0.54	0.54	0.54			
			6	0.70	2.12	1.11	0.82	0.38	0.38	0.38	0.38			
			26	0.36	1.51	0.48	1.54	0.27	0.27	0.27	0.27			
			48	0.36	1.51	0.48	1.54	0.27	0.27	0.27	0.27			
Dog/ Beagle	NFK-13	10	PO	6	19.4	23.6	7.0	13.8						
				12	9.7	13.6	6.3	8.7						
				26	3.0	7.6	4.2	6.2						

* = Concentration in mcg eq/ml
% = Percent of Dose

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TABLE 5. IN VITRO PROTEIN BINDING OF CETIRIZINE IN DIFFERENT SPECIES

<u>Species</u>	<u>NDA Report No.</u>	<u>Concentration Range (mcg/ml)</u>	<u>% Protein Bound</u>
Rat/ Sprague Dawley	NPK-6	0.05 - 10	83
Rabbit/ New Zealand	NPK-12	0.02 - 50	94
Dog/Beagle	NPK-14	0.05 - 20	90
Baboon	NPK-20	0.1 - 10.0	85
Monkey/ Cynomolgus	NPK-21	0.1 - 10.0	85

Summary and evaluation:

Cetirizine, code name 7071 and chemically known as 2-(2-(4(4-chlorophenyl)piperidinylmethyl)-1-piperazinyl)-ethoxy-acetic acid dihydrochloride, is to be marketed as an antihistamine (H₁-receptor antagonist). The tablet formulation is indicated for seasonal and perennial allergic rhinitis and chronic idiopathic urticaria. The proposed dosage is 5 to 10 mg a day given as a single dose. The daily dosage, however, may be increased to a maximum of 20 mg if sufficient response has not been obtained. Cetirizine is a member of piperazine class of compounds (diphenylmethane piperazine group) that include cyclizine, chlorcyclizine, meclizine and hydroxyzine. Cetirizine is a human metabolite of hydroxyzine which has been marketed as Atarax by Pfizer for more than 30 years. According to the Applicant, cetirizine possesses less sedating effect than hydroxyzine. Other members of piperazine compounds that are not marketed in this country include cinnarizine (antihistamine), flunarizine (vasodilator) and oxatomide (anti-allergic agent).

The preclinical studies were carried out by

Most of the studies were in compliance with the GLP; some had deviations that should not affect the data interpretation.

Efficacy:

Note: The ED₅₀ values on pages 238-239 are different from those listed under individual studies (e.g. NP-2, NP-4, NP-8, NP-10 on pages 531-5193). The following review is based on the results from individual studies. The applicant will be asked to clarify the discrepancies.

The efficacy as an antihistamine (H₁ receptor antagonist) and anti-allergic agent was demonstrated in various standard tests. These tests included in vivo studies of lethality, bronchospasm and cutaneous reaction induced by histamine, bronchospasm induced by antigen and in vitro studies in guinea pig ileum, guinea pig trachea and human bronchi.

In histamine-induced lethality test, cetirizine was effective at 0.1 mg/kg (po) in the guinea pig-the most sensitive species. The onset was 1 hr and the duration was 12 hrs at this dose. The ED₅₀ value was 0.35 mg/kg (po). In histamine-induced bronchospasm in guinea pigs, cetirizine had ED₅₀ of 0.09 mg/kg (iv) and 0.46 mg/kg (id) and was less potent than clemastine and mepyramine. In histamine-induced cutaneous reaction test, the oral ED₅₀ values were 0.046 mg/kg (mice), 1.9 mg/kg (rat) and 1.8 mg/kg (guinea pig). In dogs the efficacy (50-75%) against histamine- or antigen-cutaneous reaction was observed in 1-2 hr at 0.1-1 mg/kg po and lasted 4-24 hrs. In this test cetirizine was more potent than terfenadine, clemastine, mepyramine and astemizole, but was equally potent as hydroxyzine. In Rhesus monkeys not only the histamine-induced, but also Compound 48/80, Substance P, Vasoactive Intestinal Peptide induced cutaneous reactions were inhibited at 10 mg/monkey (or 10 mg/kg, the exact dose unknown, see p 58 and p 5247, np-13) po at 2 hrs.

The anti-histamine and anti-allergic activities were further shown in antigen-induced bronchospasm tests. Cetirizine was effective in reducing the bronchospasms in passively immunized guinea pigs (ED₅₀ of 0.3 mg/kg po against iv antigen and effective at 4.6 mg/kg po against aerosol antigen). Against iv antigen challenge, cetirizine was equi-potent as hydroxyzine, was more potent than clemastine and terfenadine, but was less potent than mepyramine. Against aerosol antigen challenge, cetirizine was shown to be more potent than either mepyramine or clemastine.

In passively immunized rats (by anti-IgE serum), the bronchospasm was mainly due to the serotonin released from the mast cells on the respiratory smooth muscles of lungs and bronchi. Cetirizine and mepyramine had low efficacy, whereas hydroxyzine was effective. In compound 48/80-induced lethality in rats (both serotonin and histamine were released), cetirizine was highly effective (oral ED₅₀ of 0.14 mg/kg) and hydroxyzine (44 mg/kg po) was not effective.

The data suggested some anti-serotonin activity for cetirizine.

The anti-histamine activity was also demonstrated in in vitro studies such as guinea pig ileum, guinea pig trachea and human bronchi. In guinea pig ileum, cetirizine was less potent than hydroxyzine, terfenadine, mepyramine and clemastine. The specificity as an antihistamine, however, was demonstrated: cetirizine was without significant effect against Ach-, serotonin-, nicotine-induced contractions. The specificity as an antihistamine was also demonstrated in in vivo studies which included evaluating the efficacy against serotonin-, Ach- and histamine-induced bronchospasms in guinea pigs, against Compound 48/80-induced lethality, and serotonin- and histamine-induced cutaneous reactions in rats. It should be noted that some anti-serotonin activity (3-30X less potent than antihistamine activity) was demonstrated in these in vivo tests.

The antihistamine activity was further demonstrated in the histamine-induced hypotension in dogs. Significant reversal of BP were observed at 0.12-1.19 mg/kg (iv) which by themselves did not show cardiovascular effects in anesthetized dogs. But contrary to the findings in rats, no antiserotonin activity was demonstrated in dogs: the serotonin-induced hypertension was not affected.

The high potency as antihistamine was demonstrated in the isolated H₁ receptor preparations. Cetirizine bound to H₁ receptors from the brain and the lung of the guinea pig with as high affinity as terfenadine. But hydroxyzine, a sedating antihistamine, showed higher affinity (6-10X) than either cetirizine or terfenadine in this test. Although in isolated H₁ receptors, cetirizine showed equally high affinity for both brain and lung preparations, the penetration through the blood brain barrier following systemic administration, nonetheless, was low.

In in vivo mouse study following 10 mg/kg ip, cetirizine penetrated through the blood brain barrier to less extent than those of chlorpheniramine and hydroxyzine (10% occupancy of brain H₁ receptor by cetirizine vs 85% occupancy by either chlorpheniramine or hydroxyzine): one of the bases for cetirizine as less sedating antihistamine. In another mouse study, the ratio of oral ED₅₀'s (3.9 mg/kg for inhibiting brain H₁ receptor binding vs 0.4 mg/kg for antihistamine skin reaction) showed better separation for cetirizine than for terfenadine or mepyramine. Pharmacokinetic studies also showed low concentrations in the brains of rats and dogs following either single or chronic administration.

In in vitro preparations isolated from guinea pig brain, no significant activity against serotonin, dopamine, alpha-1 adrenergic, muscarinic receptors and calcium channel was observed; some of these receptors may involve in the sedating effect of antihistamines.

No effect on anti-IgE-mediator release from human basophils was observed; higher doses caused mediators release due to cytotoxicity.

Thus the efficacy as an anti-histamine and anti-allergic agent acting through a mechanism of an H₁ receptor antagonist was demonstrated in the standard preclinical tests. Although the potency of cetirizine varied with the tests, cetirizine was shown to be more potent than hydroxyzine, terfenadine, clemastine and mepyramine in many of the tests where comparison drugs were included. Following oral administration the onset was generally observed in 1 hr and the duration is dose-dependent ranging from 4-24 hrs.

Neuropharmacology

The effects on CNS were evaluated in behavior, interaction and EEG studies.

The behavioral studies included general behavior studies in mice and rats, spontaneous exploratory activity and habituation to a new environment in rats, learning and retention of passive avoidance in rats, conditioned responses in dogs and retention and extinction of a conditioned food response in rats.

The general behavior studies showed no effects in mice at 45 mg/kg (ip & po) and in rats at 4.6 mg/kg (ip) or at 138 mg/kg (po). Sedation was observed at high doses of 92 mg/kg (ip) and at 138 mg/kg (po) in mice and at 46 mg/kg (ip) and 461 mg/kg (po) in rats. Deaths following stimulation and/or depression of CNS occurred at even higher doses: 138-462 mg/kg (ip) and 462-1384 mg/kg (po) in mice and 92 mg/kg (ip) and 462-923 mg/kg (po) in rats. In mice comparison was made following intraperitoneal administration of mepyramine and terfenadine. Mepyramine was without effect at 1 mg/kg and was stimulating/depressing at 3-96 mg/kg; terfenadine was without effect at 14 mg/kg and was stimulating/depressing at 47-141 mg/kg. In rats comparison was made with hydroxyzine only. Hydroxyzine was without effect at 13 mg/kg (ip) and at 48 mg/kg (po), but was sedating at higher doses of 48 mg/kg (ip) and at 134 mg/kg (po). The data suggest that cetirizine is less sedating than hydroxyzine, mepyramine or terfenadine.

No significant effects on learning, perceptive-motor, memory, motor coordination were observed in rats or dogs at 15 to 46 mg/kg (po or ip).

No neuroleptic, anticonvulsant, antiepileptic or interaction with pentobarbital in mice were observed up to 45 mg/kg (ip or po). No interaction with alcohol was observed in rats at 15 mg/kg po. In rabbits EEG study showed sedative effect (decreased durations of arousal at 1.5 mg/kg iv and increased duration of sleep at 46 mg/kg iv) though the arousal to the sound was not affected.

Thus the data showed that cetirizine was less sedating than hydroxyzine, mepyramine and terfenadine. Cetirizine was not shown to possess significant CNS effects, but at high dose cetirizine was also sedating.

Cardiovascular effects:

Both in vivo (rat and dog) and in vitro (rat aorta and perfused heart and guinea pig atrium) studies were carried out.

In anesthetized rats no significant cardiovascular effects were observed at 15 mg/kg (iv). At 26 mg/kg (iv) decreased blood pressure and at 46 mg/kg lethality were observed. In anesthetized dogs, slight increases of heart rate and blood pressure were observed at 15 mg/kg (iv), increased heart rate and decreased respiratory rate were observed at 15 mg/kg (id). ECG changes (conduction block) and decreased blood pressure were observed at sublethal cumulative doses of 67 mg/kg iv or 670 mg/kg id in dogs. In conscious dogs increased heart rate and blood pressure were observed at 12 mg/kg (iv), but no effect on ECG was observed. No modulation effects on the muscarinic, adrenergic (alpha and beta) receptors of the heart, no vagolytic, arrhythmic-inducing or inhibiting activities were observed.

The data therefore showed that cardiovascular effects were minimal. In dogs at 15 mg/kg (iv or id) some 10-20% increases of heart rate and blood pressure were observed. Sublethal doses caused conduction block and decreased blood pressure.

H₂ receptor activity:

No significant H₂ receptor activity was demonstrated. The conclusion was based on the results obtained from both in vivo (stress-induced ulcer in rats at 50 mg/kg po) and in vitro studies (rat aorta, atrium and heart preparations and isolated membrane preparation from guinea pig brain).

Anticholinergic activity:

In mice no mydriasis was observed at 138 mg/kg (po) or at 46 mg/kg (ip); no effects on oxotremorine-induced salivation and tremor was observed at 46 mg/kg (ip).

Thus no significant anticholinergic activity was demonstrated.

Analgesic and local anesthetic activity:

No significant analgesic activity was observed in acetic acid-writhing test in mice up to 92 mg/kg (po) or in tail-flick test in rats up to 138 mg/kg (sc). No local anesthetic activity was observed in corneal reflex test in guinea pigs up to a concentration of 14.6 mg/ml .

Anti-inflammatory activity and delayed hypersensitivity

No effects on the inflammatory response (carrageenan-induced paw edema in rats) or delayed hypersensitivity (sheep red cells-induced paw edema in mice) were observed at 46 mg/kg (iv) and 3 mg/kg (sc), respectively.

Pharmacology of PO26 (oxidative O-dealkylation product): the only identified metabolite in the urine and feces of all animal species and human studied. PO26 was a minor metabolite accounting for 5-10% dose in either urine or feces. PO26 was also detected in the plasma.

Efficacy:

In guinea pigs both the in vivo study of histamine-induced bronchospasm and the in vitro study of isolated ileum preparation, cetirizine is 30X more potent than PO26. In histamine-induced cutaneous reactions in mice and dogs, cetirizine was significantly more potent than PO26 which was also shown to be devoid of activity against antigen-induced bronchospasm in guinea pigs.

Behavioral effects:

General behavior study in mice following intraperitoneal administration showed "no-effect" doses at 46 mg/kg for cetirizine and at 11 mg/kg for PO26.

The only identified metabolite PO26 did not possess significant anti-histamine and anti-allergic activities. PO26 did not show significant CNS activity.

Toxicity:

The toxicity of Cetirizine was evaluated in acute (oral and intravenous studies in mice, rats and dogs), subacute (15-day and 1-month studies in mice and rats), and chronic (6-month studies in rats and dogs and 1-year studies in dogs and monkeys) studies.

Oral LD₅₀ values were 600 and 752 mg/kg in male and female mice and 703 and 865 mg/kg in male and female rats, respectively. The oral lethal dose was not determined in dogs due to vomiting at 160 mg/kg and above. The intravenous LD₅₀ values were 336 and 301 mg/kg in male and female mice, and 66 and 70 mg/kg in male and female rats, respectively. The intravenous lethal dose for dogs is 125 mg/kg. In the rat, the vast difference in the LD₅₀ values from oral and intravenous administrations indicated poor oral absorption and/or significant first pass effect in this species.

In rodents, the signs following oral and intravenous administrations were similar and were CNS-related. Sedation, unsteady gait, body tremors, jerking, hypertonicity of the hind legs, convulsions, dyspnea and cyanosis were observed. In dogs, increased heart rate at 80 mg/kg (po), nervousness and vomiting at 160 mg/kg (po); nervousness, unsteady gait, body tremors, muscular weakness at 70 mg/kg (iv) were observed. The surviving rodents and dogs appeared normal after 24 hrs. Necropsies were unremarkable, except for necrosis of tails following intravenous injection in the rodents.

Repeated dose toxicity studies showed species-specific effects/target organ toxicity in the livers of the rodents only, but not in the livers of either Beagle dogs or Cynomolgus monkeys.

The adverse liver effects observed in rodents (mouse and rat) included increased liver weight with grossly enlarged liver, elevated liver enzymes such as SGPT/SGOT, increased/decreased (generally more increased) cholesterol and triglycerides/total lipids and microscopic findings of hypertrophy, vacuolation, fat deposition/steatosis of hepatocytes in periportal, centrilobular or midzonal areas (necrosis only rarely). The applicant attributed the liver hypertrophy to enzyme induction and considered vacuolation and fat deposition as of toxicological significance.

The liver effects were observed at low doses (10-20 mg/kg) in rodents following either gavage or diet administration for as short as 15 days. Some of the rodent studies were dose-range finding studies for carcinogenicity testings (mouse and rat), whereas other studies were designed to evaluate the reversibility of the liver effects with recovery periods of 4-weeks and 13-weeks following 1-month treatment (mouse and rat). In rats one chronic 6-month study (8, 25 and 75 mg/kg) was carried out with interim sacrifice at 3 months. Dose- and duration-related frequency and severity of liver effects were again shown. Three histopathological findings of hypertrophy, vacuolation and fat deposition of hepatocytes in the periportal, centrilobular or mid-zonal areas were observed at 8-75 mg/kg in male rats and at 25-75 mg/kg in female rats. At 8 mg/kg (M) and 25 mg/kg (F) predominately the hypertrophy with some vacuolation were observed. At 75 mg/kg (the highest dose and the most affected group) extensive hypertrophy and vacuolation with some fat depositions were observed in many of the rats. The NOEL's was 8 mg/kg for female rats (20X maximum human dose of 20 mg/day), but was not established for male rats.

In both subacute and chronic studies, the liver effects were more prominent in male rodents, particularly the male rat and were attributed to greater extent of metabolism of the compound in these animals. Enzyme induction (increased microsomal enzymes and protein), proliferation of smooth endoplasmic reticulum (electron microscopic study) were observed in the rodents. The adverse liver effects (elevated liver enzymes, microsomal drug metabolizing enzymes, microsomal proteins and organ weights) were reversible following 4-week of recovery period. The histopathological changes, however, showed signs of reversibility only after 13-week of recovery.

The NOEL's in mice ranged 1-5 mg/kg (M) and 5-9 mg/kg (F) in different subacute studies of 15 days to 1 month. The liver effects were observed at 3-10 mg/kg (M) and at 10-40 mg/kg (F). In rats, the NOEL's ranged 18-25 mg/kg (M + F) in two 1-month studies. The affected levels were 54-75 mg/kg (M + F). In the 15-day study in rats, however, the affected levels (10-20 mg/kg) and the NOEL's (5 mg/kg) were lower than those of 1-month study. The reason was not given. The studies, however, were carried out by different laboratories. In rats other non-specific effects such as signs, body weight and food consumption were seen only at high doses of 75-160 mg/kg. Drug-related deaths were rare and occurred at high doses of 160-225 mg/kg (1-month) or 75 mg/kg (6-month).

In Beagle dogs and Cynomolgus monkeys, no specific target organ toxicities were established in both subacute and chronic studies. Deaths occurred only at high doses of 75 mg/kg (dogs) and 150 mg/kg (monkeys). Weight losses, decreased food consumption and signs were observed in dogs at 135 mg/kg (1-month), 25 mg/kg (6-month) and 15 mg/kg (1-year) and in monkeys at 50 mg/kg (14-day and 4-Week) and 45 mg/kg (1-year). The signs depending on the doses included vomiting, salivation, tremor, ataxia, quiet behavior, hypothermia, poor coat/piloerection and loose mucus feces in both dogs and monkeys. The relative "no-effect" levels were noted in dogs at 45 mg/kg (1-month), 8 mg/kg (6-month) and 4 mg/kg (1-year) and in monkeys at 17 mg/kg (4-Week), and 15 mg/kg (1-year). These "no-effect" doses were 10X maximum human dose of 20 mg/day in dogs and 40X maximum human dose in monkeys following chronic administration. Non-specific adverse effects on body weight, food consumption and signs occurred at 40X human dose in dogs and at 112X human dose in monkeys.

From the pharmacokinetic data, dogs and monkeys shared more similar ADME patterns with human than the rodents. Therefore, the animal toxicity studies particularly those from the dog and the monkey provided adequate margin of safety for the proposed human use. The liver effects in rodents appear to be species-specific. The available human data did not show significant drug-related liver effects. It should be noted that in the female rat, the NOEL's for liver (from 6-month study) was 8 mg/kg, but NOEL's for stomach was not established (drug-related ulceration of stomach occurred from the low dose of 3 mg/kg in the 2-year carcinogenicity study). In the male rat, the NOEL's for liver (from 6-month study) was not established, but was shown to be at 3 mg/kg from the 2-year carcinogenicity study. The stomach effect was considered another species specific effect, since it was not found in other species.

Thus the toxicological profiles from four species of laboratory animals support the relative safe use for the proposed 10-20 mg/day in human. The

species specific target organ toxicities (liver and stomach) in the rodents, however, should be included in the Package Insert under "Animal Toxicology" section.

Carcinogenicity studies in two species were carried out by
4 according to the GLP rules and regulations.

In a mouse 2-year feeding study, 5 groups of CD-1 mice (52/sex/group) consisted of 2 control groups and 3 dosed groups at 1, 4 and 16 mg/kg, which approximated 5X, 20X and 80X human dose of 10 mg/day or 2.5X, 10X and 40X maximum human dose of 20 mg/day.

During and at the end of the study, no drug-related effects were observed in mortality, signs, body weight, food consumption and blood smears. The target organ toxicities of liver such as hypertrophy, vacuolation and fat deposition were not observed. Thus it can be questioned whether MTD was employed, especially in the female mice. The MTD's, however, were selected based on the profiles from 3 subacute toxicity (15 day-4 week) studies which showed liver effects at 3-10 mg/kg (M) and at 10-27 mg/kg (F). The selection of 16 mg/kg as high dose or MTD therefore was justified.

The neoplastic changes included increases of benign liver tumors in 16 mg/kg-male mice and lymphosarcoma in multiple organs in 16 mg/kg-female mice. The statistical analysis and evaluation by Division of Biomatrix (HFD-715) concluded that benign liver tumor was significant (same conclusion by the Applicant). The dosage represents 80X human dose of 10 mg/day or 40X maximum human dose of 20 mg/day. Lymphosarcoma in multiple organs were not statistically significant. The non-neoplastic changes included liver masses in male mice at 16 mg/kg level.

In a rat 2-year feeding study, 5 groups of rats (50/sex/group) consisted of 2 control groups and 3 dosed groups at 3, 8 and 20 mg/kg, or approximately 15X, 40X and 100X human dose of 10 mg/day or 7.5X, 20X and 50X maximum human dose of 20 mg/day.

During and at the end of the study, no drug-related effects were observed on mortality, signs, body weight, food consumption and blood smears in these rats. Drug-related target organ toxicities of the livers (enlarged/swollen liver with periportal fat deposition, and vacuolation), however, were observed at 8-20 mg/kg (M) and at 8 mg/kg (F). The MTD was employed.

The neoplastic changes included thyroid follicular adenoma in 20 mg/kg male rats, pituitary carcinoma in 8 mg/kg female rats and malignant liver tumors in 8 mg/kg male rats. The malignant liver tumors and pituitary carcinoma were not considered biologically significant, because the high dose group was not affected. The thyroid follicular adenoma in 20-mg/kg male rats was statistically significant, the trend over groups 1-5 was also significant. In addition, for combined benign and malignant follicular tumors, the test for trend over groups 1 to 5 was also significant. The thyroid follicular adenoma was considered a common tumor in male rats based on the historical control data showing greater than 1% incidence. The statistical evaluation by HFD-715 concluded the finding not significant (for a common tumor type to be significant, the p-value should be less than 0.01). Mammary gland fibroadenoma with epithelial atypia appeared to increase in the dosed female groups, but was not found to be statistically significant.

The significant non-neoplastic changes were ulceration of stomach in 3, 8 and 20 mg/kg female rats and liver effects (enlarged liver with fat deposition, and vacuolation) in 8-20 mg/kg male rats and 8 mg/kg female rats. Enlarged kidneys with progressive glomerulonephrosis in dosed male and female groups were probably due to old age and exaggerated by the compound. The stomach and kidney effects were not observed in other rat studies of shorter durations (1-6 month). Subchronic and chronic studies in dogs and monkeys did not show stomach and kidneys effects either. The stomach effect in female rats probably represents another species specific effect.

From the results of the carcinogenicity studies, cetirizine induced benign liver tumors in male mice at 16 mg/kg or 40X maximum human dose of 20 mg/day. Since no significant finding of either benign or malignant liver tumors were observed in rats, the significant finding of this common liver tumor in male mice alone should not affect the approvability of the application. The thyroid follicular adenoma in the male rats at 20 mg/kg was not considered significant from statistical point of view. The findings of benign liver tumors in male mice and thyroid follicular adenoma in male rats should be included in the Package Insert.

Reproduction studies:

In comparison with the rat, the mouse exhibited a pharmacokinetic pattern relatively closer to man (both mouse and man metabolize cetirizine to less extent than rat). Therefore the mouse was chosen by Applicant as the species in the Segment I, II and III studies. In addition, Segment II reproduction studies were carried out in the rat and the rabbit.

The Segment I study was carried out in the dosed male and dosed female mice at 4, 16 and 64 mg/kg. The durations were in males 8 weeks prior to mating and through mating and in females 2 weeks prior to mating and continued on until either sacrificing on day 17.5 of pregnancy or after rearing young to day 21 postpartum. The study also extended to the development and reproductive functions of F₁ and F₂ generations. The results showed that the pregnancy rate was decreased slightly at 64 mg/kg (90% vs 100% control). This was probably due to the effects on the mating performance: delayed and reduced mating performance (more mid and high dosed mice mated on or after 6 days and showed no positive mating). In addition, increased gestation period, lower litter size and some malformations (cleft palate, partial or bilateral open eyes) at 64 mg/kg, total skeletal variants/anomalies (sternbrae: unossified, reduced, bipartite; cervical ribs, reduced metatarsals and occipital) at 16-64 mg/kg, but mostly at 64 mg/kg, were observed. The relative "no-effect" dose was 4 mg/kg. F₁ and F₂ generations did not show adverse effect on their development or reproductive function. In this study, high dosed dams but not the offsprings showed increased liver weight with histopathology of hepatocyte hypertrophy at 64 mg/kg.

Segment II studies were carried out in mice (6, 24, 96 mg/kg), rats (8, 25, 75, 225 mg/kg) and rabbits (15, 45 and 135 mg/kg). No significant embryocidal or teratogenic effects were observed in mice and rabbits up to the highest doses tested or 240X and 338X maximum human doses, respectively. In rats embryocidal effects (percent of pre- and post-implantation losses) at 225 mg/kg (562X maximum human dose), but no teratogenic effects were observed. Skeletal variants or anomalies (refer to the preceding paragraph) were observed at 135 mg/kg (rabbits) or from 25 mg/kg (rats).

Although the results of Segment II reproduction studies in mice, rats and rabbits showed that cetirizine was not teratogenic, it should be noted that other structurally related antihistamines such as cyclizine, meclizine, chlorcyclizine and hydroxyzine are known teratogens in the laboratory animals. Cleft palates were observed in 1 fetus of 16 mg/kg and 4 fetuses of 64 mg/kg in Segment I mouse study. In light of negative findings from all three Segment II studies in 3 species (i.e. mouse, rat and rabbit), the finding of cleft palate from Segment I study are not considered significant. Other anomalies in the kidneys (pelvic cavitation/hypertrophy/hemorrhage/displacement/hydronephrosis in rats and in rabbits) and in brain (meningocele, hydrocephaly, microcephaly with incomplete development of frontal and parietal bones in rabbits) were sporadically observed in the dosed groups without apparent dose-related effects. The cyclizine compounds, however, have not been shown to be teratogens in human.

Segment III reproduction study in mice (6, 24 and 96 mg/kg) suggested that nursing and/or lactating performance was affected at 96 mg/kg because of lower pup weight gains from Day 4 to weaning (Day 21). No significant adverse effects on the development of the pups were evident based on several parameters monitored. Late fetal development or labor did not appear to be affected. Increased liver weights were again observed in the dams of 96 mg/kg. Thus the relative "no-effect" dose in this segment was at 6 mg/kg. Nursing/lactating performance (decreased pup weight gains on Day 4-weaning) was probably affected at 96 mg/kg (240X maximum human dose).

Based on the results from all reproduction studies, the relative "no-effect" doses were 4-6 mg/kg in mice, 8 mg/kg in rats and 15 mg/kg in rabbits. These doses represent at least 20X human dose of 10 mg/day or 10X maximum human dose of 20 mg/day. Adverse reproductive effects in mice included male and/or female mating performance (delayed mating days and no positive mating resulting in slightly lower pregnancy rate) at 64 mg/kg or 160X maximum human dose and lactating/nursing performance (decreased pup weight gains on Day 4 to weaning) at 96 mg/kg or 240X maximum human dose. Skeletal variants/anomalies were generally affected at high doses of 64 mg/kg in mice, 225 mg/kg in rats and at 135 mg/kg in rabbits.

Embryocidal effects in rats were observed at 225 mg/kg or 562X maximum human dose. It should be noted that the mouse, though metabolizing cetirizine to less extent than the rat, still metabolizes cetirizine to greater extent than human. The animal reproduction studies, nonetheless, revealed a profile that provides adequate margin of safety for the drug to be used in women of childbearing potential. The adverse effects at high doses should be included in the package insert.

In the package insert cetirizine is placed under Pregnancy Category C. The wording, however, should be as follows: Cetirizine has not been shown to be teratogenic in mice, rats or rabbits. Cetirizine has been shown to have an embryocidal effect only in rats (at 225 mg/kg or 562X maximum human dose of 20 mg/day), but not in mice (at 96 mg/kg or 240X maximum human dose) or in rabbits (at 135 mg/kg or 338X maximum human dose). Mating performance of male and/or female mice (delayed and reduced matings) appeared to be affected at 96 mg/kg (240X maximum human dose). Skeletal variants/anomalies together with maternal toxicity were predominately observed at the high doses of 64 mg/kg (or 160X maximum human dose) in mice, 225 mg/kg (or 562X maximum human dose) in rats and 135 mg/kg (or 338X maximum human dose) in rabbits. Nursing/lactating performance (retarded pup weight gains on Days 4-21 postpartum) were affected at 96 mg/kg (or 240X maximum human dose) in mice. There are no adequate and well-controlled studies in pregnant women. Cetirizine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Mutagenesis Studies:

Four studies were carried out. Ames Test (8-5000 mcg/plate), Chromosomal Aberrations Assay in Human Peripheral Lymphocytes (20-500 mcg/ml), Mouse Lymphoma TK Locus Assay (100-460 mcg/ml), and Micronucleus Test in Mouse (14-350 mg/kg/day) showed negative results suggesting no mutagenic potential for the compound.

Absorption, distribution, metabolism and excretion:

Twenty four studies were conducted in six animal species (mouse, rat, rabbit, dog, baboon and cynomolgus monkey). Both C^{14} -cetirizine and cold drug were used in animal and human studies. The results showed qualitative similarity among animals and man; though dogs and monkeys exhibited patterns closer to those of man.

Absorption:

Cetirizine is well and rapidly absorbed following oral doses (10 mg/kg) in all animal species and man. The peak plasma concentrations of 8-19 mcg/ml were reached in 1 hr (mouse, rabbit, monkey) and 3 hrs (dog) and of 300 mcg/ml was reached in 1 hr (man). The rat is the species that showed extensive metabolism resulting in lower peak plasma levels of unchanged drug of 2 mcg/ml (M) and 4 mcg/ml (F), reached in half hour. In addition, the rat is the species that showed sex-related difference: the male metabolized cetirizine to even greater extent than the female. The oral bioavailability is 71-100% in mouse, rabbit and dog, 51-87% in baboon and monkey and only 36-46% in rat. The pharmacokinetics are linear up to 10 mg/kg in all species and man except the rat. The elimination half-life is less than 1 hr (rat), 1-3 hrs (mouse, rabbit and monkey) and 7-9 hrs (dog and man). The apparent volume of distribution was 0.45 l/kg in man. In animals and man no significant accumulation was observed.

Distribution:

In rats and dogs, liver and kidneys had the highest levels, followed by lungs, plasma, adrenal, spleen, heart and pituitary gland. The cerebrum and cerebellum had the lowest level. Placental transfer was observed in the rat (radioautography) but not in the rabbit (measurement of tissue radioactivity level). The drug was secreted in the milk of dogs. The drug showed high plasma protein binding in all species and man (90% and more).

Metabolism:

Cetirizine was not extensively metabolized except in the rat and mouse. Male rodents metabolized the compound to the greatest extent (80-90% dose). Oxidative O-dealkylation to P026 is the only metabolite identified in both urine and feces of all animal species tested and the man. P026, however, appeared to be a minor metabolite, accounting no more than 5-10% dose in either urine or feces from either rats or dogs. In these species, there are additional 4-7 unidentified metabolites. The biotransformation pathways therefore are not fully known. In man about 20% of the dose was metabolized; less than 4% as P026.

Excretion:

Both urine and feces contributed to the excretion which was generally completed in 96 hrs. In the rat excretion of unchanged drug were low (1-20% in male urine and 9-33% in female urine following chronic dosings at 8-225 mg/kg/day). Urinary excretion accounted for 12-53% dose and fecal excretion accounted for 65-83% dose in rats. In mice, urinary excretion accounted for 37-58% dose and fecal excretion accounted for 44-66% dose. In man 60% of the administered dose was excreted unchanged in urine. Nonrenal clearance accounted for 20% of total body clearance.

In both rodents, females had higher urinary excretion than fecal excretion and males had higher fecal excretion than urinary excretion. In dogs following oral 0.6 mg/kg/day for 9 days, urinary excretion accounted for 40% dose and fecal excretion accounted for 46% dose over 96 hrs. In urine unchanged drug represented 32-40% dose. The accumulation rate was 14% in 9 days. In primates (baboon and monkey), 30% dose was collected in 72 hr-urine as unchanged drug.

Enterohepatic circulation occurred in rats, dogs and monkeys, especially the male rodents

In summary, dogs, baboons and monkeys eliminated a constant proportion of unchanged drug in urine over wide ranges of doses whereas rats showed dose-dependent rates of elimination. There were sex-related differences in rats and mice but not in dogs and primates. The rodents, especially the male rat, metabolized the compound extensively. From the data, dogs, monkeys and man share more similar patterns of ADME.

Conclusions:

- (1) Cetirizine has been shown to possess antihistamine activity. Its potency varied with the models and tests, ranging from 1X-10X that of hydroxyzine. In many studies where comparison drugs were included cetirizine was shown to be more potent than terfenadine, clemastine and mepyramine. Following oral administration, the effect was generally observed in 1 hr, and the duration varied with doses ranging from 4 to 24 hrs in different studies.
- (2) Cetirizine crossed the blood brain barrier to less extent than hydroxyzine. EEG study in rabbits showed sedative effects at intravenous dose of 1.3 mg/kg. Additional behavioral studies did not show significant CNS effects at oral dose below 14 mg/kg. Higher doses caused excitation and/or depression.
- (3) No significant cardiovascular effects were observed except at high doses of 14-461 mg/kg which progressively cause decreased BP/tachycardia/ECG changes/respiratory depression/death. No significant H₂-receptor, anticholinergic, analgesic, local anesthetic or anti-inflammatory activities were demonstrated in animal studies. No effects on mediator release were shown. No active metabolite was demonstrated.
- (2) Acute toxicity was low in rodents and dogs. Repeated-dose treatment showed species-specific target organ toxicity in rodents only. In mice and rats, liver appeared to be the target organ with hypertrophy, vacuolation/steatosis (fat deposition). The liver effects, mostly reversible, were attributed to extensive metabolism and enzyme induction (hypertrophy/enlargement) and toxic effect (vacuolation and fat deposition). Male rat with the highest extent of metabolism was the most sensitive species. The liver effects were observed at 8 mg/kg (male rats) and 25 mg/kg (female rats) in the 6-month study. The "no-effect" level was not established in male rats and was established at 8 mg/kg in female rats.

In both beagle dogs and cynomolgus monkeys, no specific target organ toxicity was demonstrated in the 1-year studies. Non-specific effects such as body weight and/or signs of salivation and vomiting were observed at 15 mg/kg (dogs) and at 45 mg/kg (monkeys); the relative "no-effect" doses were 4 mg/kg (dogs) and 15 mg/kg (monkeys).

Cetirizine was not carcinogenic or tumorigenic in female rats or in female mice. In male rodents, benign tumors were increased. In male mice, significant increases of benign liver tumors (common benign tumors in male mice) and liver masses were observed at 16 mg/kg (40X maximum human dose). The finding, represents species-specific, should be included in the labeling. Thyroid follicular adenoma observed at 20 mg/kg (or 50X maximum human dose) in the male rat should be included in the labeling.

Cetirizine was not shown to be mutagenic in four in vitro and in vivo mutagenesis studies.

- (3) Pharmacokinetic studies showed qualitative similarity among animals and man. The compound was absorbed following oral administration and distributed to liver, kidneys and lungs. Cetirizine crossed placental blood barrier in the rat but not in the rabbit. Cetirizine was secreted in the milk of the dog. Both urine and feces contributed to the excretion which generally was completed in 96 hrs. The most significant finding was the extent of metabolism between rodents and other animal species (i.e. dog, monkey). Cetirizine was extensively metabolized in rats (especially male rats-90% metabolized), followed by mice (60%), dogs (30-40%) and man (20%). Therefore unchanged drug accounted for 30-40% (dogs) and 10-20% (rats) each in the urine and the feces. An oxidative O-dealkylation product, P026, and additional 4-7 unidentified metabolites were present in both urine and feces. No active metabolite was identified. Comparatively, dog and monkey exhibited patterns closer to those of human.
- (4) Cetirizine has not been shown to be teratogenic in the mouse, the rat and the rabbit. Embryocidal effect was observed in rats at 225 mg/kg (562X maximum human dose), but not in mice (96 mg/kg or 240X maximum human dose) or in rabbits (135 mg/kg or 338X maximum human dose). Skeletal variants/anomalies were observed at 64 mg/kg (160X maximum human dose) in mice, at 75 mg/kg (188X maximum human dose) in rats and at 135 mg/kg (338X maximum human dose) in rabbits. Maternal toxicity was observed at high doses of 225 mg/kg in rats and at 135 mg/kg in rabbits. Mating performance (delayed and reduced matings) were affected at high doses of 64 mg/kg (160X maximum human dose) in mice. Lactating and/or nursing performance (decreased pup weight gains on Day 4-21 postpartum) were affected at 96 mg/kg (or 240X maximum human dose) in mice.
- (5) The Deficiencies in the Package Insert should be amended before the application can be approved.
- (a) An "Animal Toxicology" section should be included. Species-specific target organ toxicities in the livers (male and female mice and rats) and stomach (female rats only) should be described.
- (b) Under Carcinogenesis, mutagenesis, impairment of fertility, the actual dosage (16 mg/kg) at which benign liver tumors in male mice was observed should be included in addition to the human multiples which are described. The finding of thyroid follicular adenoma in male rats at 20 mg/kg or 50X maximum human dose of 20 mg/day should be included.
- (c) Under "Overdosage" section, oral (LD₅₀ values or) minimal lethal doses in the rodents should be included in addition to the human multiples.

(d) Under "Pregnancy Category C", the following wording is recommended:

Cetirizine has not been shown to be teratogenic in mice, rats or rabbits. Cetirizine has been shown to have an embryocidal effect in rats (at 225 mg/kg or 562X maximum human dose of 20 mg/day), but not in mice (at 96 mg/kg or 240X maximum human dose of 20 mg/day) or in rabbits (at 135 mg/kg or 338X maximum human dose). Adverse reproductive effects generally associated with maternal toxicity were observed at high doses or high multiples of the maximal human dose. Mating performance of male and/or female mice (delayed and reduced matings) appeared affected at 96 mg/kg (240X maximal human dose). Skeletal variants/anomalies mostly due to reduced- and/or un-ossification were observed at 64 mg/kg (160X maximum human dose) in mice, at 225 mg/kg (562X maximum human dose) in rats and at 135 mg/kg (338X maximum human dose) in rabbits. Nursing/lactating performance (retarded pup weight gains on Day 4-21 postpartum) was affected at 96 mg/kg (240X maximum human dose) in mice. There are no adequate and well-controlled studies in pregnant women. Cetirizine should be used during pregnancy only if potential benefit justifies the potential risk to the fetus.

Recommendations:

From the conclusions (1)-(4) above, cetirizine has been studied extensively in the laboratory animals to document its pharmacological and toxicological profiles. Cetirizine can be labeled to support its relatively safe and efficacious use in human. The application is therefore approvable based on pharmacology. However, before the application can be approved, the deficiencies in the Package Insert should be amended.

To Medical Officer:

Although adverse liver effects in the rodents appear to be species-specific, the clinical studies should be appraised for liver enzymes profile (toxicity).

Pharmacology Portion of Letter to Applicant:

From pharmacology standpoint, in order to provide assurance of relatively safe and efficacious use of cetirizine in human, the Package Insert should be amended before the application can be approved.

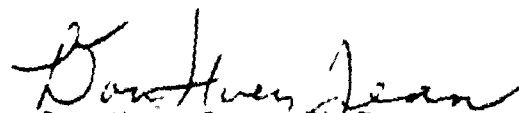
The deficiencies in the Package Insert are as follows:

- (a) An "Animal Toxicology" section should be included. Species-specific target organ toxicities in the livers (male and female mice and rats) and stomach (female rats only) should be described.
- (b) Under Carcinogenesis, mutagenesis, impairment of fertility, the actual dosage (16 mg/kg) at which benign liver tumors in male mice was observed should be included in addition to the human multiples which are used solely. The finding of thyroid follicular adenoma in male rats at 20 mg/kg or 50X maximum human dose of 20 mg/day should be included.

- (c) Under "Overdosage" section, oral (LD₅₀ values or) minimal lethal doses in the rodents should be included in addition to the human multiples.
- (d) Under "Pregnancy Category C", the following wording is recommended:

Cetirizine has not been shown to be teratogenic in mice, rats or rabbits. Cetirizine has been shown to have an embryocidal effect in rats (at 225 mg/kg or 562X maximum human dose of 20 mg/day), but not in mice (at 96 mg/kg or 240X maximum human dose of 20 mg/day) or in rabbits (at 135 mg/kg or 338X maximum human dose). Adverse reproductive effects generally associated with maternal toxicity were observed at high doses or high multiples of the maximal human dose. Mating performance of male and/or female mice (delayed and reduced matings) appeared affected at 96 mg/kg (240X maximal human dose). Skeletal variants/anomalies mostly due to reduced- and/or unossification were observed at 64 mg/kg (160X maximum human dose) in mice, at 225 mg/kg (562X maximum human dose) in rats and at 135 mg/kg (338X maximum human dose) in rabbits. Nursing/lactating performance (retarded pup weight gains on Day 4-21 postpartum) was affected at 96 mg/kg (240X maximum human dose) in mice. There are no adequate and well-controlled studies in pregnant women. Cetirizine should be used during pregnancy only if potential benefit justifies the potential risk to the fetus.

It was noted that the ED₅₀ values on pages 2 38 to 2 39 are different from those listed under individual studies (e.g. NP-2, NP-4, NP-8, NP-10 on pages 5 31 to 5 193). Likewise, under NP-13, the dosage for monkey was not clear (10 mg/kg on page 5 8 and 10 mg/animal on page 5 247). Please clarify the discrepancies.


Dou Huey Jean, Ph.D.
Pharmacologist

cc NDA 19-835
HFD-160
HFD-340
CSO-Ledet
R/D DJean 4/11/89
R/D Init. by JInscoc
Typed by LGiesick 4/19/89, 9/29/89
Wang #7234P &
pgs. 99-119 7241P

Clinical signs: Noisy respiration was noted in high-dose group on Day 1. After 2 weeks no differences among 4 groups.

Body weight and food consumption:

No significant effects were observed in F. For male rats, the changes were as follows:

	<u>BW</u>	<u>FC</u>
L:	-7%	-9%
M:	-13%	-9%
H:	-22%	-22%

Blood analysis:

Hematology: F: no significant changes. In high-M rats, slight decreases of RBC, Hct, Hgb and MCV (5-10%) increases of MCHC (5%) and platelets (17%).

Chemistry: inc. ALAT (SGPT): 47-52%
(in the high dose group) AP: 20-30%
globulins (alpha and beta): 16-32%
albumin/globulin ratio: 10-14%
BUN: 15%

Urinalysis: in high-M, increased epithelial cells and decreased phosphates in the centrifuged deposit.

Ophthalmology: not performed.

Drug monitoring: urinary unchanged drug higher in F than M (mostly in free form). After 1 month no accumulation of unchanged drug or induction of metabolism was apparent.

Organ weight:

Liver: dose related increases of absolute and relative weights in the M and H groups.

Pathology:

Gross pathology: no significant findings.

Histopathology: in the mid (3M) and the high dose (10M) male rats, increased fat desposition and hepatocyte necrosis in the centrilobular and mediolobular areas (degenerative and necrotic lesions of the liver parenchyma in the midzonal and central areas of the lobules).

Histopathological review of livers from preliminary study of P071 toxicity to rats in repeated oral administration for one month(T-3).

The study (T-7) was performed by the sponsor, the liver slides were reviewed again by
The results were as follows:

P071 one-month rat gavage study
Re-evaluation of H & E stained and GRC stained sections of liver:
Summary of treatment-related changes

	25		75		225	
	mg/kg/day		mg/kg/day		mg/kg/day	
	d	9	d	9	d	9
<u>H & E stained liver sections</u>						
Hypertrophy						
Centrilobular						
Slight	0	0	4	2	0	0
Minimal	0	0	1	1	0	3
Moderate	0	0	0	0	1	2
Centrilobular/Midzonal						
Minimal	0	0	0	0	1	1
Moderate	0	0	0	0	7	0
Vacuolation						
Centrilobular						
Minimal	0	0	0	0	3	0
Moderate	0	0	0	0	0	1
Midzonal						
Minimal	0	0	1	0	3	0
Moderate	0	0	0	0	1	0
Centrilobular necrosis (one lobe)						
	0	0	0	0	1	0
<u>GRC stained liver sections</u>						
Midzonal						
Trace	0	0	1	0	1	0
Minimal	0	0	0	0	4	0
Moderate	0	0	0	0	3	0
Midzonal (trace)/Periportal (minimal)						
Centrilobular (minimal)/Midzonal (moderate)	0	0	0	0	1	0
Periportal (minimal)/Midzonal (moderate)						
	0	0	0	0	1	0

(3) Toxicity to Rats by Continuous Dietary Administration for 4 weeks (T-~~12~~⁹).

Performed by:

Main Study: 11/8/83 - 12/6-8/83; Satellite study: 11/8/83-12/6-21/83.

Animals: Charles River CD rats of Sprague-Dawley strain (Portage, MI, U.S.A.)

No. of animals/dosage: 30 (15 M+ 15 F): 20(10M+ 10F) for main study and 10(5M+5F) for satellite study. (Urine and drug metabolizing enzymes)

Route and duration of administration: orally through dietary mixture for 4 weeks.

Dosage levels:

- (1) Control diet
- (2) 2 mg/kg/day
- (3) 6 mg/kg/day
- (4) 18 mg/kg/day
- (5) 54 mg/kg/day
- (6) 160 mg/kg/day

Results:

Mortality:

One F from satellite group of 2 mg/kg died during week 3 of acute cystitis with necrosis of urinary bladder and epithelial hyperplasia of urethra.

Clinical signs:

No signs of ill health, behavioral changes or reaction to treatment was noted.

Body weight and food consumption:

Body weight gains: lower for 160-M and F only
Food: lower for 160-M and F only

Blood analysis:

Hematology:

160-M: increased erythrocytic parameters (Hct, Hgb, RBC and MCHC); Inc. WBC, neutrophils and lymphocytes.

160-F: Inc. Lymphocytes and monocytes.

Chemistry: Statistical changes were still within normal ranges.

Na+: slight dec. in dosed M and F.

Glucose: slight inc. at 54- and 160-F.

Urinalysis: Not performed.

Organ weight: (Absolute weight) statistically significant changes were observed in Only, Inc. liver and spleen (54 and 160), thyroid (160), gonad (18, 54 and 160). Dec. adrenal (160)

Pathology:

Gross pathology:

- (1) Liver: enlargement in 4/16M and 1/16F of 160 mg/kg group.
- (2) Spleen: enlargement in 2/16 M of 6 mg/kg, 2/16 M of 18 mg/kg and 1/16 M of 160 mg/kg.
- (3) Stomach: Nodules in antrum randomly (1-5 rats) in each group, no dose-or drug-related frequencies noted.

Histopathology:

- (1) Liver: Centrilobular hepatocyte enlargement and mid-zonal/centrilobular fat deposition at 54 and 160 mg/kg levels.
- (2) Spleen: Minimally increased cellularity of red pulp in 1 1/16 M of 160 mg/kg, 4/16 M of 54 mg/kg and 1/16 M, of 18 mg/kg groups.

Assay of Drug Metabolizing Enzymes

The levels of hepatic cytochrome P₄₅₀ and drug metabolizing enzymes (aniline hydroxylase, ethyl morphine-N-demethylase and p-nitroanisole-o-demethylase) were assayed in the microsomal fraction hepatocytes following 4 weeks of treatment.

- (1) The relative "no-effect" dose was 18 mg/kg level.
- (2) Male rats showed increases of all enzymes from 54 mg/kg.
- (3) Female rats showed increases of O-demethylase and protein synthe from 54 mg/kg.

Urinary Excretion of P071:

Urinary excretion was measured during a 12-hour period on Days 1, 8, 28.

- (1) Urinary excretions were below detection limit at 18 mg/kg on all days.
- (2) The urinary excretions, ^(UD) were greater in females than in males on days and increased with the times in both M and F.
- (3) The urinary excretions, ^{of UD} generally less than 5% of the doses for M

(4) A study to determine the reversibility of hepatic changes in rats (T-10)

Performed by:

Treatment: Nov. 11, 1985-Dec. 8, 1985
Withdrawal: Dec. 9, 1985-Mar. 11, 1986

Animals:

Sprague-Dawley rats, 5-6 weeks old, Charles River, Portage, Michigan

No. of animals/dosage: 60 (30 M + 30 F): 20 (10 M + 10 F) each
sacrificed at end of 4-week treatment, 4- and
13-week withdrawal

Route and duration of administration:

Orally through dietary mix daily for 4 weeks

Dosage levels:

- (1) Control: control diet
- (2) Low dosage: 40 mg/kg/day
- (3) High dosage: 160 mg/kg/day

Results:

Mortality: 3 (control: 1 F, Low: 1 M, High: 1F).

Clinical signs: unremarkable

Body weight and food consumption:

Lower weight gains in high-M only. Food/efficiency: unremarkable.

LIVER STUDIES:

Parameters	40		160 mg/kg/day	
	<u>Dosing</u>	<u>Withdrawal</u>	<u>Dosing</u>	<u>Withdrawal</u>
<u>Chemistry</u>	unremarkable in both groups			
<u>Lipid analysis</u>				
Inc. cholest.			M	recovered(4 wk)
Inc. tot.lipid	M	recov.(4 wk)	M	recovered (4 wk)
Inc.triglycer.	M	recov.(4 wk)		
<u>Enzymes</u>				
Micro. protein				
p-450	M + F	recov.(4 wk)	M + F	recovered (4 wk)
P-NOD*			M + F	recovered (4 wk)
<u>Organ wt</u>				
abos.(inc)	M	recov.(4 wk)	M	recovered (4 wk)
<u>Gross pathology</u>				
unremarkable				
<u>Histopathology</u>				
Enlargement				
centrilobular				
hepatocytes	M	recov (4 wk)	M + F	recovered (4 wk)
+ fat depos.				
in midzone			M + F	recovered (4 wk)

*P-NOD: p-nitroanisole-O-demethylase

A study to determine the reversibility of hepatic changes in rats.
Electron microscopy of liver (T-11).

An extension of Study T-10, only rats from control and high dose groups sacrificed at the end of 4-week treatment and 4-week of withdrawal were examined.

In this electron microscopical examination of liver from rats treated with compound P071 for 4 weeks followed by 4 and 11 weeks withdrawal, the results may be summarized as follows:

minimally increased amounts of smooth endoplasmic reticulum in occasional hepatocytes from 10/10 male and 8/10 female rats treated with 160 mg/kg/day and 3/10 male rats treated with 40 mg/kg/day at termination;

occasional concentric membranous bodies in hepatocytes from 7/10 male rats treated with 160 mg/kg/day and 2/10 male rats treated with 40 mg/kg/day at termination;

increased lipid in hepatocytes from rats treated with 160 mg/kg/day at termination.

These changes were not seen in rats from the 160 mg/kg/day treatment group allowed a 4-week recovery period.

NOTE:

Study T-9: The satellite study was for drug monitoring of urine (days 1, 8 and 28).

- (1) Urinary excretion increased with dosing days.
- (2) Urinary excretion of unchanged drug accounting for 5% dose was higher in F than M.
- (3) Metabolites were not indentified.

Study T-10: only liver effects (enzymes, fat contents, light and electron microscopies) were studied.

- (1) All liver effects (increased total lipids, triglycerides and cholesterol, histopathological changes of hypertrophy, fat deposition, vacuolation and EM findings of increased smooth endoplasmic reticulum, lipid droplets, concentric membrane bodies) were reversible after 4-13 weeks recovery period (most parameters recovered in 4 weeks).
- (2) Enzyme induction occurred at 40-160 mg/kg (M + F) more in M. The induction was reversible after 4-13 weeks recovery period.

(5) Chronic Toxicology studies: Oral toxicity study in rats (repeated dosage for 6 months). (T-12)

Performed by : (1), February 22, 1982-August 23/September 2, 1982.

Animals: Sprague-Dawley rats, 7 weeks old. M: 131 gm and F: 97 gm

No. of animals/dosage: 50 (25 M and 25 F)/dosage. Interim sacrifice at 3-month: 10 (5M + 5F)/dosage.

Route and duration of administration: orally by gavage, 7 days/week for 6 months. Interim sacrifice at 3 months.

Dosage: in dist. water

- (1) Control: vehicle
- (2) Low dosage: 8 mg/kg/day
- (3) Mid dosage: 25
- (4) High dosage: 75

Results:

Mortality: total 34 (22 M and 12 F). 26 deaths (C:3, L:3, M: 10 and H: 10): intubation in the trachea; 1 death (M): accidental; 7 deaths (L:2, M:2 and H:3): undetermined cause.

Clinical signs: High dose group: quieter, but hyperactive when handled in this group and mid dose group.

Body weight and food consumption: no significant finding.

Blood analysis:

Hematology: slight decreases of RBC and PCV in high group.

Chemistry: marked inc. of SDH; slight inc. of ASAT (SGOT) and ALAT (SGPT) and slight dec. of triglycerides in mid and high groups (started at 6 weeks)

Urinalysis: no significant finding.

Drug monitoring: Urinary excretion of unchanged drug was higher in F than M, esp. in low group.

Absorption and urinary excretion of UCB P071 in M and F did not appear to be affected following chronic dosings.

Organ weight:

Liver: both absolute and relative weights were increased in mid and high groups (at 3-month) and in high group (at 6-month).

Kidneys: slight increase (abs and rel) in high (M &F) and mid (M) group at 6 months.

Adrenals and thyroids: slight increase in high-M.

Pathology:

Gross pathology: no significant finding.

Histopathology:

A dose related increase in the frequency and severity of peri-acinar hepatocytic hypertrophy (male rats from low dose and female rats at high dose only) and slight to moderate peri-acinar hepatocytic large droplet fatty infiltration (male rats from mid dose and female rats at high dose only) were observed. More male rats were affected. EM study of livers of control and high dose, (3 M + 3 F) each group, revealed increased smooth endoplasmic reticulum and lipid droplets in all 3 male and 1 female rats of high dose group.

Interim sacrifice at 3-month:

Liver effects progressed from 3 months to 6 months while treatment continued.

Six-month toxicity study in rats with test substance P071.
Electron microscopy of selected hepatic tissues of control and group 4 treated rats (T-13)

An extension of Study T-12, the results were based on the observations from three rats of each sex from control and 75 mg/kg/day groups. The results are copied as follows:

In the limited numbers of animals observed, ultrastructural changes in the hepatic tissue of the rat were almost totally confined to the males with an evident increase in smooth endoplasmic reticulum in the periactinar region and a slight increase in the centriactinar region. There were elevated numbers of lipid droplets observed in both centriactinar and periactinar regions with some clumping of lipid droplets in the periactinar region which on occasion formed very large lipid droplets. Many lipid droplets of varying size had a 'vacuolar' appearance, a not uncommon effect caused by storage of tissues in formaldehyde.

The female treated rats had numbers of lipid droplets similar to the female controls, and with the exception of the periactinar region of 4F 011 which had a slight increase in smooth endoplasmic reticulum, no observable increases in smooth endoplasmic reticulum were found in the centriactinar or the periactinar region.

In both male and female treated rats all other hepatic ultrastructural features were regarded as similar to those observed in controls.

U 1 Day animals

(1) Subchronic toxicity study: Toxicity to dogs in repeated oral administration for one month (T-14)

NDA 19-835

Page 51

Performed by: (1), April 14, 1981 - May 14, 1981.

Animals: Beagle dogs, 12-15 months old.

No. of animals/dosage: 6 (3M + 3F)/dosage.

Route and duration of administration: orally 7 days/week for 1 month.

Dosage levels: in gelatin capsules.

(1) Control:	0
(2) Low:	15 mg/kg/day
(3) Mid:	45
(4) High:	135

Results:

Mortality: none

Clinical signs:

- (1) Vomiting: drug-and dose-related increased incidences in all dose groups.
- (2) Impaired condition (body tremor, salivation, ataxia, reduced food consumption): in 2 high-dose females at end of treatment.

Body weight and food consumption:

Both showed decreases in high dose females (mostly due to 2 females).

Blood analysis:

Hematology: unremarkable

Chemistry: Increased-AP in high dose M and F and increased α_2 globulins in high dose F.

Urinalysis: Significant decreases of specific gravity in high-dose M (-22%) and F (-34%); volume increased.

Ophthalmology: not performed.

Heart rate and EKG: no significant findings.

Organ weight: Relative weights of

kidneys: increased in high dose male and female dogs.

adrenals: increased in high dose male and female dogs

Pathology:

Gross pathology: unremarkable.

Microscopic pathology: unremarkable.

(2) Chronic toxicity study: Oral toxicity study in beagle dogs,
Repeated dosage for 6 months (F15).

Performed by: ~~RD~~ January 13, 1982 - July 13, 1982

Histopathology:

Animals: Beagle dogs, 7-9 months old.

No. of animals/dosage: 10 (5M + 5F)/dosage.

Route and duration of administration: orally 7 days/week for 6 months.

Interim sacrifice at 3 months, (2 M + 2 F) from each group.

Dosage levels: in gelatin capsules.

- (1) Control: empty gelatin
- (2) Low: 3 mg/kg/day
- (3) Mid: 25
- (4) High: 75

Results:

Mortality: 2 males of high group. One died on Day 87 after displaying respiratory difficulties. Another male dog was sacrificed on Day 182. Autopsy revealed dense foam in trachea and an atrophy of mandibular salivary glands. Histopathological examination showed slight, diffuse acute tracheitis.

Clinical signs:

- (1) Vomiting: drug and dose-related increases of incidences.
- (2) Behavior changes: high dose dogs were quieter, but became nervous when touched.

Body weight and food consumption:

Body weight: reduced weight gains were observed in mid and high-dose F only. (Starting from week 2, dose and duration related decreases were observed).

Food consumption: in mid and high F only, correlating to reduced weight gains.

Blood analysis:

Hematology:

MCV: 10% decreases in high M and F.

RBC: 10% increases in high M and F.

Chemistry:

Cholesterol and triglycerides: tendency to decrease in high M.

Alk. phosphatase: slight increases in high M and F.

Urinalysis: tendency to slight decreases of specific gravity in high-dose group.

Ophthalmology: unremarkable.

Heart rate and EKG: no significant finding.

Organ weight: No significant changes were observed at 3-month, or at 6-month for male dogs. At 6 months, mid and high F showed increased relative weights of most organs (due to the suppressed weight gains at these levels).

Pathology:

Gross pathology: no significant findings at 3- or 6-months.

Histopathology: no significant findings at 3- and 6-months.

(3) One-year Oral Toxicity Study of Cetirizine P071) in Beagle Dogs
(IND Report T-29, Report 208/851114/PFZ) (F-18)

Performed by:

June 28, 1984 - June 28, 1985

Animals:

Beagle Dogs, from Hacking and Churchill, Cambell Farm, Wt. 10.6 kg (M)
9.2 kg (F), age: 24-28 weeks

No. of Animals/dosage:

10 (5M + 5F)

Route of Administration:

Orally through gelatin capsules daily for 52 weeks.

Duration of Treatment:

Daily for 52 weeks.

Dosage groups: (mg/kg/day)

(1) Control:	empty gelatin capsule
(2) Low dosage group:	4
(3) Mid dosage group:	15
(4) High dosage group:	60

Results:

Signs:

Vomiting: dose-related within 1-hour of dosing in M and F, only
occasional in low-dose group.

Mortality: None

Body weight: M (mid & high): decreased weight gains during 52 weeks.

Food consumption: No significant finding.

Physical examinations: on pre-dose, weeks 12, 24, 38, and 50.

ECG: sig. increase QTC in HD-M only at week 50.

BP: some increase in dosed F during pre-dose and week 50

Ophthalmic examination: pre-dose, weeks 12, 24, 38, and 50.
Unremarkable.

Hematology/bone marrow/coagulation:

Changes (mostly inc) in RBC, Hgb, McHc and APTT in HD and HD female during weeks 12 and 24.

Bone marrow smears: normal in cellularity, morphology and cell distribution at sacrifice.

Blood chemistry: No significant finding.

Urinalysis: Unremarkable.

Organ weights: Unremarkable.

Gross pathology: Unremarkable.

Histopathology: Unremarkable.

ADME data: Week 52 data

* F > M

(1) Dose (mg/kg/day)	Tmax(hr)	Cmax(ug/ml)	AUC(ug.hr/ml)	Bile/plasma
4	1.5	5.8	65.0	17.8
15	1.3	29.7	325.7	26.1
60	2.4	101.5*	1456.1	30.1

(2) Steady state reached in 1 week

(3) No accumulation was apparent.

(4) Except at HD where F > M in peak plasma levels, no sex difference in pharmacokinetics were observed.

Hepatic drug metabolizing enzymes: at sacrifice.

Parameters: microsomal protein, cytochrome P-450, aniline hydroxylase, ethylmorphine-N-demethylase, phenacetin-N-demethylase: no significant effect.

①) Monkey studies: (1)-(3)

(1) Preliminary Oral Toxicity Study in Cynomolgus Monkeys ~~(T-16)~~ (T-16):

Performed by:

Animals:

Wild-caught cynomolgus monkeys (*Macaca fascicularis*)

No. of animals/dosage: 2 (1 M+ 1 F), each pair was studied at a time.

Route and duration of administration:

Orally by gavage as a solution in distilled water, daily for 14 days.

Dosage levels: (4 ml/kg of 5% solution, except*)

(1) Control: distilled water

(2) Low dosage: 50 mg/kg/day

(3) Mid dosage: 100 mg/kg/day

(4) High dosage: 200 mg/kg/day *(vol. of 4 ml/kg - 1 day; 2.5% - 8 ml/kg - 13 days).

Results:

Mortality: none.

Clinical signs:

Salivation and vomiting from 50 mg/kg.

Quiet behavior/pilo-erection/tremor/loose, mucus feces: 200 mg/kg.

Body weight and food consumption:

Body weight: losses from 50 mg/kg (F), 100 mg/kg (*M and F) and 200 mg/kg (*M and F). *more losses.

Food: decreased in both M and F of 200 mg/kg group.

Blood analysis:

Hematology:

RBC: dec. from 50 mg/kg on Day 11.

Pathology: liver findings of fat deposition in both monkeys of 200 mg/kg group; F monkey had pallid and mottled liver. Bot monkeys had congested lungs.

(2) 4-week Oral Toxicity Study in Cynomolgus Monkeys (T-25)¹⁷. - -

Performed by:

Animals:

Wild-caught monkeys (*Macaca fasciculatrix*).

No. of animals/dosage: 6 (3M+ 3F)

Route and duration of administration:

Orally by gavage of solution in distilled water daily for 4 weeks.

Dosage levels:

- (1) Control: vehicle
- (2) Low dosage: 17 mg/kg/day
- (3) Mid dosage: 50 mg/kg/day
- (4) High dosage: 150 mg/kg/day

Results:

Mortality:

One F from 150 mg/kg group sacrificed on Day 22.

Clinical signs:

Vomiting (shortly after dosing), huddled posture, poor condition of the coat, limb tremors, abdominal scratching motion and drop in body temperature: at 150 mg/kg level.

Body weight and food consumption:

Body weight: marked losses in high dose group and moderate losses in 2 F of 50 mg/kg group.

Food: only the sacrificed F showed dec. food consumption.

Blood analysis:

Hematology:

No significant trends.

Chemistry:

- (1) Dec. ornithine carboxyltransferase: at 50 and 150 mg/kg.
- (2) Dec. sorbitol dehydrogenase: at 17, 50 and 150 mg/kg.
- (3) Inc. triglycerides: at 150 mg/kg.

Urinalysis: marginally dec. specific gravity in 150 mg/kg group.

Ophthalmology: unremarkable.

Heart rate and ECG:

ECG: only the sacrificed F showed low HR with sinus arrhythmia.

Organ weight:

Kidneys and lungs: increases of absolute and relative wts. only in 150 mg/kg group.

Pathology:

Gross pathology: No significant finding.

Histopathology: No significant finding.

Assay of Drug Metabolizing enzymes: at end of 4 weeks.

- (1) Liver weight: both absolute and relative weights were lower in F of 150 mg/kg group.
- (2) Total microsomal protein: lower in the F of 150 mg/kg.
- (3) Three hepatic microsomal enzymes (ethylmorphine-*N*-demethylase, aniline hydroxylase and *p*-nitroanisole *O*-demethylase) showed increased activities in F monkeys of 50 and 150 mg/kg groups and in M monkeys of 17 and 150 mg/kg groups, but no statistical significance was established.

(3) One-Year Oral Toxicity Study of Cetirizine (UCB P071) in Cynomolgus Monkeys (IND Report T-30, HRC Report UCB 220-g/86186) (T-19).

Performed by:

October 4, 1984 - October 4, 1985

Animals:

Wild-Caught Cynomolgus Monkeys (*Macaca fascicularis*), from Shamrock Farms, Great Britain, wt. 2-3 kg, age: 2-4 yrs

No. of animals/dosage: 10 (5M + 5F)

Route and duration of administration:

Oral by gavage, as a solution in water daily for 52 weeks.

Dosage levels: (mg/kg/day)

- (1) Control: vehicle
- (2) Low dosage: .5
- (3) Mid dosage: 15
- (4) High dosage: 45

Results:

Mortality: None.

Clinical signs: Salivation: mainly at HD

Body weight and food consumption: No significant effect.

Blood analysis:

Hematology: No consistent/significant findings.
Bone Marrow smear: no effect.

Chemistry: No consistent changes.

Urinalysis: Inc. volume and dec. sp. gr. at HD

Ophthalmology: Unremarkable.

Heart rate and ECG: Unremarkable.

Organ weight: Testes: inc. abso & rel. wt. at HD

Pathology:

Gross pathology: Unremarkable.

Histopathology: Unremarkable.

ADME data:

* F M

Week 52 data

(1)Dose (mg/kg/day)	Tmax(hr)	Cmax(ug/ml)	AUC(ug.hr/ml)	Bile/plasma
5	0.9	3.3	9.9	
15	1.2	10.0	32.4	
45	1.5	31.9	134.4	

(2) Steady states reached in 1 week.

(3) No accumulation was apparent.

(4) No sex difference in pharmacokinetics were observed.

Hepatic drug metabolizing enzymes: at sacrifice.

Parameters: Microsomal protein, cytochrome P-450, aniline hydroxylase, p-nitroanisole-o-demethylase and ethylmorphine-N-demethylase: no significant effect.

Carcinogenicity Studies: 1-2.

1. Two-Year Dietary Mouse Carcinogenicity Study (T-20).

GLP statement: yes.

Performed by:

Animals: Charles River CD-1 mice, approximately 5-6 weeks old at the start of treatment, obtained from Charles River Breeding Lab., Margate, Kent, UK. M: 27 gm and F: 19 gm.

No of animals/dosage: 104 (52M + 52F).

Route, mode and duration of administration:

Orally through dietary mixture daily for 104 weeks or 2 years.

Dosage selection: based on 4-week dietary study that showed drug-related toxicological effects in livers. Lipid deposition and elevated liver enzymes at 27-81 mg/kg in male mice. Female mice showed elevated triglycerise at 27-81 mg/kg. Centrilobular hepatocyte hypertrophy (enlargement) in 3-81 mg/kg M mice was considered of no toxicological significance because it was related to enzyme adaptive changes.

Dosage levels (mg/kg/group): weekly analyses (body weight, food consumption and inclusion levels of test compound) revealed all within target ranges.

(1) Control: 0
(2) Control: 0
(3) Low dose group: 1
(4) Mid dose group: 4
(5) High dose group: 16

Health check group: 20 (10M + 10F) no lesions or infectious diseases found on 6/13/84 (sacrificed and macroscopic and histopathological examination).

Results:

Signs: no significant signs attributable to treatment.

Body weight:

Weight gains comparable among groups during study period.

Food consumption: comparable among groups during study period.

Blood Smears:

Taken from all surviving mice during weeks 52, 53, 57 and at termination showed no significant effect.

Mortality: no significant finding. Cause of death attributed to injuries from fighting among males during the first 13 weeks. Mortalities ranged 50-58% (M) and 29-54% (F). One of the contributing factors to female deaths was lymphosarcoma accounting for 4, 3, 3, 9 and 9 deaths in Groups 1-5, respectively in female mice. Distribution of deaths are as follows:

	Group and dosage (mg/kg/day)									
	1 st Control	2 nd Control	3 rd 1	4 th 4	5 th 16	1 st Control	2 nd Control	3 rd 1	4 th 4	5 th 16
Initial group size	52	52	52	52	52	52	52	52	52	52
No. sporadic deaths occurring weeks:										
1 - 26	0	1	3	2	1	0	1	0	0	0
27 - 52	2	2	5	2	5	1	3*	1	3	0
53 - 78	6	14	9	5	4	5	7	4	6	6
79 - 104	18	13	13	19	18	18	17	10	12	15
105 - 106	0	0	0	0	0	0	0	0	0	1
Terminal sacrifice	26	22	22	24	24	28	24	17	31	30
% survival of mice at termination	50	42	42	46	46	54	46	71	60	58

* Includes 2 mice, Nos. 339 and 340 (#443 and 444) sacrificed in week 44 after receiving inappropriate diets

Pathology:

Gross pathology: no significant finding, except high-dose males with higher incidences of liver mass than control. In addition, high-dose males that were dead or sacrificed during study period also having higher incidence of liver mass.

NUMBER OF MALE MICE WITH:

	1		2		3		4		5	
	10	11	12	13	14	15	16	17	18	19
MICE EXAMINED:	26	26	30	32	30	32	34	34	36	34

D: found dead or sacrificed; T: terminal sacrifice

LIVER	10	11	12	13	14	15	16	17	18	19
MASS OF LIVER	0	0	0	1	0	0	1	1	0	1
NETICUS	1	1	1	3	3	2	1	4	2	4
Pale area of areas	0	0	1	2	0	1	2	0	0	0
Dark area of areas	0	0	0	0	0	1	1	1	0	4
Cyst or cysts	0	1	0	0	0	0	0	1	0	0
Pitted	0	0	0	0	0	0	0	1	0	0
Irregular surface depression	0	0	0	0	0	0	1	0	1	0
Pale	4	7	11	4	6	4	4	3	9	3
Labial markings accentuated	0	0	0	1	0	0	0	2	0	0
Enlarged	1	0	2	1	1	0	1	0	3	0

Histopathology:

Neoplastic changes:

(1) Benign liver cell tumor: increased incidence of benign liver cell tumors was observed in high-dose male mice only. In addition, a greater number of them also was found bearing multiple benign liver cell tumors (see tables). Statistical analysis on liver cell tumors (benign and malignant combined) and on malignant liver cell tumors alone for male mice was

performed. The high-dose male mice had significantly more liver cell tumors than control (p=0.02). The test for trend over all groups was significant (p=0.01). The test for trend for the first 4 groups excluding the high-dose group, however, was not significant. No significance was found in the incidence of malignant liver tumor.

(4) Incidence of male mice with liver cell tumours

	Group				
	1	2	3	4	5
Benign	13	14	15	15	25
Malignant	7	5	7	5	8
Benign and/or malignant	18	16	19	16	27
Number of animals examined	52	52	52	52	52

(5) Incidence of male animals with benign liver cell tumours

	Group				
	1	2	3	4	5
Benign liver cell tumour (one)	12	13 ^a	9	8	12 ^a
Benign liver cell tumour (two)	0	2	4	4	9 ^a
Benign liver cell tumour (three)	1	2	1	2	3
Benign liver cell tumour (four)	0	0	1	1	1
Animals with any benign liver cell tumour	13	14	15	15	25
Percentage	25.0	26.9	28.8	28.8	48.1
Animals examined	52	52	52	52	52

NOTES: In comparison with the main tables:

- ^a includes the animal with the infarcted liver cell tumour, but excludes the animal with the benign tumour in the CHO section
- ^b includes the animal with the benign liver cell tumour in the CHO section
- ^c includes the animal with the necrotic benign liver cell tumour

Historical control data from 9 studies from the performing lab. showed an incidence of 3.8%-25.9%. The concurrent control groups showed incidences of 25.0% and 26.9%, within historical control ranges.

Incidence of liver cell tumours in untreated control male mice

	Study								
	81K	82A	82B	82C	82D	82E	82F	83A	83B
Benign liver cell tumours	2	13	15	6	15	12	12	16	9
Percentage	3.8	25.0	28.8	11.5	28.8	23.1	23.1	30.8	17.3
No. of mice	52	52	52	52	52	52	52	52	52

(2) lymphosarcoma in multiple organs: increased in 16 mg/kg female mice (35, 51, 30, 27 and 56 total incidences in groups 1-5, respectively).

Non-neoplastic changes:

Some macroscopic findings mostly at high dose: liver masses/cysts (M), fluid in abdomen/thoracic cavity, subcutis edema/hemorrhage, stomach (depression in corpus mucosa, dark/blood contents) and ovarian cysts (F). Histopathology did not reveal significant finding in treated mice.

Body weight: no significant finding.

Food consumption: no significant finding.

Efficiency of food utilization: no significant finding except for mid F and high F with higher efficiency during month 4-6.

Blood smears: no significant finding at Week 52, 78 and 104.

Pathology: gross and histopathology were performed.

Neoplastic changes: thyroid follicular adenoma, pituitary tumors (carcinoma and adenoma) and liver malignant tumor were increased in some dosed groups.

(1) Thyroid follicular adenoma:

Number of thyroid follicular tumours in male rats

Groups	1	2	3	4	5
Adenoma	1	3	1	2	6
Adenocarcinoma	2	1	0	2	1
Total	3	4	1	4	7
Number of rats examined	50	50	50	50	50

- This number includes a thyroid follicular cystadenoma

Incidence of thyroid follicular tumours in untreated male Sprague-Dawley rats (Historical control values)

Study identifier	A	B	C	D	E	F	G	I	J	K	L	M	N	O	P
Number of rats with:															
Adenoma	3	2	2	6	3	1	4	0	4	2	1	2	3	6	2
Adenocarcinoma	0	1	0	1	1	0	0	0	1	0	1	2	0	1	1
No. of rats examined:	99	50	100	50	98	49	100	100	99	50	49	99	50	100	50

Increased incidence was observed at 20 mg/kg male rats. The historical data showed thyroid follicular adenoma in male Sprague-Dawley rats ranged 0-12%. The statistical analysis by sponsor concluded as follows:

Male rats receiving 20 mg/kg/day ucb P071 showed significantly more benign follicular tumors than the pooled controls, $P = 0.047$ and the test for trend over Groups 1 to 5 was significant $P = 0.009$, but did not persist when the high dose group was excluded.

For combined benign and malignant follicular tumors the test for trend over Groups 1 to 5 was significant $P = 0.03$, although the pairwise comparison between the high dose group and the pooled controls was not significant.

The incidence of benign follicular tumors in male rats receiving 20 mg/kg/day ucb P071 of 6/50 is within the range of historical control values in this laboratory. In addition, there was no evidence of a treatment-related effect on non-neoplastic lesions in the thyroid gland. Bearing these facts in mind, the increased incidence of thyroid follicular tumors was considered of no biological significance.

(2) Pituitary tumors:

Pituitary carcinoma increased in 8 mg/kg female rats. Pituitary adenoma increased in 8 and 20 mg/kg female rats. When the carcinoma and adenoma are combined, the incidences were increased in 8 and 20 mg/kg female rats

Number of pituitary tumours in female rats

Groups	1	2	3	4	5
Adenoma	26	31	27	30	32
Carcinoma	2	1	1	7	3
Total	28	32	28	37	35
Number of rats examined	50	50	50	50	50

Incidence of pituitary tumours in
untreated female Sprague-Dawley rats
(Historical control values)

Study identity	A	B	C	D	E	F	G	I	J	K	L	M	N	O	P
Number of rats with:															
Adenoma	63	30	95	28	72	34	32	52	56	36	27	54	31	59	31
Carcinoma	8	1	8	2	11	1	4	7	3	9	2	7	1	4	4
No. of rats examined	100	49	98	49	100	50	99	100	95	50	49	101	48	100	50

The historical control data in female S-D rats revealed adenoma at 60-82% and carcinoma at 2-11%.

The statistical analysis by Sponsor concluded as follows:

For malignant pituitary tumors in females the 8 mg/kg/day group showed significantly more tumors than the controls, $P=0.01$. Since the 20 mg/kg/day group was not significantly different from the controls the test for a linear trend across Groups 1 to 5 was not significant, but the test for non-linearity was $P=0.04$.

Where benign or malignant pituitary tumors combined were analysed the 8 mg/kg/day group showed a higher incidence of tumors than controls, but again the test for trend was not significant.

The incidence of pituitary carcinoma in female rats receiving 8 mg/kg/day ucb P071 (7/50) is greater than the historical control data, however, in the absence of an increased incidence of this change at the high dose level this result, confined to the intermediate dose level, is considered unlikely to be of any toxicological importance.

Moreover the incidence of pituitary tumors in female rats receiving 8 mg/kg/day and 20 mg/kg/day ucb P071 of 37/50 and 35/50 is within the range of historical control values in this laboratory (see table) and as such this result is considered to be of no biological significance.

- (3) Liver malignant tumors:
Liver malignant tumors increased in 8 mg/kg male rats.

Group	Number of liver cell tumours in male rats				
	1	2	3	4	5
Benign	1	0	0	1	0
Malignant	0	1	0	3	2
Total tumours	1	1	0	4	2
No. of rats examined	50	50	50	50	50

The statistical analysis revealed no significant differences from controls.

- (4) Mammary gland:
Fibroadenoma with epithelial atypia (2, 2, 4, 4, and 5 for C, C, low, mid and high, respectively) appeared increase in the dosed groups.

Non-neoplastic changes:

(1) Stomach:

Ulceration in the non-glandular stomach was observed from 3 to 20 mg/kg in female rats (see Table). Minimal to marked hyperplasia and hyperkeratosis of the epithelium of the non-glandular region (18, 14, 18, 24 and 20 for males, and 13, 18, 21, 19 and 26 for females for C, C, low, mid and high groups, respectively) occurred in all groups, but showed treatment-related effects at 8 mg/kg (males) and at 20 mg/kg (females). Pale (5, 3, 7, 8 and 9, respectively) increased at 3-20 mg/kg (males). Depression (7, 7, 13, 14 and 12, respectively), or thickness (2, 4, 5, 7 and 7, respectively) of forestomach increased at 3-20 mg/kg (females). The "NOEL" was not established in both male and female rats.

Incidence of ulceration in the non-glandular stomach

Group	1	2	3	4	5
Ulceration non-glandular stomach	3	6	10	10	11
No. of rats examined	50	50	50	50	50

(2) Liver:

Masses (2, 0, 1, 4, 2 for males and 1, 0, 1, 0, 0 for females) showed increase only in 8 mg/kg male rats. For male rats, enlarged (10, 7, 6, 16 and 16) /swollen (12, 14, 11, 18 and 19) /darken (25, 29, 34, 37 and 26) liver and periportal fat deposition (17, 22, 20, 26 and 27) increased at 8-20 mg/kg. Centrilobular vacuolation (13, 7, 8, 15 and 21 for males, and 13, 10, 7, 10 and 17 for females) increased at 20 mg/kg. The "NOEL" appears to be at 3 mg/kg for both male and female rats.

(3) Kidneys:

Enlarged with minimal to marked progressive glomerulonephrosis (34, 36, 37, 41 and 42 for males, 21, 25, 31, 27 and 22 for females for C, C, low, mid and high groups, respectively) occurred in all groups, but showed some treatment- and dose-related effects in male and female rats.

(4) Thyroids:

Epithelial whorls were 3, 4, 2, 1 and 6 (male rats) and 3, 4, 1, 7 and 7 (female rats) for C, C, low, mid and high groups, respectively.

(5) Pituitary: Enlarged (27, 33, 33, 43 and 35 for C, C, low, mid and high groups, respectively) with microscopic finding of dilated/congested sinusoids (15, 22, 22, 29 and 24 for C, C, low, mid and high groups, respectively) in female rats at 8-20 mg/kg.

(6) Pancreas: masses (6, 5, 2, 12 and 8 for C, C, low, mid and high groups, respectively) in 8-20 mg/kg female rats.

(Cetirizine: 071)
SUMMARY OF REPRODUCTION STUDIES
(Oral by Gavage)

Segment	I	II	II	II	III
Species	mouse	rat	rabbit	mouse	mouse
Duration (1) M: 8wks prior to mating, continued on until sacr. (2)F: 2 wks prior to mating, continued on until (a) Day 17.5 pregnancy (b) Day 21 postpartum	Day 6-15	Day 6-18		Day 6-15	Day 15 Day 21 psotpartum
No. (1) M:20 (2) F:40: Day 21, from each group for F ₁ & F ₂	25-26F	16-18F		30F	32F
Doses mg/gk/day	4 16 64*	8 25 75 225	15 45 135	6 24 *96	6 24 *96
*increased liver weight					
Adult data:					
Effect doses:	64	75-225	135	96	96
	(pregnancy/ mating perf)	(wt./sign/ death)	(wt./deaths)	(wt.)	(wt.)
					(96:nursing/ lactating performance)
No effect doses:	16	25	45	24	24

(continued)
(Cetirizine: 071)
SUMMARY OF REPRODUCTION STUDIES
(Oral by Gavage)

Litter data:	I (mouse)	II (rat)	II (rabbit)	II (mouse)	III (mouse)
Effect doses:	64 (embryocidal) 64(malformations (cleft palate) 16-64(skeletal variants/anomalies)	225(embryocidal) 25-225 (skeletal anomalies/variants)	135 (skeletal anomalies/ variants)	NE	96 (lower pup wt/ day 4-21 lower M/F @birth & weaning.
No-effect doses:	4	8	45	96	24
Significance:					
Embryocidal:	NE	225	NE	NE	NE
Teratogenicity:	64(?)		NE	NE	
Skeletal(anomaly variants)	16-64	25-225	135		
Pregnancy/mating	64				
Nursing/lactating:					96
F1 & F2 generations (no treatments)	No effects: development and reproductive functions Liver and kidney weight			(F1 only) No effect: development and liver and kidney wt.	

Reproduction Studies: 1-5

i. Segment I Reproduction Study:

Fertility and General Reproductive Performance of the Mouse (T-26).

Performed by:

March 24, 1984 - July 20, 1984

Animals:

Mice (CD-1 strain) from Charles River UK Ltd. Margate, Kent.
M (weeks old), F (9 weeks old).

Route and duration of administration: orally by gastric intubation

- (1) Dosed M: 8 weeks prior to mating and continued until sacrificing.
- (2) Dosed F: 2 weeks prior to mating and continued on until either sacrificed on Day 17.5 of pregnancy or after rearing young to Day 21 postpartum.

Dosage levels: (0.1 ml/10gm)

- (1) Control: distilled water
- (2) Low: 4 mg/kg
- (3) Mid: 16 mg/kg
- (4) High: 64 mg/kg

Results:

Maternal data:

Mortality: Total 3 (1 F of 16 mg/kg, 2M of 64 mg/kg)

Body weight and signs:

Body weight and food consumption were slightly lower at 64 mg/kg level, only food consumption attained statistical significance.

Signs: reported as unremarkable.

Pregnancy: pregnancy rate slightly lower only at 64 mg/kg level.

Mating performance: median precoital time was 3 days for all groups, but more mice of mid and high groups mated on or after 6 days. In addition, more mice of mid and high groups showed no positive mating.

Labor: not commented upon.

Necropsy: no significant finding. Liver: centrilobular hypertrophy at 64 mg/kg level.

Liver: relative weight was significantly increased only at 64 mg/kg level
F sacrificed on Day 17.5: relative liver wt. increased at 16 mg level.

Length of gestation: *slightly* prolonged only in high group.

Litter data: On Day 21, 16 M and 16 F pups per group were retained for further study.

Litter Size: from dams allowed to litter.

Control, low and mid groups: had litter size of 10.1 - 10.3.
High group: 9.1 (statistically significant).

Survival:

Pup survivals at birth and through day 4-21 were not adversely affected by drug.

Sex ratio: 50% at birth and day 21.

Body weight: Pups weight: comparable at birth, not adversely affected from day 4-21.

Malformations:

Cleft palate: higher incidences (both in terms of litters and fetuses) at 64 mg/kg (control and low: 0, mid: 1 fetus, high: 4 fetuses).

Skeletal anomalies and variants:

unossified 5th metacarpals, total variant sternabrae (unossified, reduced, asymmetric/bipartite) affected cervical vertebrae, reduced metatarsals and occipitals were higher (in terms of litters and fetuses) at 16 and 64 mg/kg.

Visceral anomalies (dilatation of renal pelvis, abdominal hemorrhage ect.): lower among dosed groups.

Necropsy:

Macroscopic findings on weaned litters showed no significant effects.

Liver and kidneys weight: from 1 M and 1 F of weaned litters showed comparable relative weights.

F₁ Generation (No Treatment)

Pre weaning development: group mean age (days post coitum).
Surface righting: 23 days for all groups
Air righting: 28 days for all groups
Startle response: 30.5 days for all groups

Post-weaning development:

(a) Signs and mortality:

No signs in F₁ generation; one F from 64 mg/kg parents was sacrificed on Day 55 (age) - failed to show vaginal opening.

(b) Body weight: no significant effects noted.

(c) Vaginal opening: comparable opening age in all groups.

(d) Pupil reflex test: comparable among groups (tested at week 4).

(e) Behavioral tests: tested at 5 weeks of age.

(i) Actimat (testing activity):

(ii) Rotarod test (testing motor coordination and balance)

(iii) Passive avoidance (tested at 7 weeks of age for learning):
no effects seen.

(f) Mating performance and pregnancy rate:

(i) Mating performance (median pre-coital times and positive indication of mating): similar among groups.

(ii) Pregnancy rate: 100% in all groups.

(g) Gestation period: 18.6 days (18-19 days) in all groups.

(h) Terminal autopsy: no significant finding.

Liver and kidneys weights: relative weights were comparable among groups.

Litter data:

(a) Total litter loss: two dams showed total litter loss. One from 64 mg/kg parents and the other from 4 mg/kg parents.

(b) Litter size and pup mortality: comparable among groups.

(c) Litter and mean pup weight: comparable.

(d) Terminal autopsy: no significant finding. Liver and kidneys weight: relative weights of both organs taken from 1M and 1F from each litter were comparable among groups.

Significant = mouse

TABLE 5
Mating performance and pregnancy rate - F0 generation

Group	Dosage ucb P071 (mg/kg/day)	Number of females paired	Number of successful mating pairs on Days:								Total No.	Pregnancy rate (%)	Median pre-coital times days	Observation at mating	
			1	2	3	4	5	6	>6	Vaginal plug				No indicat. of mating	
1	0	40	11	6 ^a	11 ^a	8	0	1	3	40	100	3.0	39	1	
2	4	40	6	11 ^a	13 ^{aa}	5	1	0	4	40	100	3.0	39	1	
3	16	39	7	9 ^a	15 ^{aa}	6	0	1	1	39	100	3.0	36	3	
4	64	40	9	2	12 ^a	3	0	3	7 ^{aaa}	36	90	3.0	32	4	

^a Includes one (aa, two aaa, three) female(s) with no indication of mating on day of conception - day determined retrospectively assuming a 19 day gestation
^b Time by which half of the paired females had conceived

Segment I: mouse

TABLE 10

Group mean incidence of malformations and anomalies

Group	Doseage (mg/kg/day)	Number of litters	Number of foetuses									
			Malformations					Anomalies				
			Examined	Affected litters	Mean	Examined	Total	Mean	Examined	Total	Mean	
1	0	201	2	4	2.3	98	4	5.2	99	7	19.8	
2	4	225	1	1	0.4	111	8	6.8	112	7	6.7	
3	16	211	3	3	1.6	105	12	16.7	103	1	1.1	
4	64	173	5	9	5.5	82	12	15.3	82	1	1.2	

1 Foetuses with malformations excluded

2 Skeletal anomalies: statistical analysis non-significant at Kruskal-Wallis test (P>0.05)

3 Background data

4 Data from control and inactive test groups from three mouse teratology studies using CD-1 mice performed at Harlan Olac Research Centre 1981 - 84.

Number of litters examined	370	Type of malformations observed
Number of foetuses examined	3015	Cleft palate 17
Number of foetuses with malformations	34	Neural tube defects 6
		(e.g. craniorhachischisis) 5
		Digital and limb defects 4
		Open eye 11
		Others 11

5 Includes foetuses with multiple malformations

2. Reproduction Study: teratogenicity study in mouse (T-27)

Performed by :

August 23, 1984 - September 5, 1984

Animals:

Mice (CrL: COBS CD-1 (ICR) BR strain) from Charles River
U.K. Margate, Kent. 20-27 gm

Route and duration of administration:

Orally by gastric intubation from Day 6-15 of pregnancy; sacrificed
on Day 17.5 of pregnancy.

No. of animals/group

30F/group:

Dosage levels: (0.1 ml/10 gm)

- (1) Control: distilled water
- (2) Low: 6 mg/kg/day
- (3) Mid: 24 mg/kg/day
- (4) High: 96 mg/kg/day

Results:

Mortality: None

Signs: Incidental signs of eye discharge, fur loss, noisy respiration.

Body weight and food:

Mean weight gains slightly higher at mid and high doses during the
later part of pregnancy.

Food consumption slightly lower in all dosed groups from Day 8-13.

Pregnancy Rate: comparable among groups.

Necropsy:

Liver: absolute and relative weights significantly increased at 96 mg/kg level.

Kidneys: weights decreased at 96 and 6 mg/kg

Resorption: no apparent drug-effect.

Implantations: Pre-and post-implantation losses showed no drug-related effect.

Litter data:

Litter Size: comparable among groups

Sex ratio: no significant difference

Body weight: comparable

Visceral anomaly: No effect

External anomaly: no effect

Skeletal anomaly: no effect.

TABLE 7
Group mean incidence of malformations and anomalies

Group	Dosage ucb P071 (mg/kg/day)	Number of litters	Number of fetuses								
			Malformations			Anomalies ¹					
						Skeletal			Visceral (Wilson technique)		
			Examined	Total No.	Mean %	Examined	Total No.	Mean %	Examined	Total No.	Mean %
1	0	23	199	0	0.0	100	10	8.1	99	3	3.4
2	6	20	181	1	0.4	91	5	4.7	89	6	7.7
3	24	21	212	2	0.8	104	8	8.1	106	1	1.0
4	96	24	250	1	0.4	124	6	5.6	125	6	4.6

¹ Fetuses with malformations excluded

3. On oral teratological study in rats.

Performed by

November 4-December 9, 1981.

Animals: Sprague-Dawley rats (OFA, CD-IOPs caw), 10 weeks old, weight 229 gm.

No. of animal/dosage: 25-26

Route and duration of administration: orally by gavage the compound (in dist. water) from Day 6-Day 15 of gestation.

Dosage level:

- (1) Control: water
- (2) Low: 8 mg/kg/day
- (3) Mid: 25
- (4) High: 75
- (5) Highest: 225

Results:

(A) Maternal data:

- (a) Mortality: 8 deaths (1 F from 75 mg/kg and 2 F from 225 mg/kg were considered accidental deaths due to trachea intubation; 5 F from 225 mg/kg died of toxic effects of drug. Blood on the muzzle and respiratory difficulties, reduced body weight gains were observed before deaths). Autopsy revealed flatulence in most deaths.
- (b) Clinical signs:
 - Hair losses: in 8 and 75 mg/kg/day rats
 - Respiratory difficulties: in 75 and 225 mg/kg/day rats.
 - Arched back, nervousness and difficult to handle: 225 mg/kg/day rats.
- (c) Body weight and food consumption: weight gains and food consumption were suppressed only in 225 mg/kg/day rat.
- (d) Pregnancy rate: comparable among groups.
- (e) No macroscopic abnormalities were observed.

(B) Litter Data:

(a) Pre- and post-implantation losses:

Although not statistically significant, both pre- and post-implantation losses (%) were considerably higher at 225 mg/kg level, mainly due to 4 litters.

(b) Fetal weight:

Mean fetal weights were significantly lower in 8, 75 and 225 mg/kg groups, but may not be biologically significant because of the nominal values. More runts at 225 mg/kg.

(c) Malformations: Unremarkable

One fetus from 8 mg/kg group had major anomalies (absence of lower jaw with eyes and ears displaced). This fetus also had major visceral anomaly (left microphthalmia) and lower body weight. Another pup from 225 mg/kg had left microphthalmia and lower body weight.

(d) Visceral anomalies: Unremarkable.

Visceral minor anomalies (increased renal pelvic cavitation, uni- or bilateral with papilla present) were found in control and dose groups. Hypertrophy of one or both kidneys with or without hemorrhage/slightly external or medial displacement of kidney were observed in 3 fetuses of 8 mg/kg, 1 fetus of 25 mg/kg, 2 fetuses of 225 mg/kg.

(e) Skeletal anomalies/variants:

Skeletal minor anomalies (retarded ossification of isolated bones of the skull-parietal, interparietal or multiple-bone-, sternbrae-bipartite or irregular, thoracic or caudal vertebrae-reduced or unossified) were higher in 25, 75 and 225 mg/kg groups with no dose-related effect. Pronounced retardation of ossification were observed in 2 pups of 2 litters from 75 mg/kg groups and 7 pups of 1 litter from 225 mg/kg group.

Significant differences

TABLE VI

litter data : means per litter

Company Jose (log/kg) (females)	Mr of pregn (females)	# gravid	Mean	Nr of litters conclid	Corpora lutea	Implen- tations	live foetus	Dead foetus	Early resorpt	Late resorpt	Mean total loss	Pre- implant loss	Post- implant loss	foetal weight (g)		Placental weight (g)	
														Mean litter (1)	Mean foetal (2)	Mean litter (1)	Mean foetal (2)
Control	26/26	100	A - B	26	18.4	14.4	13.4	0	0.92	0.08	1.00	19.55	6.94	51.33	3.82	7.29	0.54
PO11	23/25	92	A - B	23	19.0	14.5	13.7	0	0.65	0.09	0.74	21.31	4.90	51.20	3.73	7.28	0.53
PO11	23/25	92	A	23	17.4	12.5	11.6	0	0.65	0.22	0.87	20.43	11.19	44.70	3.86	6.55	0.54
1011	22/26	84.62	A - B	21	17.4	14.3	13.7	0	0.40	0.14	0.52	16.40	4.37	53.20	3.89	7.33	0.54
PO11	25/26	96.15	A - B	17	19.6	13.6	12.0	0	1.12	0.53	1.65	29.79	12.55	44.59	3.72	6.63	0.55

Comparison of means : each group versus control by two-sample : Wilcoxon test (1)
Student t test (2)

Segment II : nat

Table VII

Group mean incidence of major and minor anomalies - Summary.

Doses	Total nr of foetuses examined		Nr of foetus and litters											
			Major malformations					Minor anomalies (x)						
			Wilson's		Skeletal ex.			Wilson's		Skeletal variants				
	M. (i)	S. (ii)	Total malf. (1)	Nr litter (2)	Mean % (3)	Total malf. (1)	Nr litter (2)	Mean % (3)	Total anom. (1)	Nr litter (2)	Mean % (3) (a)	Total anom. (1)	Nr litter (2)	Mean % (3) (b)
Control	176	173	0	0/26	0	0	0/26	0	18	12/26	10.1	12	10/26	6.8
P071 8 mg/kg	158	150	1	1/23	0.9	0	0/23	0	31	16/23 NS	19.6 NS	16	10/23 NS	9.6 NS
P071 25 mg/kg	136	131	0	0/22	0	0	0/22	0	17	12/22 NS	11.5 NS	17	11/22 NS	17.9 NS
P071 75 mg/kg	141	146	0	0/21	0	0	0/21	0	30	15/21 NS	20.7 NS	22	13/21 NS	18.5 NS
P071 225 mg/kg	102	102	1	1/17	0.8	0	0/17	0	15	7/17 NS	14.4 NS	18	9/17 NS	17.2 NS

(1) Wilson's technique = W
(ii) Skeletal examination = S

- (1) Number of foetuses presenting malformations or anomalies.
- (2) Number of litters affected versus number of litters examined.
- (3) Mean of percentages of foetuses affected per litter per group.
- (a) Comparison of means ; each group versus control group by two-sample : Wilcoxon test.
- (b) Comparison between treated group and control is made with a Chi² test.
- (x) Foetuses showing major malformations excluded.

4. Oral teratological study in rabbits: (T-25)

Performed by March 9, 1982-April 20, 1982

Animals: New Zealand White rabbits, 6 months old, 3.5 kg.

No. of animals/group: 14-18 females

Route and duration of administration:
orally by gavage the compound (in dist. water) from Day 6-Day 18 of pregnancy.

Dosage levels: mg/kg/day

(1) Control:	water	(17 rabbits)
(2) Low	15 mg/kg	(16 rabbits)
(3) Mid	45	(16 rabbits)
(4) High	135	(18 rabbits)
(5) Positive control:	150 mg/kg/day thalidomide (as 0.5% of methylcellulose suspension).	(14 rabbits).

Results:

(A) Maternal data:

(a) Mortality: 3 (1 control and 2 high dose rabbits).

One control and one high dose females were sacrificed on Day 15-17 of pregnancy. Autopsy revealed tracheal intubation as cause of death. Another high dose rabbit was found dead on Day 9. Tracheal intubation was also the cause of death. These 3 rabbits were not included in calculations.

(b) clinical signs: none reported.

(c) Body weight and food consumption:

During the treatment, only high dose group showed suppressed weight gains (-23%) than control group. After the treatment period, all 3 dosed groups showed lower weight gains. Thalidomide showed an 80% lower weight gains during this period. Food consumption (by visual inspection only) showed decreases in some control and treated rabbits.

(d) Pregnancy rate: comparable among groups.

(e) No macroscopic abnormalities were observed in dams.

(B) Litter data:

(a) Pre- and post-implantation losses:

No significant findings were observed up to 135 mg/kg level, whereas significant post-implantation losses were seen in thalidomide group which had fewer live fetuses.

(b) Fetal weight: both fetal and placental weights were lower in thalidomide group only.

(c) Malformations: unremarkable (none in control group, 2 fetuses from 15 mg/kg, 2 fetuses from 45 mg/kg and 1 fetus from 135 mg/kg groups).

These anomalies included internal hydrocephaly, meningocele, microcephaly, failure of development of the frontal and parietal bones, kidneys smaller or missing descending tubules in medulla or hydronephrosis. In the thalidomide group, in addition to the aforementioned anomalies, missing digits, fibula reduced to a trace, absences of talus, malrotation of limbs, reduced caudal vertebrae and agenesis of kidneys were observed in 50% of litters.

(d) Visceral anomalies: Unremarkable.

(e) Skeletal anomalies/variants:

These included 4th and 5th sternbrae fused, reduced ossification in control, 15 and 45 mg/kg groups. At 135 mg/kg, in addition to the aforementioned skeletal anomalies, fontantella very enlarged, sternbrae irregular were also observed. Higher incidences of skeletal minor anomalies were observed at 135 mg/kg level and thalidomide group.

TABLE V

litter data : mean per litter

Compound & doses mg/kg/ day	Compounds & doses mg/kg/ day	% of preg- nancy	nr of litters	Mean corpore lutea	Implan- tations	Live foetus	Dead foetus	Early resorpt	Late resorpt	Mean total loss	Pre- implant loss	Post implant loss	Foetal weight Mean by group of litter weight	Foetal weight Mean by group of individual foetal weight	Placental weight Mean by group of placental litter weight	Placental weight Mean by group of individual placental weight
Control	17/17	100	16	A-B 12.3	9.4	8.1	0	0.94	(1) 0.26	1.38	19.91	14.02	(1) 352.08	(2) 43.33	(1) 50.55	(1) 6.22
P071	16/16	100	16	A-B 11.7	8.6	7.8	0.06	0.44	0.38	0.81	23.74	10.02	MS 342.08	MS 44.14	MS 48.29	MS 6.41
P071	15/16	93.0	15	A-B 11.7	8.3	8.0	0	0.27	0.07	0.23	28.39	3.81	MS 330.94	MS 41.37	MS 45.95	MS 5.74
P071	15/18	88.9	14	A-B 11.9	9.1	8.1	0	0.57	0.36	0.93	21.62	9.26	MS 343.61	MS 42.20	MS 48.50	MS 6.17
Inalid	17/14	92.9	13	A-B 11.1	9.7	5.5	0.08	2.54	1.62	4.15	12.46	41.87	MS 219.07	MS 40.11	MS 30.63	MS 5.61

Regression analysis : analysis of variance for regression

Control versus treated
linearity
around linearity

MS
MS
MS

MS
MS
MS

MS
MS
MS

MS
MS
MS

MS
MS
MS

MS
MS
MS

MS
MS
MS

Comparison of means : each group versus control by two-sample Wilcoxon test (1)
Student t test(2)

TABLE VI

Group mean incidence of major malformations and minor anomalies - Summary

Compound and doses (mg/kg/day)	Number of foetuses and number of litters									
	Total number of foetuses examined	Major malformations			Minor anomalies (a)					
		Nr of foetuses with (2)	Mean % per litter (1)	Nr of litters with (2)	Gross autopsy			Skeletal examination		
					Nr of foetuses with (2)	Mean % per litter (1)	Nr of litter with (2)	Nr of foetuses with (2)	Mean % per litter (1)	Nr of litter with (2)
Control	130	0	0	0/16	0	0	0/16	5	3.6	3/16
ucb P071 15	124	(b) 2 NS	2.1 NS	1/16	0	0	0/16 NS	4	3.8 NS	3/16 NS
ucb P071 45	120	2 NS	1.7 NS	2/15 NS	1 NS	0.8 NS	1/15 NS	4 NS	2.9 NS	3/15 NS
ucb P071 135	114	1 NS	0.7 NS	1/14 NS	0	0	0/14 NS	14 ■	10.9 NS	7/14 ■
Thalidomide 150	71	(b)34 ■■■	50.5 ■■	11/13 ■■	3 ■	4.10 NS	2/13 NS	20 ■■■	26.8 ■■	10/13 ■■

(a) Foetus showing major malformations excluded

(b) 1 dead foetus excluded (see table IV)

Comparison of means : each group versus control : - Wilcoxon test (1)
- (Chi)² test (2)

(5) Segment III Reproduction Study: Peri- and post-natal reproduction study
in mouse. (T-28)

Performed by:

September 15 - October 12, 1984

Animals: Mice (CrL.: COBS CD-1 (ICR) BR strain), from Charles River
U.K. Ltd. Margate, Kent.

Route and duration of administration:

Orally by gastric intubation from Day 15 of pregnancy to Day 21 postpartum.

No. of animals/group: 32 F/group

Dosage levels: (0.1 ml/10gm)

- (1) Control: distilled water
- (2) Low: 6 mg/kg/day
- (3) Mid: 24 mg/kg/day
- (4) High: 96 mg/kg/day

Results:

Maternal data:

Mortality: None

Body weight and signs:

Reduced body weight and food consumption were observed at 96 mg/kg level
during postpartum.

No unusual signs observed.

Necropsy:

Significant increase of liver weight (absolute and relative) at 96 mg/kg
level.

Pregnancy: comparable among groups (91%-97%)

Labor: Not commented on.

Nursing performance:

Judging from lower pup weight gain from Day 4 postpartum to weaning,
nursing performance was probably affected at 96 mg/kg.

Length of gestation: No significant effect.

Necropsy: Unremarkable

Liver: weight increase at 96 mg/kg.

Kidneys: no effect.

Litter data:

Litter size: Comparable among 4 groups

Survival: No significant difference among 4 groups.

Pre-weaning development: surface and air righting reflex were comparable among 4 groups. Startle response: Statistically delayed from 24 mg/kg level, but not of biological significance because of marginal differences.

Sex ratio:

Lower M/F ratio observed at 96 mg/kg level at birth and weaning.

Body weight:

From Day 4 postpartum to weaning on Day 21:

Significantly lower pup weight at 96 mg/kg level only.

Anomaly: None reported; cold pups were noted in 2 litters (24 mg/kg) and 3 litters (96 mg/kg) and none in control and low groups.

Liver and kidney weight (1 M and 1 F pups per litter for these organ weight data): no significant findings.

V. GENETIC TOXICOLOGY STUDIES

Summary of mutagenicity testings

: (1), (2) and (4)
(3)

Tests	(1) Ames	(2) Clastogenic Activity Assay	(3) Forward Mutation Assay	(4) Micronucleus test
Study No.	T-29	T-30	T-31	T-32
Date	March, 1982	March-May, 1982	1986	July-Sept. 1982
Strains/Cells	Salmonella typhimurium TA 1535, 1537, 1538 TA 98 and 100	Human peripheral lymphocytes	mouse lymphoma L5178Y cells	mice 10(5M +5F)
Positive control	yes	cyclophosphamide	yes	Chlorambucil 30 mg/kg/day
Solvent	water	water	water	water
Conc. or dosages	5, 50, 500 and 5,000 ug/plate (+ S-9 mix)	20,100 500 ug/ml (+ S-9)	260-420 (-S-9) 150-300 (+S-9) (ug/ml)	14,70 and 350 mg/kg day P.O. for 2 days
Cytotox. positive@	5000 ug/pl	500 ug/ml	420 (-S-9) 300 (+S-9)	
Results	No increase of revertants (+9-S)	no damage to chromosomal structure	no increase of mutant frequency	N/A no increase of micronuclei (+ S-9)
Remarks	Negative	Negative	Negative	Negative

V. ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION:

Table 1. Pharmacokinetics of Cetirizine in Animals (10 mg/kg) and in Man (10 mg)¹

Parameter	Mouse		Rat		Rabbit		Dog	Monkey	Man
	M	F	M	F	M	F	(M&F)	(M&F)	(M)
C _{max} (mcg/ml)	11.6	11.3	1.6	4.2	13.6 ²	13.4 ²	18.6	8.3	0.7
T _{inax} (hr)	0.7	0.7	0.5	0.5	0.7	0.7	3.0	1.3	1.0
AUC (hr.mcg/ml)	65.4	52.3	-	-	29.0 ²	35.0 ²	334.0	23.8	3.0
Half-Life (hr)	3.5	3.0	0.5 ⁴	0.7 ⁴	1.9	2.8	10.0	1.4 ⁴	8.0
Urinary Excretion of unchanged cetirizine (% dose) ⁵	24.1	29.8	1.5	9.6	60.7	65.8	34.2 ⁶	35.0	60.0
NDA Report No.	NPK-1		NPK-5		NPK-12		NPK-13	NPK-21	CPK-1.

- ¹ Mean data of 2-10 animals, or 35 human subjects in 2 single dose bioequivalence studies, expressed as the dihydrochloride salt.
- ² Adjusted to 10 mg/kg.
- ³ Calculated for 10 mg/kg (based on 50 kg man) C_{max} = 20 and AUC = 170.
- ⁴ Determined after IV administration.
- ⁵ 72 hours;
- ⁶ 96 hours.
- ⁷ Mean daily excretion of unchanged cetirizine from multiple dose study; no excretion data was collected in the bioequivalence studies.

TABLE I. PHARMACOKINETIC STUDY DATA SUMMARY IN ANIMAL SPECIES

SITE(S)/ STRAIN	NDA REPORT PRO.	DOSE (mg/kg)	ROUTE OF ADMINISTRATION	NUMBER OF ANIMALS	Cmax (ng/ml)		Tmax (hr)		PARAMETERS TK (%)		AUC (ng·hr/ml)		Bioavailability (%)																									
					M	F	M	F	M	F	M	F	M	F																								
Dog/ Beagle	NPK-1	10	IV	70	17.6	11.7	0.67	0.67	2.8	3.1	61.7*	97.3*	106	91																								
									2.3	2.0	63.6*	92.3*																										
Dog/ Muttie	NPK-3	10	IV	7*	17.0	26.9	0.3	0.3	0.3	0.7			36*	66*																								
															10	PO	60	1.6	6.2	0.3	0.3																	
																												1	PO	6	1.6	1.3	0.67	0.67	1.9	2.8	2.9	3.3
15	PO	6	14.0	10.3	1.0	1.0	2.0	2.2																														
63	PO	6	30.2	63.7	1.3	1.0	1.3	1.6																														
133	PO	6	163.6	167.8	3.0	1.3	3.3	3.0																														
Dog/ Beagle	NPK-13	10	IV	8	2.7**		2		8.6		61.8**		101	97																								
									7.7		63.5**																											
									9.3		361**																											
									10		336**																											
Dog/ Beagle	NPK-14	0.6	PO	9	1.67	1.93	1.34	2.38	8.2	7.9																												
									1.80	1.98					1.08	1.90	11.3	10.3																				
Dog/ Beagle	NPK-15	10	PO	3	29.6		1.3		9.9	27.5																												
Monkey/ Cynomolgus	NPK-20	10	IV	2	0.3***	0.3***	2***	0.3***	1.2***	1.3***	2.1***	1.6***	61**																									
									1	IV	2	3.8***			6.1***	0.3***	0.3***	3.0***	3.2***																			
									10	PO	2	3.8***			6.1***	0.3***	0.3***	21.8***	21.1***																			
									10	IV	2	1.7***			1.6***	1.7***	1.6***	68.1***	35.7***																			
Monkey/ Cynomolgus	NPK-21	10	PO	2	0.8***	0.9***	1***	2***	1.6***	1.6***	2.6***	2.8***	66.6																									
									1	IV	2	6.8***			9.7***	2***	0.3***	1.3***	2.8***																			
									10	PO	2	6.8***			9.7***	2***	0.3***	26.6***	23.3***																			
									10	IV	2	1.6***			1.6***	1.6***	1.6***	66.5***	31.1***																			

* Determined from urinary excretion of retentive.
 ** Numbers in center of column indicate combined M&F results.
 *** Results of individual animal.
 * - AUC (16 hr)
 ** - AUC (48 hr)
 *** - AUC (28 hr)
 **** - AUC (12 hr)

TABLE 2. EXCRETION OF CETIRIZINE IN DIFFERENT ANIMAL SPECIES

Species/ Strain	NDA Report No.	Dose (mg/kg)	Route of Administration	Sampling Time (hr)	Total Amount Excreted (% dose Cetirizine)			
					Urine		Feces	
					Male	Female	Male	Female
Mouse/NMPL	NPK-1	10	IV	0-72	31.8	36.2		
		10	PO	0-72	24.1	29.8		
Mouse/OE-1 SPF	NPK-2	10	IV	0-96	41.5*	53.8*	66.3*	43.2*
		10	PO	0-96	36.5*	57.6*	59.8*	46.4*
Rat/Wistar	NPK-5	10	IV	0-72	4.1	20.8		
		10	PO	0-72	1.5	9.6		
Rat/ Sprague Dawley	NPK-6	1	IV	0-96	11.8*	21.6*	79.1*	76.6*
		5	PO	0-96	16.4*	25.8*	82.6*	71.6*
		25	PO	0-96	15.4*	41.1*	73.2*	53.6*
		75	PO	0-96	20.0*	52.8*	64.6*	43.2*
Rat/ Sprague Dawley	NPK-8	1	PO	0-8	4.4*		5.9*	
		10	PO	0-24	5.3*		64.8*	
		100	PO	0-48	23.8*		64.6*	
Rat/ Sprague Dawley	NPK-9	25	PO	0-24	1.5	17.9		
		75	PO	0-24	11.5	22.5		
		225	PO	0-24	17.4	23.5		
		25 x 1 month	PO	0-24	5.8	20.6		
		75 x 1 month	PO	0-24	20.8	22.0		
		225 x 1 month	PO	0-24	16.3	32.7		

TABLE 2. (Cont.) EXCRETION OF CETIRIZINE IN DIFFERENT ANIMAL SPECIES

Species/ Strain	NDA Report No.	Dose (mg/kg)	Route of Administration	Sampling Time (hr)	Total Amount Excreted (% dose Cetirizine)			
					Urine		Feces	
					Male	Female	Male	Female
Rat/ Sprague Dawley	NPK-11	8	PO	Day 1				
				0-24	0.6	5.6		
		25	PO	0-24	6.9	10.5		
		75	PO	0-24	15.3	21.6		
		8	PO	Day 9				
				0-24	0.6	11.8		
		25	PO	0-24	2.9	14.2		
75	PO	0-24	14.2	14.1				
8	PO	Day 43						
		0-24	0.4	8.9				
25	PO	0-24	6.8	15.0				
75	PO	0-24	10.3	22.2				
8	PO	Day 180						
		0-24	1.4	12.7				
25	PO	0-24	9.8	19.5				
75	PO	0-24	19.4	19.8				
Rabbit/ New Zealand	NPK-12	1	PO	0-72	60.7	65.8		
		1	IV	0-72	46.7	64.7		
		15	PO	0-72	49.1	69.3		
		45	PO	0-72	62.4	76.4		
		135	PO	0-72	51.2	71.0		

TABLE 2. (Cont.) EXCRETION OF CETIRIZINE IN DIFFERENT ANIMAL SPECIES

Species/ Strain	NDA Report No.	Dose (mg/kg)	Route of Administration	Sampling Time (hr)	Total Amount Excreted (% dose Cetirizine)			
					Urine		Feces	
					Male	Female	Male	Female
Dog/Beagle	NPK-13	1	IV	0-96	25.7			
		1	PO	0-96	27.3			
		10	IV	0-96	31.9			
		10	PO	0-96	34.2			
Dog/Beagle	NPK-14	0.6 x 9 days	PO	Day 1	25.6*		6.6*	
				2	37.5*		30.4*	
				3	35.3*		45.2*	
				4	38.1*		31.3*	
				5	42.5*		53.0*	
				6	41.0*		55.8*	
				7	40.9*		41.7*	
				8	38.7*		68.0*	
Dog/Beagle	NPK-15	10	PO	0-120	40.1*		55.7*	
Dog/Beagle	NPK-17	15	PO	0-24	23.5			
		45	PO	0-24	31.0			
		135	PO	0-24	32.3			

TABLE 2. (Cont.) EXCRETION OF CETIRIZINE IN DIFFERENT ANIMAL SPECIES

Species/ Strain	NDA Report No.	Dose (mg/kg)	Route of Administration	Sampling Time (hr)	Total Amount Excreted (% dose Cetirizine)					
					Urine		Feces			
					Male	Female	Male	Female		
Dog/Beagle	NPK-18	8	PO	Day 1						
				0-24	16.2					
				0-24	19.8					
		25	PO	0-24	17.1					
				0-24	32.3					
				0-24	27.4					
		75	PO	0-24	34.5					
				0-24	33.9					
				0-24	34.8					
		8	PO	Day 9	43.8					
				0-24	45.2					
				0-24	37.0					
		25	PO	0-24	41.2					
				0-24	34.5					
				0-24	26.9					
75	PO	0-24	29.0							
		0-24	32.5							
		0-24	37.3							
Baboon/Papio Spp.	NPK-20	1	PO	0-72	34.5					
				0-72	26.9					
		10	IV	0-72	29.0					
				0-72	32.5					
		10	IV	0-72	37.3					
				0-72	39.3					
		Monkey/Cynomolgus	NPK-21	1	PO	0-72	35.0			
						0-72	19.7			
10	IV			0-72	37.3					
				0-72	39.3					

TABLE 2. (Cont.) EXCRETION OF CETIRIZINE IN DIFFERENT ANIMAL SPECIES

Species/ Strain	NDA Report No.	Dose (mg/kg)	Route of Administration	Sampling Time (hr)	Total Amount Excreted (% dose Cetirizine)			
					Urine		Feces	
					Male	Female	Male	Female
Monkey/Cynomolgus	NPK-23	17	PO	Day 1				
				0-24	28.9			
				0-24	29.6			
		50	PO	0-24	31.5			
				0-24	38.2			
				0-24	25.0			
		150	PO	0-24	32.4			
				0-24	29.5			
				0-24	25.8			
Monkey/Cynomolgus	NPK-24	5	PO	Day 28				
				0-24	32.5			
				0-24	26.1			
		15	PO	0-24	28.6			
				0-24	26.1			
				0-24	28.6			

* = Percentage of Dose of Radioactivity Excreted

TABLE 2. METABOLIC PROFILE OF CUTRIZINE IN DIFFERENT ANIMALS

Species/ Strain	NDA Report No.	Dose (mg/kg)	Route of Administration	Biological Fluid	Sampling Time (hr)	Radioactivity (% of Dose)		Other	
						Male	Female	Male	Female
Mouse/NR1	NPK-1	10	IV	Urine	0-22	31.8	36.2	1.3	1.2
		10	PO	Urine	0-22	29.1	29.8	1.3	2.3
Mouse/DF1 SIF	NPK-2	10	IV	Plasma	0-0.5	23.3	27.6	N.D.*	N.D.
					0-0.5	16.7	17.9	N.D.	N.D.
					0-1.5	16.0	17.2	N.D.	N.D.
					1	10.8	13.3	0.11	0.10
					2	9.4	9.8	0.30	0.09
					4	3.3	6.3	0.37	0.35
					6	4.2	2.7	0.59	0.55
					8	3.2	1.9	0.69	0.28
					16	2.5	1.1	0.66	0.50
					16	0.20	N.D.	N.D.	N.D.
Rat/ Sprague-Dawley	NPK-6	10	PO	Plasma*	0-4	17	17	3	18
					4	23	23	2	2
					8	34	34	3	13
					12	37	37	3	8
					16	26	26	11	12
					24	33	33	2	2
					32	37	37	3	20
					40	50	50	5	3
					48	27	27	8	13
					56	30	30	5	11
		100	PO	Urine	0-8	0.1	0.1	N.D.	0.2
					0-12	0.1	0.1	0.1	1.2
					0-24	2.4	2.4	0.4	2.8
					0-8	11.9	11.9	0.1	1.4
					0-12	21.5	21.5	1.0	2.9
					0-24	33.3	33.3	6.1	1.5
					0-48	33.0	33.0	0.3	4.8
					0-8	0.4	0.4	1.4	1.7
					0-12	3.0	3.0	3.2	31.8
					0-24	13.9	13.9	3.3	31.9
		100	PO	Feces	0-12	2.9	2.9	6.3	23.4
					0-24	4.4	4.4	0.8	17.4
					0-48	13.7	13.7	3.8	31.2

TABLE 3. (Cont.) METABOLIC PROFILE OF CETRIZINE IN DIFFERENT ANIMALS

Species/ Strain	NDA Report No.	Dose (mg/kg)	Route of Administration	Biological Fluid	Sampling Time (hr)	Radioactivity (% of Dose)							
						Cetirizine		P326		Other			
						Male	Female	Male	Female	Male	Female		
Dog/Beagle	NPK-14	0.6	PO	Urine	Day 1	20.3		0.22					
					Day 2	32.8		0.43					
					Day 3	28.0		0.32					
					Day 4	25.1		0.43					
					Day 5	33.2		0.48					
					Day 6	30.6		0.40					
					Day 7	31.7		0.34					
					Day 8	30.0		0.32					
Dog/Beagle	NPK-15	10	PO	Urine	0-48	31.5		0		7.9			
				Feces	0-48	27.4		4.8		20.0			
Dog/Beagle	NPK-18	8	PO	Plasma	Day 1								
					1.5	22.9		0.13					
					4	24.4		0.21					
					8	12.1		0.30					
					24	4.9		0.24					
					25	PO	Plasma	1.5	64.3		0.06		
								4	69.2		0.28		
								8	37.9		0.64		
		24	18.4					0.62					
		75	PO	Plasma	1.5	105.5		0.52					
					4	127.1		0.79					
					8	85.9		1.34					
					24	52.1		2.18					
		8	PO	Plasma	Day 180								
					0	13.4		0.77					
					1.5	37.1		0.82					
					4	35.4		0.97					
					8	20.4		1.13					
					24	9.9		0.74					
					25	PO	Plasma	0	32.7		1.85		
1.5	82.3								1.75				
4	89.3		2.27										
8	58.2		1.66										
24	40.1		1.54										
75	PO	Plasma	0	95.4		5.76							
			1.5	185.2		8.92							
			4	217.9		8.37							
			8	144.6		7.10							
24	90.0		4.94										

* ND = none detected

† Data expressed as % sample radioactivity

TABLE 4. TISSUE DISTRIBUTION OF RADIOACTIVITY AFTER ADMINISTRATION OF INC-CEPHIRIZINE

SPECIES/ STAIN	NDA REINVEST NO.	DOSE (mg/kg)	ROUTE OF ADMINISTRATION	SAMPLING TIME (hr)	PLASMA		LIVER		LUNG		KIDNEY		BRAIN						
					M	F	M	F	M	F	M	F	M	F	M	F			
Muscle/ GIT 557	NPK-2	10	IV	0.033	29.7	28.7	66.3	37.3	0.081	0.167	0.237	0.103	0.003	0.017					
					0.083	22.3	20.6	67.3	31.8	0.044	0.082	0.144	0.232	0.004	0.011				
					0.167	16.7	15.2	38.3	34.6	0.078	0.137	0.232	0.009	0.017					
					0.3	12.4	10.1	35.6	30.2	0.19	0.317	0.082	0.003	0.004					
					1	11.1	10.4	23.2	23.1	0.009	0.240	0.050	0.001	0.003					
					2	6.6	7.0	21.6	19.1	0.10	0.625	0.009	0.009						
					4	5.8	3.7	22.3	10.5	0.080	0.103	0.426	0.393						
					6	5.0	2.9	16.4	8.8	0.096	0.069	0.421	0.376						
					8	6.0	2.8	11.9	8.8	0.033	0.079	0.213	0.164						
					16	0.3	0.2	1.6	0.6	0.034	0.031	0.163	0.093						
					Muscle/ Sprague Dawley	NPK-6	1	PO	1	0.035	0.133	0.774	1.662	0.081	0.167	0.237	0.103	0.003	0.017
									2	0.049	0.031	0.763	0.703	0.044	0.082	0.144	0.232	0.004	0.011
									4	0.096	0.030	0.287	0.273	0.078	0.137	0.232	0.009	0.017	
									8	0.046	0.032	0.274	0.181	0.19	0.317	0.082	0.003	0.004	
									24	0.028	0.012	0.083	0.060	0.009	0.240	0.050	0.001	0.003	
									1	0.210	-	1.33	-	0.10	0.625	0.009	0.009		
2	0.140	0.079	1.13	0.793					0.080	0.103	0.426	0.393							
4	0.161	0.077	0.99	0.994					0.096	0.069	0.421	0.376							
8	0.118	0.046	0.67	0.316					0.033	0.079	0.213	0.164							
24	0.073	0.028	0.26	0.081					0.034	0.031	0.163	0.093							
Muscle/ Sprague Dawley	NPK-8	1	PO	1					0.03	0.03	4.63*	0.02*	0.02*	0.16*	0.004	0.011			
				2					0.27	0.27	28.0*	0.53*	0.53*	1.24*	0.004	0.011			
				4					0.04	0.04	0.5*	0.01*	0.01*	0.03*	0.004	0.011			
				10					1	1.85	21.0*	0.14*	0.17*	1.17*	0.004	0.011			
									2	0.21	0.21	0.43*	0.43*	0.38*	0.004	0.011			
									4	1.29	9.3*	0.23*	0.23*	0.38*	0.004	0.011			
					8	0.26	0.26	0.01*	0.01*	0.17*	0.004	0.011							
				100	1	0.34	2.6*	0.03*	0.03*	0.17*	0.004	0.011							
					2	61.9	14.2*	0.34*	0.34*	2.03*	0.004	0.011							
					4	20.0	8.3*	0.22*	0.22*	1.62*	0.004	0.011							
					8	11.1	5.4*	0.23*	0.23*	0.59*	0.004	0.011							
				24	1	2.9	1.7*	0.08*	0.08*	0.13*	0.004	0.011							
					2	2.7	2.1*	0.10*	0.10*	0.18*	0.004	0.011							
					4	0.8	0.7*	0.02*	0.02*	0.03*	0.004	0.011							
					8	0.8	0.7*	0.02*	0.02*	0.03*	0.004	0.011							

TABLE 3. (Cont.) TISSUE DISTRIBUTION OF RADIOACTIVITY AFTER ADMINISTRATION OF INC-CETIRIZINE

SUCCESSION NUMBER	NDA REPORT NO.	DOSE (mg/kg)	ROUTE OF ADMINISTRATION	SAMPLING TIME (hr)	PLASMA		LIVER		LUNG		KIDNEY		M	F	M	F	M	F			
					M	F	M	F	M	F	M	F									
Male/Beagle	NIX-12	1	PO	0.57	1.06	0.12	0.63	0.63	6.00	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03		
				3	0.76	1.03	0.33	1.93	0.33	1.93	0.33	1.93	0.33	1.93	0.33	1.93	0.33	1.93	0.33	1.93	
				6	0.37	0.85	0.34	0.84	0.34	0.84	0.34	0.84	0.34	0.84	0.34	0.84	0.34	0.84	0.34	0.84	
Dog/Beagle	NIX-16	0.6 (pregnant)	PO	0.67	0.21	1.91	0.19	1.48	0.19	1.48	0.19	1.48	0.19	1.48	0.19	1.48	0.19	1.48	0.19	1.48	
				3	0.25	1.28	0.35	3.19	0.35	3.19	0.35	3.19	0.35	3.19	0.35	3.19	0.35	3.19	0.35	3.19	
				6	0.23	0.62	0.23	0.23	0.23	0.23	0.23	0.23	0.23	0.23	0.23	0.23	0.23	0.23	0.23	0.23	0.23
				24	0.03	0.17	0.17	0.03	0.66	0.03	0.66	0.03	0.66	0.03	0.66	0.03	0.66	0.03	0.66	0.03	0.66
				2	2.37	2.71	2.71	1.06	1.31	1.06	1.31	1.06	1.31	1.06	1.31	1.06	1.31	1.06	1.31	1.06	1.31
				6	0.76	0.75	0.75	0.21	0.37	0.21	0.37	0.21	0.37	0.21	0.37	0.21	0.37	0.21	0.37	0.21	0.37
Dog/Beagle	NIX-15	0.6 x 9 days	PO	2	1.96	2.37	1.33	2.12	1.33	2.12	1.33	2.12	1.33	2.12	1.33	2.12	1.33	2.12	1.33	2.12	
				6	0.70	2.12	1.11	0.82	0.82	0.82	0.82	0.82	0.82	0.82	0.82	0.82	0.82	0.82	0.82	0.82	
				12	14.9	23.6	9.0	11.8	9.0	11.8	9.0	11.8	9.0	11.8	9.0	11.8	9.0	11.8	9.0	11.8	
				24	5.0	7.6	6.2	8.7	6.2	8.7	6.2	8.7	6.2	8.7	6.2	8.7	6.2	8.7	6.2	8.7	

* Concentration in mg eq/ml
* Percent of dose

John Paul

TABLE 5. IN VITRO PROTEIN BINDING OF CETIRIZINE IN DIFFERENT SPECIES

<u>Species</u>	<u>NDA Report No.</u>	<u>Concentration Range (mcg/ml)</u>	<u>% Protein Bound</u>
Rat/ Sprague Dawley	NPK-6	0.05 - 10	83
Rabbit/ New Zealand	NPK-12	0.02 - 50	94
Dog/Beagle	NPK-14	0.05 - 20	90
Baboon	NPK-20	0.1 - 10.0	85
Monkey/ Cynomolgus	NPK-21	0.1 - 10.0	85

Summary and evaluation:

Cetirizine, code name 9071 and chemically known as 2-(2-(4(4-chlorophenyl)piperazinyl)-ethoxy)-acetic acid dihydrochloride, is to be marketed as an antihistamine (H₁-receptor antagonist). The tablet formulation is indicated for seasonal and perennial allergic rhinitis and chronic idiopathic urticaria. The proposed dosage is 5 to 10 mg a day given as a single dose. The daily dosage, however, may be increased to a maximum of 20 mg if sufficient response has not been obtained. Cetirizine is a member of piperazine class of compounds (diphenylmethane piperazine group) that include cyclizine, chlorcyclizine, meclizine and hydroxyzine. Cetirizine is a human metabolite of hydroxyzine which has been marketed as Atarax by Pfizer for more than 30 years. According to the Applicant, cetirizine possesses less sedating effect than hydroxyzine. Other members of piperazine compounds that are not marketed in this country include cinnarizine (antihistamine), flunarizine (vasodilator) and oxatomide (anti-allergic agent).

The preclinical studies were carried out by

Most of the studies were in compliance with the GLP; some had deviations that should not affect the data interpretation.

Efficacy:

Note: The ED₅₀ values on pages 2 38-2 39 are different from those listed under individual studies (e.g. NP-2, NP-4, NP-8, NP-10 on pages 5 31-5 193). The following review is based on the results from individual studies. The applicant will be asked to clarify the discrepancies.

The efficacy as an antihistamine (H₁ receptor antagonist) and anti-allergic agent was demonstrated in various standard tests. These tests included in vivo studies of lethality, bronchospasm and cutaneous reaction induced by histamine, bronchospasm induced by antigen and in vitro studies in guinea pig ileum, guinea pig trachea and human bronchi.

In histamine-induced lethality test, cetirizine was effective at 0.1 mg/kg (po) in the guinea pig-the most sensitive species. The onset was 1 hr and the duration was 12 hrs at this dose. The ED₅₀ value was 0.35 mg/kg (po). In histamine-induced bronchospasm in guinea pigs, cetirizine had ED₅₀ of 0.09 mg/kg (iv) and 0.46 mg/kg (id) and was less potent than clemastine and mepyramine. In histamine-induced cutaneous reaction test, the oral ED₅₀ values were 0.046 mg/kg (mice), 1.9 mg/kg (rat) and 1.8 mg/kg (guinea pig). In dogs the efficacy (50-75%) against histamine- or antigen-cutaneous reaction was observed in 1-2 hr at 0.1-1 mg/kg po and lasted 4-24 hrs. In this test cetirizine was more potent than terfenadine, clemastine, mepyramine and astemizole, but was equally potent as hydroxyzine. In Rhesus monkeys not only the histamine-induced, but also Compound 48/80, Substance P, Vasoactive Intestinal Peptide induced cutaneous reactions were inhibited at 10 mg/monkey (or 10 mg/kg, the exact dose unknown. see p 58 and p 5247, np-13) po at 2 hrs.

The anti-histamine and anti-allergic activities were further shown in antigen-induced bronchospasm tests. Cetirizine was effective in reducing the bronchospasms in passively immunized guinea pigs (ED₅₀ of 0.3 mg/kg po against iv antigen and effective at 4.6 mg/kg po against aerosol antigen). Against iv antigen challenge, cetirizine was equi-potent as hydroxyzine, was more potent than clemastine and terfenadine, but was less potent than mepyramine. Against aerosol antigen challenge, cetirizine was shown to be more potent than either mepyramine or clemastine.

In passively immunized rats (by anti-IgE serum), the bronchospasm was mainly due to the serotonin released from the mast cells on the respiratory smooth muscles of lungs and bronchi. Cetirizine and mepyramine had low efficacy, whereas hydroxyzine was effective. In compound 48/80-induced lethality in rats (both serotonin and histamine were released), cetirizine was highly effective (oral ED₅₀ of 0.14 mg/kg) and hydroxyzine (44 mg/kg po) was not effective.

The data suggested some anti-serotonin activity for cetirizine.

The anti-histamine activity was also demonstrated in in vitro studies such as guinea pig ileum, guinea pig trachea and human bronchi. In guinea pig ileum, cetirizine was less potent than hydroxyzine, terfenadine, mepyramine and clemastine. The specificity as an antihistamine, however, was demonstrated: cetirizine was without significant effect against Ach-, serotonin-, nicotine-induced contractions. The specificity as an antihistamine was also demonstrated in in vivo studies which included evaluating the efficacy against serotonin-, Ach- and histamine-induced bronchospasms in guinea pigs, against Compound 48/80-induced lethality, and serotonin- and histamine-induced cutaneous reactions in rats. It should be noted that some anti-serotonin activity (3-30X less potent than antihistamine activity) was demonstrated in these in vivo tests.

The antihistamine activity was further demonstrated in the histamine-induced hypotension in dogs. Significant reversal of BP were observed at 0.12-1.19 mg/kg (iv) which by themselves did not show cardiovascular effects in anesthetized dogs. But contrary to the findings in rats, no antiserotonin activity was demonstrated in dogs: the serotonin-induced hypertension was not affected.

The high potency as antihistamine was demonstrated in the isolated H₁ receptor preparations. Cetirizine bound to H₁ receptors from the brain and the lung of the guinea pig with as high affinity as terfenadine. But hydroxyzine, a sedating antihistamine, showed higher affinity (6-10X) than either cetirizine or terfenadine in this test. Although in isolated H₁ receptors, cetirizine showed equally high affinity for both brain and lung preparations, the penetration through the blood brain barrier following systemic administrations, nonetheless, was low.

In in vivo mouse study following 10 mg/kg ip, cetirizine penetrated through the blood brain barrier to less extent than those of chlorpheniramine and hydroxyzine (10% occupancy of brain H₁ receptor by cetirizine vs 85% occupancy by either chlorpheniramine or hydroxyzine): one of the bases for cetirizine as less sedating antihistamine. In another mouse study, the ratio of oral ED₅₀'s (3.9 mg/kg for inhibiting brain H₁ receptor binding vs 0.4 mg/kg for antihistamine skin reaction) showed better separation for cetirizine than for terfenadine or mepyramine. Pharmacokinetic studies also showed low concentrations in the brains of rats and dogs following either single or chronic administration.

In in vitro preparations isolated from guinea pig brain, no significant activity against serotonin, dopamine, alpha-1 adrenergic, muscarinic receptors and calcium channel was observed; some of these receptors may involve in the sedating effect of antihistamines.

No effect on anti-IgE-mediator release from human basophils was observed; higher doses caused mediators release due to cytotoxicity.

Thus the efficacy as an anti-histamine and anti-allergic agent acting through a mechanism of an H₁ receptor antagonist was demonstrated in the standard preclinical tests. Although the potency of cetirizine varied with the tests, cetirizine was shown to be more potent than hydroxyzine, terfenadine, clemastine and mepyramine in many of the tests where comparison drugs were included. Following oral administration the onset was generally observed in 1 hr and the duration is dose-dependent ranging from 4-24 hrs.

Neuropharmacology

The effects on CNS were evaluated in behavior, interaction and EEG studies.

The behavioral studies included general behavior studies in mice and rats, spontaneous exploratory activity and habituation to a new environment in rats, learning and retention of passive avoidance in rats, conditioned responses in dogs and retention and extinction of a conditioned food response in rats.

The general behavior studies showed no effects in mice at 45 mg/kg (ip & po) and in rats at 4.6 mg/kg (ip) or at 138 mg/kg (po). Sedation was observed at high doses of 92 mg/kg (ip) and at 138 mg/kg (po) in mice and at 46 mg/kg (ip) and 461 mg/kg (po) in rats. Deaths following stimulation and/or depression of CNS occurred at even higher doses: 138-462 mg/kg (ip) and 462-1384 mg/kg (po) in mice and 92 mg/kg (ip) and 462-923 mg/kg (po) in rats. In mice comparison was made following intraperitoneal administration of mepyramine and terfenadine. Mepyramine was without effect at 1 mg/kg and was stimulating/depressing at 3-96 mg/kg; terfenadine was without effect at 14 mg/kg and was stimulating/depressing at 47-141 mg/kg. In rats comparison was made with hydroxyzine only. Hydroxyzine was without effect at 13 mg/kg (ip) and at 48 mg/kg (po), but was sedating at higher doses of 48 mg/kg (ip) and at 134 mg/kg (po). The data suggest that cetirizine is less sedating than hydroxyzine, mepyramine or terfenadine.

No significant effects on learning, perceptive-motor, memory, motor coordination were observed in rats or dogs at 15 to 46 mg/kg (po or ip).

No neuroleptic, anticonvulsant, antiepileptic or interaction with pentobarbital in mice were observed up to 45 mg/kg (ip or po). No interaction with alcohol was observed in rats at 15 mg/kg po. In rabbits EEG study showed sedative effect (decreased durations of arousal at 1.5 mg/kg iv and increased duration of sleep at 46 mg/kg iv) though the arousal to the sound was not affected.

Thus the data showed that cetirizine was less sedating than hydroxyzine, mepyramine and terfenadine. Cetirizine was not shown to possess significant CNS effects, but at high dose cetirizine was also sedating.

Cardiovascular effects:

Both in vivo (rat and dog) and in vitro (rat aorta and perfused heart and guinea pig atrium) studies were carried out.

In anesthetized rats no significant cardiovascular effects were observed at 15 mg/kg (iv). At 26 mg/kg (iv) decreased blood pressure and at 46 mg/kg lethality were observed. In anesthetized dogs, slight increases of heart rate and blood pressure were observed at 15 mg/kg (iv), increased heart rate and decreased respiratory rate were observed at 15 mg/kg (id). ECG changes (conduction block) and decreased blood pressure were observed at sublethal cumulative doses of 67 mg/kg iv or 670 mg/kg id in dogs. In conscious dogs increased heart rate and blood pressure were observed at 12 mg/kg (iv), but no effect on ECG was observed. No modulation effects on the muscarinic, adrenergic (alpha and beta) receptors of the heart, no vagolytic, arrhythmic-inducing or inhibiting activities were observed.

The data therefore showed that cardiovascular effects were minimal. In dogs at 15 mg/kg (iv or id) some 10-20% increases of heart rate and blood pressure were observed. Sublethal doses caused conduction block and decreased blood pressure.

H₂ receptor activity:

No significant H₂ receptor activity was demonstrated. The conclusion was based on the results obtained from both in vivo (stress-induced ulcer in rats at 50 mg/kg po) and in vitro studies (rat aorta, atrium and heart preparations and isolated membrane preparation from guinea pig brain).

Anticholinergic activity:

In mice no mydriasis was observed at 138 mg/kg (po) or at 46 mg/kg (ip); no effects on oxotremorine-induced salivation and tremor was observed at 46 mg/kg (ip).

Thus no significant anticholinergic activity was demonstrated.

Analgesic and local anesthetic activity:

No significant analgesic activity was observed in acetic acid-writhing test in mice up to 92 mg/kg (po) or in tail-flick test in rats up to 138 mg/kg (sc). No local anesthetic activity was observed in corneal reflex test in guinea pigs up to a concentration of 14.6 mg/ml .

Anti-inflammatory activity and delayed hypersensitivity

No effects on the inflammatory response (carrageenan-induced paw edema in rats) or delayed hypersensitivity (sheep red cells-induced paw edema in mice) were observed at 46 mg/kg (iv) and 3 mg/kg (sc), respectively.

Pharmacology of PO26 (oxidative O-dealkylation product): the only identified metabolite in the urine and feces of all animal species and human studied. PO26 was a minor metabolite accounting for 5-10% dose in either urine or feces. PO26 was also detected in the plasma.

Efficacy:

In guinea pigs both the in vivo study of histamine-induced bronchospasm and the in vitro study of isolated ileum preparation, cetirizine is 30X more potent than PO26. In histamine-induced cutaneous reactions in mice and dogs, cetirizine was significantly more potent than PO26 which was also shown to be devoid of activity against antigen-induced bronchospasm in guinea pigs.

Behavioral effects:

General behavior study in mice following intraperitoneal administration showed "no-effect" doses at 46 mg/kg for cetirizine and at 11 mg/kg for PO26.

The only identified metabolite PO26 did not possess significant anti-histamine and anti-allergic activities. PO26 did not show significant CNS activity.

Toxicity:

The toxicity of Cetirizine was evaluated in acute (oral and intravenous studies in mice, rats and dogs), subacute (15-day and 1-month studies in mice and rats), and chronic (6-month studies in rats and dogs and 1-year studies in dogs and monkeys) studies.

Oral LD₅₀ values were 600 and 752 mg/kg in male and female mice and 703 and 865 mg/kg in male and female rats, respectively. The oral lethal dose was not determined in dogs due to vomiting at 160 mg/kg and above. The intravenous LD₅₀ values were 336 and 301 mg/kg in male and female mice, and 66 and 70 mg/kg in male and female rats, respectively. The intravenous lethal dose for dogs is 125 mg/kg. In the rat, the vast difference in the LD₅₀ values from oral and intravenous administrations indicated poor oral absorption and/or significant first pass effect in this species.

In rodents, the signs following oral and intravenous administrations were similar and were CNS-related. Sedation, unsteady gait, body tremors, jerking, hypertonicity of the hind legs, convulsions, dyspnea and cyanosis were observed. In dogs, increased heart rate at 80 mg/kg (po), nervousness and vomiting at 160 mg/kg (po); nervousness, unsteady gait, body tremors, muscular weakness at 70 mg/kg (iv) were observed. The surviving rodents and dogs appeared normal after 24 hrs. Necropsies were unremarkable, except for necrosis of tails following intravenous injection in the rodents.

Repeated dose toxicity studies showed species-specific effects/target organ toxicity in the livers of the rodents only, but not in the livers of either Beagle dogs or Cynomolgus monkeys.

The adverse liver effects observed in rodents (mouse and rat) included increased liver weight with grossly enlarged liver, elevated liver enzymes such as SGPT/SGOT, increased/decreased (generally more increased) cholesterol and triglycerides/total lipids and microscopic findings of hypertrophy, vacuolation, fat deposition/steatosis of hepatocytes in periportal, centrilobular or midzonal areas (necrosis only rarely). The applicant attributed the liver hypertrophy to enzyme induction and considered vacuolation and fat deposition as of toxicological significance.

The liver effects were observed at low-doses (10-20 mg/kg) in rodents following either gavage or diet administration for as short as 15 days. Some of the rodent studies were dose-range finding studies for carcinogenicity testings (mouse and rat), whereas other studies were designed to evaluate the reversibility of the liver effects with recovery periods of 4-weeks and 13-weeks following 1-month treatment (mouse and rat). In rats one chronic 6-month study (8, 25 and 75 mg/kg) was carried out with interim sacrifice at 3 months. Dose- and duration-related frequency and severity of liver effects were again shown. Three histopathological findings of hypertrophy, vacuolation and fat deposition of hepatocytes in the periportal, centrilobular or mid-zonal areas were observed at 8-75 mg/kg in male rats and at 25-75 mg/kg in female rats. At 8 mg/kg (M) and 25 mg/kg (F) predominately the hypertrophy with some vacuolation were observed. At 75 mg/kg (the highest dose and the most affected group) extensive hypertrophy and vacuolation with some fat depositions were observed in many of the rats. The NOEL's was 8 mg/kg for female rats (20X maximum human dose of 20 mg/day), but was not established for male rats.

In both subacute and chronic studies, the liver effects were more prominent in male rodents, particularly the male rat and were attributed to greater extent of metabolism of the compound in these animals. Enzyme induction (increased microsomal enzymes and protein), proliferation of smooth endoplasmic reticulum (electron microscopic study) were observed in the rodents. The adverse liver effects (elevated liver enzymes, microsomal drug metabolizing enzymes, microsomal proteins and organ weights) were reversible following 4-week of recovery period. The histopathological changes, however, showed signs of reversibility only after 13-week of recovery.

The NOEL's in mice ranged 1-5 mg/kg (M) and 5-9 mg/kg (F) in different subacute studies of 15 days to 1 month. The liver effects were observed at 3-10 mg/kg (M) and at 10-40 mg/kg (F). In rats, the NOEL's ranged 18-25 mg/kg (M + F) in two 1-month studies. The affected levels were 54-75 mg/kg (M + F). In the 15-day study in rats, however, the affected levels (10-20 mg/kg) and the NOEL's (5 mg/kg) were lower than those of 1-month study. The reason was not given. The studies, however, were carried out by different laboratories. In rats other non-specific effects such as signs, body weight and food consumption were seen only at high doses of 75-160 mg/kg. Drug-related deaths were rare and occurred at high doses of 160-225 mg/kg (1-month) or 75 mg/kg (6-month).

In Beagle dogs and Cynomolgus monkeys, no specific target organ toxicities were established in both subacute and chronic studies. Deaths occurred only at high doses of 75 mg/kg (dogs) and 150 mg/kg (monkeys). Weight losses, decreased food consumption and signs were observed in dogs at 135 mg/kg (1-month), 25 mg/kg (6-month) and 15 mg/kg (1-year) and in monkeys at 50 mg/kg (14-day and 4-Week) and 45 mg/kg (1-year). The signs depending on the doses included vomiting, salivation, tremor, ataxia, quiet behavior, hypothermia, poor coat/piloerection and loose mucus feces in both dogs and monkeys. The relative "no-effect" levels were noted in dogs at 45 mg/kg (1-month), 8 mg/kg (6-month) and 4 mg/kg (1-year) and in monkeys at 17 mg/kg (4-Week), and 15 mg/kg (1-year). These "no-effect" doses were 10X maximum human dose of 20 mg/day in dogs and 40X maximum human dose in monkeys following chronic administration. Non-specific adverse effects on body weight, food consumption and signs occurred at 40X human dose in dogs and at 112X human dose in monkeys.

From the pharmacokinetic data, dogs and monkeys shared more similar ADME patterns with human than the rodents. Therefore, the animal toxicity studies particularly those from the dog and the monkey provided adequate margin of safety for the proposed human use. The liver effects in rodents appear to be species-specific. The available human data did not show significant drug-related liver effects. It should be noted that in the female rat, the NOEL's for liver (from 6-month study) was 8 mg/kg, but NOEL's for stomach was not established (drug-related ulceration of stomach occurred from the low dose of 3 mg/kg in the 2-year carcinogenicity study). In the male rat, the NOEL's for liver (from 6-month study) was not established, but was shown to be at 3 mg/kg from the 2-year carcinogenicity study. The stomach effect was considered another species specific effect, since it was not found in other species.

Thus the toxicological profiles from four species of laboratory animals support the relative safe use for the proposed 10-20 mg/day in human. The

species specific target organ toxicities (liver and stomach) in the rodents, however, should be included in the Package Insert under "Animal Toxicology" section.

Carcinogenicity studies in two species were carried out by
4 according to the GLP rules and regulations.

In a mouse 2-year feeding study, 5 groups of CD-1 mice (52/sex/group) consisted of 2 control groups and 3 dosed groups at 1, 4 and 16 mg/kg, which approximated 5X, 20X and 80X human dose of 10 mg/day or 2.5X, 10X and 40X maximum human dose of 20 mg/day.

During and at the end of the study, no drug-related effects were observed in mortality, signs, body weight, food consumption and blood smears. The target organ toxicities of liver such as hypertrophy, vacuolation and fat deposition were not observed. Thus it can be questioned whether MTD was employed, especially in the female mice. The MTD's, however, were selected based on the profiles from 3 subacute toxicity (15 day-4 week) studies which showed liver effects at 3-10 mg/kg (M) and at 10-27 mg/kg (F). The selection of 16 mg/kg as high dose or MTD therefore was justified.

The neoplastic changes included increases of benign liver tumors in 16 mg/kg-male mice and lymphosarcoma in multiple organs in 16 mg/kg-female mice. The statistical analysis and evaluation by Division of Biomatrix (HFD-715) concluded that benign liver tumor was significant (same conclusion by the Applicant). The dosage represents 80X human dose of 10 mg/day or 40X maximum human dose of 20 mg/day. Lymphosarcoma in multiple organs were not statistically significant. The non-neoplastic changes included liver masses in male mice at 16 mg/kg level.

In a rat 2-year feeding study, 5 groups of rats (50/sex/group) consisted of 2 control groups and 3 dosed groups at 3, 8 and 20 mg/kg, or approximately 15X, 40X and 100X human dose of 10 mg/day or 7.5X, 20X and 50X maximum human dose of 20 mg/day.

During and at the end of the study, no drug-related effects were observed on mortality, signs, body weight, food consumption and blood smears in these rats. Drug-related target organ toxicities of the livers (enlarged/swollen liver with periportal fat deposition, and vacuolation), however, were observed at 8-20 mg/kg (M) and at 8 mg/kg (F). The MTD was employed.

The neoplastic changes included thyroid follicular adenoma in 20 mg/kg male rats, pituitary carcinoma in 8 mg/kg female rats and malignant liver tumors in 8 mg/kg male rats. The malignant liver tumors and pituitary carcinoma were not considered biologically significant, because the high dose group was not affected. The thyroid follicular adenoma in 20-mg/kg male rats was statistically significant, the trend over groups 1-5 was also significant. In addition, for combined benign and malignant follicular tumors, the test for trend over groups 1 to 5 was also significant. The thyroid follicular adenoma was considered a common tumor in male rats based on the historical control data showing greater than 1% incidence. The statistical evaluation by HFD-715 concluded the finding not significant (for a common tumor type to be significant, the p-value should be less than 0.01). Mammary gland fibroadenoma with epithelial atypia appeared to increase in the dosed female groups, but was not found to be statistically significant.

The significant non-neoplastic changes were ulceration of stomach in 3, 8 and 20 mg/kg female rats and liver effects (enlarged liver with fat deposition, and vacuolation) in 8-20 mg/kg male rats and 8 mg/kg female rats. Enlarged kidneys with progressive glomerulonephrosis in dosed male and female groups were probably due to old age and exaggerated by the compound. The stomach and kidney effects were not observed in other rat studies of shorter durations (1-6 month). Subchronic and chronic studies in dogs and monkeys did not show stomach and kidneys effects either. The stomach effect in female rats probably represents another species specific effect.

From the results of the carcinogenicity studies, cetirizine induced benign liver tumors in male mice at 16 mg/kg or 40X maximum human dose of 20 mg/day. Since no significant finding of either benign or malignant liver tumors were observed in rats, the significant finding of this common liver tumor in male mice alone should not affect the approvability of the application. The thyroid follicular adenoma in the male rats at 20 mg/kg was not considered significant from statistical point of view. The findings of benign liver tumors in male mice and thyroid follicular adenoma in male rats should be included in the Package Insert.

Reproduction studies:

In comparison with the rat, the mouse exhibited a pharmacokinetic pattern relatively closer to man (both mouse and man metabolize cetirizine to less extent than rat). Therefore the mouse was chosen by Applicant as the species in the Segment I, II and III studies. In addition, Segment II reproduction studies were carried out in the rat and the rabbit.

The Segment I study was carried out in the dosed male and dosed female mice at 4, 16 and 64 mg/kg. The durations were in males 8 weeks prior to mating and through mating and in females 2 weeks prior to mating and continued on until either sacrificing on day 17.5 of pregnancy or after rearing young to day 21 postpartum. The study also extended to the development and reproductive functions of F₁ and F₂ generations. The results showed that the pregnancy rate was decreased slightly at 64 mg/kg (90% vs 100% control). This was probably due to the effects on the mating performance: delayed and reduced mating performance (more mid and high dosed mice mated on or after 6 days and showed no positive mating). In addition, increased gestation period, lower litter size and some malformations (cleft palate, partial or bilateral open eyes) at 64 mg/kg, total skeletal variants/anomalies (sternebrae: unossified, reduced, bipartite; cervical ribs, reduced metatarsals and occipital) at 16-64 mg/kg, but mostly at 64 mg/kg, were observed. The relative "no-effect" dose was 4 mg/kg. F₁ and F₂ generations did not show adverse effect on their development or reproductive function. In this study, high dosed dams but not the offsprings showed increased liver weight with histopathology of hepatocyte hypertrophy at 64 mg/kg.

Segment II studies were carried out in mice (6, 24, 96 mg/kg), rats (8, 25, 75, 225 mg/kg) and rabbits (15, 45 and 135 mg/kg). No significant embryocidal or teratogenic effects were observed in mice and rabbits up to the highest doses tested or 240X and 338X maximum human doses, respectively. In rats embryocidal effects (percent of pre- and post-implantation losses) at 225 mg/kg (562X maximum human dose), but no teratogenic effects were observed. Skeletal variants or anomalies (refer to the preceding paragraph) were observed at 135 mg/kg (rabbits) or from 25 mg/kg (rats).

Although the results of Segment II reproduction studies in mice, rats and rabbits showed that cetirizine was not teratogenic, it should be noted that other structurally related antihistamines such as cyclizine, meclizine, chlorcyclizine and hydroxyzine are known teratogens in the laboratory animals. Cleft palates were observed in 1 fetus of 16 mg/kg and 4 fetuses of 64 mg/kg in Segment I mouse study. In light of negative findings from all three Segment II studies in 3 species (i.e. mouse, rat and rabbit), the finding of cleft palate from Segment I study are not considered significant. Other anomalies in the kidneys (pelvic cavitation/hypertrophy/hemorrhage/displacement/hydronephrosis in rats and in rabbits) and in brain (meningocele, hydrocephaly, microcephaly with incomplete development of frontal and parietal bones in rabbits) were sporadically observed in the dosed groups without apparent dose-related effects. The cyclizine compounds, however, have not been shown to be teratogens in human.

Segment III reproduction study in mice (6, 24 and 96 mg/kg) suggested that nursing and/or lactating performance was affected at 96 mg/kg because of lower pup weight gains from Day 4 to weaning (Day 21). No significant adverse effects on the development of the pups were evident based on several parameters monitored. Late fetal development or labor did not appear to be affected. Increased liver weights were again observed in the dams of 96 mg/kg. Thus the relative "no-effect" dose in this segment was at 6 mg/kg. Nursing/lactating performance (decreased pup weight gains on Day 4-weaning) was probably affected at 96 mg/kg (240X maximum human dose).

Based on the results from all reproduction studies, the relative "no-effect" doses were 4-6 mg/kg in mice, 8 mg/kg in rats and 15 mg/kg in rabbits. These doses represent at least 20X human dose of 10 mg/day or 10X maximum human dose of 20 mg/day. Adverse reproductive effects in mice included male and/or female mating performance (delayed mating days and no positive mating resulting in slightly lower pregnancy rate) at 64 mg/kg or 160X maximum human dose and lactating/nursing performance (decreased pup weight gains on Day 4 to weaning) at 96 mg/kg or 240X maximum human dose. Skeletal variants/anomalies were generally affected at high doses of 64 mg/kg in mice, 225 mg/kg in rats and at 135 mg/kg in rabbits.

Embryocidal effects in rats were observed at 225 mg/kg or 562X maximum human dose. It should be noted that the mouse, though metabolizing cetirizine to less extent than the rat, still metabolizes cetirizine to greater extent than human. The animal reproduction studies, nonetheless, revealed a profile that provides adequate margin of safety for the drug to be used in women of childbearing potential. The adverse effects at high doses should be included in the package insert.

In the package insert cetirizine is placed under Pregnancy Category C. The wording, however, should be as follows: Cetirizine has not been shown to be teratogenic in mice, rats or rabbits. Cetirizine has been shown to have an embryocidal effect only in rats (at 225 mg/kg or 562X maximum human dose of 20 mg/day), but not in mice (at 96 mg/kg or 240X maximum human dose) or in rabbits (at 135 mg/kg or 338X maximum human dose). Mating performance of male and/or female mice (delayed and reduced matings) appeared to be affected at 96 mg/kg (240X maximum human dose). Skeletal variants/anomalies together with maternal toxicity were predominately observed at the high doses of 64 mg/kg (or 160X maximum human dose) in mice, 225 mg/kg (or 562X maximum human dose) in rats and 135 mg/kg (or 338X maximum human dose) in rabbits. Nursing/lactating performance (retarded pup weight gains on Days 4-21 postpartum) were affected at 96 mg/kg (or 240X maximum human dose) in mice. There are no adequate and well-controlled studies in pregnant women. Cetirizine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Mutagenesis Studies:

Four studies were carried out. Ames Test (8-5000 mcg/plate), Chromosomal Aberrations Assay in Human Peripheral Lymphocytes (20-500 mcg/ml), Mouse Lymphoma TK Locus Assay (100-460 mcg/ml), and Micronucleus Test in Mouse (14-350 mg/kg/day) showed negative results suggesting no mutagenic potential for the compound.

Absorption, distribution, metabolism and excretion:

Twenty four studies were conducted in six animal species (mouse, rat, rabbit, dog, baboon and cynomolgus monkey). Both C^{14} -cetirizine and cold drug were used in animal and human studies. The results showed qualitative similarity among animals and man; though dogs and monkeys exhibited patterns closer to those of man.

Absorption:

Cetirizine is well and rapidly absorbed following oral doses (10 mg/kg) in all animal species and man. The peak plasma concentrations of 8-19 mcg/ml were reached in 1 hr (mouse, rabbit monkey) and 3 hrs (dog) and of 300 mcg/ml was reached in 1 hr (man). The rat is the species that showed extensive metabolism resulting in lower peak plasma levels of unchanged drug of 2 mcg/ml (M) and 4 mcg/ml (F), reached in half hour. In addition, the rat is the species that showed sex-related difference: the male metabolized cetirizine to even greater extent than the female. The oral bioavailability is 71-100% in mouse, rabbit and dog, 51-87% in baboon and monkey and only 36-46% in rat. The pharmacokinetics are linear up to 10 mg/kg in all species and man except the rat. The elimination half-life is less than 1 hr (rat), 1-3 hrs (mouse, rabbit and monkey) and 7-9 hrs (dog and man). The apparent volume of distribution was 0.45 l/kg in man. In animals and man no significant accumulation was observed.

Distribution:

In rats and dogs, liver and kidneys had the highest levels, followed by lungs, plasma, adrenal, spleen, heart and pituitary gland. The cerebrum and cerebellum had the lowest level. Placental transfer was observed in the rat (radioautography) but not in the rabbit (measurement of tissue radioactivity level). The drug was secreted in the milk of dogs. The drug showed high plasma protein binding in all species and man (90% and more).

Metabolism:

Cetirizine was not extensively metabolized except in the rat and mouse. Male rodents metabolized the compound to the greatest extent (80-90% dose). Oxidative O-dealkylation to PO26 is the only metabolite identified in both urine and feces of all animal species tested and the man. PO26, however, appeared to be a minor metabolite, accounting no more than 5-10% dose in either urine or feces from either rats or dogs. In these species, there are additional 4-7 unidentified metabolites. The biotransformation pathways therefore are not fully known. In man about 20% of the dose was metabolized; less than 4% as PO26.

Excretion:

Both urine and feces contributed to the excretion which was generally completed in 96 hrs. In the rat excretion of unchanged drug were low (1-20% in male urine and 9-33% in female urine following chronic dosings at 8-225 mg/kg/day). Urinary excretion accounted for 12-53% dose and fecal excretion accounted for 65-83% dose in rats. In mice, urinary excretion accounted for 37-58% dose and fecal excretion accounted for 44-66% dose. In man 60% of the administered dose was excreted unchanged in urine. Nonrenal clearance accounted for 20% of total body clearance.

In both rodents, females had higher urinary excretion than fecal excretion and males had higher fecal excretion than urinary excretion. In dogs following oral 0.6 mg/kg/day for 9 days, urinary excretion accounted for 40% dose and fecal excretion accounted for 46% dose over 96 hrs. In urine unchanged drug represented 32-40% dose. The accumulation rate was 14% in 9 days. In primates (baboon and monkey), 30% dose was collected in 72 hr-urine as unchanged drug.

Enterohepatic circulation occurred in rats, dogs and monkeys, especially the male rodents

In summary, dogs, baboons and monkeys eliminated a constant proportion of unchanged drug in urine over wide ranges of doses whereas rats showed dose-dependent rates of elimination. There were sex-related differences in rats and mice but not in dogs and primates. The rodents, especially the male rat, metabolized the compound extensively. From the data, dogs, monkeys and man share more similar patterns of ADME.

Conclusions:

- (1) Cetirizine has been shown to possess antihistamine activity. Its potency varied with the models and tests, ranging from 1X-10X that of hydroxyzine. In many studies where comparison drugs were included cetirizine was shown to be more potent than terfenadine, clemastine and mepyramine. Following oral administration, the effect was generally observed in 1 hr, and the duration varied with doses ranging from 4 to 24 hrs in different studies.
- (2) Cetirizine crossed the blood brain barrier to less extent than hydroxyzine. EEG study in rabbits showed sedative effects at intravenous dose of 1.3 mg/kg. Additional behavioral studies did not show significant CNS effects at oral dose below 14 mg/kg. Higher doses caused excitation and/or depression.
- (3) No significant cardiovascular effects were observed except at high doses of 14-461 mg/kg which progressively cause decreased BP/tachycardia/ECG changes/respiratory depression/death. No significant H₂-receptor, anticholinergic, analgesic, local anesthetic or anti-inflammatory activities were demonstrated in animal studies. No effects on mediator release were shown. No active metabolite was demonstrated.
- (2) Acute toxicity was low in rodents and dogs. Repeated-dose treatment showed species-specific target organ toxicity in rodents only. In mice and rats, liver appeared to be the target organ with hypertrophy, vacuolation/steatosis (fat deposition). The liver effects, mostly reversible, were attributed to extensive metabolism and enzyme induction (hypertrophy/enlargement) and toxic effect (vacuolation and fat deposition). Male rat with the highest extent of metabolism was the most sensitive species. The liver effects were observed at 8 mg/kg (male rats) and 25 mg/kg (female rats) in the 6-month study. The "no-effect" level was not established in male rats and was established at 8 mg/kg in female rats.

In both beagle dogs and cynomolgus monkeys, no specific target organ toxicity was demonstrated in the 1-year studies. Non-specific effects such as body weight and/or signs of salivation and vomiting were observed at 15 mg/kg (dogs) and at 45 mg/kg (monkeys); the relative "no-effect" doses were 4 mg/kg (dogs) and 15 mg/kg (monkeys).

Cetirizine was not carcinogenic or tumorigenic in female rats or in female mice. In male rodents, benign tumors were increased. In male mice, significant increases of benign liver tumors (common benign tumors in male mice) and liver masses were observed at 16 mg/kg (40X maximum human dose). The finding, represents species-specific, should be included in the labeling. Thyroid follicular adenoma observed at 20 mg/kg (or 50X maximum human dose) in the male rat should be included in the labeling.

Cetirizine was not shown to be mutagenic in four in vitro and in vivo mutagenesis studies.

- (3) Pharmacokinetic studies showed qualitative similarity among animals and man. The compound was absorbed following oral administration and distributed to liver, kidneys and lungs. Cetirizine crossed placental blood barrier in the rat but not in the rabbit. Cetirizine was secreted in the milk of the dog. Both urine and feces contributed to the excretion which generally was completed in 96 hrs. The most significant finding was the extent of metabolism between rodents and other animal species (i.e. dog, monkey). Cetirizine was extensively metabolized in rats (especially male rats-90% metabolized), followed by mice (60%), dogs (30-40%) and man (20%). Therefore unchanged drug accounted for 30-40% (dogs) and 10-20% (rats) each in the urine and the feces. An oxidative O-dealkylation product, PO26, and additional 4-7 unidentified metabolites were present in both urine and feces. No active metabolite was identified. Comparatively, dog and monkey exhibited patterns closer to those of human.
- (4) Cetirizine has not been shown to be teratogenic in the mouse, the rat and the rabbit. Embryocidal effect was observed in rats at 225 mg/kg (562X maximum human dose), but not in mice (96 mg/kg or 240X maximum human dose) or in rabbits (135 mg/kg or 338X maximum human dose). Skeletal variants/anomalies were observed at 64 mg/kg (160X maximum human dose) in mice, at 75 mg/kg (188X maximum human dose) in rats and at 135 mg/kg (338X maximum human dose) in rabbits. Maternal toxicity was observed at high doses of 225 mg/kg in rats and at 135 mg/kg in rabbits. Mating performance (delayed and reduced matings) were affected at high doses of 64 mg/kg (160X maximum human dose) in mice. Lactating and/or nursing performance (decreased pup weight gains on Day 4-21 postpartum) were affected at 96 mg/kg (or 240X maximum human dose) in mice.
- (5) The Deficiencies in the Package Insert should be amended before the application can be approved.
- (a) An "Animal Toxicology" section should be included. Species-specific target organ toxicities in the livers (male and female mice and rats) and stomach (female rats only) should be described.
- (b) Under Carcinogenesis, mutagenesis, impairment of fertility, the actual dosage (16 mg/kg) at which benign liver tumors in male mice was observed should be included in addition to the human multiples which are described. The finding of thyroid follicular adenoma in male rats at 20 mg/kg or 50X maximum human dose of 20 mg/day should be included.
- (c) Under "Overdosage" section, oral (LD₅₀ values or) minimal lethal doses in the rodents should be included in addition to the human multiples.

(d) Under "Pregnancy Category C", the following wording is recommended:

Cetirizine has not been shown to be teratogenic in mice, rats or rabbits. Cetirizine has been shown to have an embryocidal effect in rats (at 225 mg/kg or 562X maximum human dose of 20 mg/day), but not in mice (at 96 mg/kg or 240X maximum human dose of 20 mg/day) or in rabbits (at 135 mg/kg or 338X maximum human dose). Adverse reproductive effects generally associated with maternal toxicity were observed at high doses or high multiples of the maximal human dose. Mating performance of male and/or female mice (delayed and reduced matings) appeared affected at 96 mg/kg (240X maximal human dose). Skeletal variants/anomalies mostly due to reduced- and/or unossification were observed at 64 mg/kg (160X maximum human dose) in mice, at 225 mg/kg (562X maximum human dose) in rats and at 135 mg/kg (338X maximum human dose) in rabbits. Nursing/lactating performance (retarded pup weight gains on Day 4-2) postpartum was affected at 96 mg/kg (240X maximum human dose) in mice. There are no adequate and well-controlled studies in pregnant women. Cetirizine should be used during pregnancy only if potential benefit justifies the potential risk to the fetus.

Recommendations:

From the conclusions (1)-(4) above, cetirizine has been studied extensively in the laboratory animals to document its pharmacological and toxicological profiles. Cetirizine can be labeled to support its relatively safe and efficacious use in human. The application is therefore approvable based on pharmacology. However, before the application can be approved, the deficiencies in the Package Insert should be amended.

To Medical Officer:

Although adverse liver effects in the rodents appear to be species-specific, the clinical studies should be appraised for liver enzymes profile (toxicity).

Pharmacology Portion of Letter to Applicant:

From pharmacology standpoint, in order to provide assurance of relatively safe and efficacious use of cetirizine in human, the Package Insert should be amended before the application can be approved.

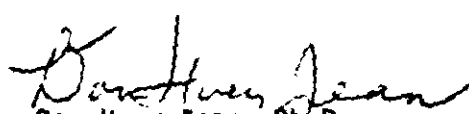
The deficiencies in the Package Insert are as follows:

- (a) An "Animal Toxicology" section should be included. Species-specific target organ toxicities in the livers (male and female mice and rats) and stomach (female rats only) should be described.
- (b) Under Carcinogenesis, mutagenesis, impairment of fertility, the actual dosage (16 mg/kg) at which benign liver tumors in male mice was observed should be included in addition to the human multiples which are used solely. The finding of thyroid follicular adenoma in male rats at 20 mg/kg or 50X maximum human dose of 20 mg/day should be included.

- (c) Under "Overdosage" section, oral (LD₅₀ values or) minimal lethal doses in the rodents should be included in addition to the human multiples.
- (d) Under "Pregnancy Category C", the following wording is recommended:

Cetirizine has not been shown to be teratogenic in mice, rats or rabbits. Cetirizine has been shown to have an embryocidal effect in rats (at 225 mg/kg or 562X maximum human dose of 20 mg/day), but not in mice (at 96 mg/kg or 240X maximum human dose of 20 mg/day) or in rabbits (at 135 mg/kg or 338X maximum human dose). Adverse reproductive effects generally associated with maternal toxicity were observed at high doses or high multiples of the maximal human dose. Mating performance of male and/or female mice (delayed and reduced matings) appeared affected at 96 mg/kg (240X maximal human dose). Skeletal variants/anomalies mostly due to reduced- and/or un-ossification were observed at 64 mg/kg (160X maximum human dose) in mice, at 225 mg/kg (562X maximum human dose) in rats and at 135 mg/kg (338X maximum human dose) in rabbits. Nursing/lactating performance (retarded pup weight gains on Day 4-21 postpartum) was affected at 96 mg/kg (240X maximum human dose) in mice. There are no adequate and well-controlled studies in pregnant women. Cetirizine should be used during pregnancy only if potential benefit justifies the potential risk to the fetus.

It was noted that the ED₅₀ values on pages 2 38 to 2 39 are different from those listed under individual studies (e.g. NP-2, NP-4, NP-8, NP-10 on pages 5 31 to 5 193). Likewise, under NP-13, the dosage for monkey was not clear (10 mg/kg on page 5 8 and 10 mg/animal on page 5 247). Please clarify the discrepancies.


Dou Huey Jean, Ph.D.
Pharmacologist

cc NDA 19-835
HFD-160
HFD-340
CSO-Ledet
R/D DJean 4/11/89
R/D Init. by JInscoc
Typed by LGiesick 4/19/89, 9/29/89
Wang #7234P &
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