

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

*APPLICATION NUMBER:*

**NDA 19-835/S-015**

**NDA 20-346/S-008**

**Name:** Zyrtec (Cetirizine HCl) Tablets  
Zyrtec (Cetirizine HCl) Syrup

**Sponsor:** Pfizer

**Approval Date:** October 21, 2002

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*APPLICATION NUMBER:*

**NDA 19-835/S-015**

**NDA 20-346/S-008**

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**CENTER FOR DRUG EVALUATION AND RESEARCH**

***APPLICATION NUMBER:***

**NDA 19-835/S-015**

**NDA 20-346/S-008**

**APPROVAL LETTER**



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 19-835/S-015  
NDA 20-346/S-008

Pfizer Pharmaceuticals  
235 East 42<sup>nd</sup> Street - 150/7/12  
New York, NY 10017

Attention: John P. Kennedy  
Director, Worldwide Regulatory Strategy

Dear Mr. Kennedy:

Please refer to your supplemental new drug applications dated December 21, 2001, received December 21, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyrtec (cetirizine hydrochloride) Tablets, 5 and 10 mg, and Syrup, 1mg/ml.

We acknowledge receipt of your submissions dated December 21, 2001, and January 30, February 20, March 18, June 20, August 26 and 30, September 25, October 9, 10, 14, and October 21, 2002.

These supplemental new drug applications provide for the use of Zyrtec (cetirizine hydrochloride) Tablets and Syrup for the relief of symptoms associated with perennial allergic rhinitis in adults and children 6 months of age and older.

These supplemental new drug applications also provide for the use of Zyrtec (cetirizine hydrochloride) Tablets and Syrup for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 months of age and older.

We have completed the review of these applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text and with the minor editorial revisions indicated in the enclosed labeling. Accordingly the applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted labeling (package insert submitted October 21, 2002). These revisions are terms of the approval of these applications.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper 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 heavyweight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplements NDA 19-835/S-015, NDA 20-346/S-008." Approval of these submissions by FDA is not required before the labeling is used.

NDA 19-835/S-015  
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In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH, HF-2  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Dr. Craig Ostroff, Regulatory Management Officer, at 301-827-5585.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, M.D., Ph.D.  
Acting Director  
Division of Pulmonary and Allergy Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**

/s/

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Badrul Chowdhury  
10/21/02 05:59:16 PM

# **CENTER FOR DRUG EVALUATION AND RESEARCH**

***APPLICATION NUMBER:***

**NDA 19-835/S-015**

**NDA 20-346/S-008**

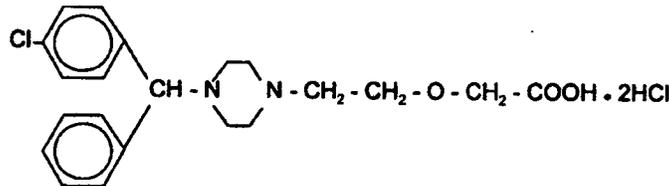
**LABELING**

70-4573-00-5

**ZYRTEC®**  
**(cetirizine hydrochloride)**  
**Tablets and Syrup**  
***For Oral Use***

**DESCRIPTION**

Cetirizine hydrochloride, the active component of ZYRTEC® tablets and syrup, is an orally active and selective H<sub>1</sub>-receptor antagonist. The chemical name is (±) - [2- [4- [ (4-chlorophenyl)phenylmethyl] -1- piperazinyl] ethoxy]acetic acid, dihydrochloride. Cetirizine hydrochloride is a racemic compound with an empirical formula of C<sub>21</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>3</sub>•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 tablets are formulated as white, film-coated, rounded-off rectangular shaped tablets for oral administration and are available in 5 and 10 mg strengths. Inactive ingredients are: lactose; magnesium stearate; povidone; titanium dioxide; hydroxypropyl methylcellulose; polyethylene glycol; and corn starch.

ZYRTEC syrup is a colorless to slightly yellow syrup containing cetirizine hydrochloride at a concentration of 1 mg/mL (5 mg/5 mL) for oral administration. The pH is between 4 and 5. The inactive ingredients of the syrup are: banana flavor; glacial acetic acid; glycerin; grape flavor; methylparaben; propylene glycol; propylparaben; sodium acetate; sugar syrup; and water.

**CLINICAL PHARMACOLOGY**

**Mechanism of Actions:** Cetirizine, a human metabolite of hydroxyzine, is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H<sub>1</sub> 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 H<sub>1</sub> receptors. Autoradiographic studies with radiolabeled cetirizine in the rat have shown negligible penetration into the brain. *Ex vivo* experiments in the mouse have shown that systemically administered cetirizine does not significantly occupy cerebral H<sub>1</sub> receptors.

**Pharmacokinetics:**

**Absorption:** Cetirizine was rapidly absorbed with a time to maximum concentration (T<sub>max</sub>) of approximately 1 hour following oral administration of tablets or syrup in adults. Comparable bioavailability was found between the tablet and syrup dosage forms. When healthy volunteers were administered multiple doses of cetirizine (10 mg tablets once daily for 10 days), a mean peak plasma concentration (C<sub>max</sub>) of 311 ng/mL was observed. No accumulation was observed. Cetirizine pharmacokinetics were linear for oral doses ranging from 5 to 60 mg. Food had no effect on the extent of cetirizine exposure (AUC) but T<sub>max</sub> was delayed by 1.7 hours and C<sub>max</sub> was decreased by 23% in the presence of food.

**Distribution:** The mean plasma protein binding of cetirizine is 93%, independent of concentration in the range of 25-1000 ng/mL, which includes the therapeutic plasma levels observed.

**Metabolism:** A mass balance study in 6 healthy male volunteers indicated that 70% of the administered radioactivity was recovered in the urine and 10% in the feces. Approximately 50% of the radioactivity was identified in the urine as unchanged drug. Most of the rapid increase in peak plasma radioactivity was associated with parent drug, suggesting a low degree of first-pass metabolism. Cetirizine is metabolized to a limited extent by oxidative O-dealkylation to a metabolite with negligible antihistaminic activity. The enzyme or enzymes responsible for this metabolism have not been identified.

**Elimination:** The mean elimination half-life in 146 healthy volunteers across multiple pharmacokinetic studies was 8.3 hours and the apparent total body clearance for cetirizine was approximately 53 mL/min.

**Interaction Studies**

Pharmacokinetic interaction studies with cetirizine in adults were conducted with pseudoephedrine, antipyrine, ketoconazole, erythromycin and azithromycin. No interactions were observed. In a multiple dose study of theophylline (400 mg once daily for 3 days) and cetirizine (20 mg once daily for 3 days), a 16% decrease in the clearance of cetirizine was observed. The disposition of theophylline was not altered by concomitant cetirizine administration.

**Special Populations**

**Pediatric Patients:** When pediatric patients aged 7 to 12 years received a single, 5-mg oral cetirizine capsule, the mean C<sub>max</sub> was 275 ng/mL. Based on cross-study comparisons, the weight-normalized, apparent total body clearance was 33% greater and the elimination half-life was 33% shorter in this pediatric population than in adults. In pediatric patients aged 2 to 5 years who received 5 mg of cetirizine, the mean C<sub>max</sub> was 660 ng/mL. Based on cross-study comparisons, the weight-normalized apparent total body clearance was 81 to 111% greater and the elimination half-life was 33 to 41% shorter in this pediatric population than in adults. In pediatric patients aged 6 to 23 months who received a single dose of 0.25 mg/kg cetirizine oral solution (mean dose 2.3 mg), the mean C<sub>max</sub> was 390 ng/mL. Based on cross-study comparisons, the weight-normalized, apparent total body clearance was 304% greater and the elimination half-life was 63% shorter in this pediatric population compared to adults. The

average AUC(0-t) in children 6 months to < 2 years of age receiving the maximum dose of cetirizine solution (2.5mg twice a day) is expected to be two-fold higher than that observed in adults receiving a dose of 10 mg cetirizine tablets once a day.

**Geriatric Patients:** Following a single, 10-mg oral dose, the elimination half-life was prolonged by 50% and the apparent total body clearance was 40% lower in 16 geriatric subjects with a mean age of 77 years compared to 14 adult subjects with a mean age of 53 years. The decrease in cetirizine clearance in these elderly volunteers may be related to 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 in the kinetics of cetirizine have been observed.

**Renal Impairment:** The kinetics of cetirizine were studied following multiple, oral, 10-mg daily doses of cetirizine 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 cetirizine were similar in patients with mild impairment and normal volunteers. Moderately impaired patients had a 3-fold increase in half-life and a 70% decrease in clearance compared to normal volunteers.

Patients on hemodialysis (n=5) given a single, 10-mg dose of cetirizine had a 3-fold increase in half-life and a 70% decrease in clearance compared to normal volunteers. Less than 10% of the administered dose was removed during the single dialysis session.

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

**Hepatic Impairment:** 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 corresponding 40% decrease in clearance compared to 16 healthy subjects.

Dosing adjustment may be necessary in patients with hepatic impairment (see **DOSAGE AND ADMINISTRATION**).

**Pharmacodynamics:** Studies in 69 adult normal volunteers (aged 20 to 61 years) showed that ZYRTEC at doses of 5 and 10 mg strongly inhibited the skin wheal and flare caused by the intradermal injection of histamine. The onset of this activity after a single 10-mg dose occurred within 20 minutes in 50% of subjects and within one hour in 95% of subjects; this activity persisted for at least 24 hours. ZYRTEC at doses of 5 and 10 mg also strongly inhibited the wheal and flare caused by intradermal injection of histamine in 19 pediatric volunteers (aged 5 to 12 years) and the activity persisted for at least 24 hours. In a 35-day study in children aged 5 to 12, no tolerance to the antihistaminic (suppression of wheal and flare response) effects of ZYRTEC was found. In 10 infants 7 to 25 months of age who received 4 to 9 days of cetirizine in

an oral solution (0.25 mg/kg bid), there was a 90% inhibition of histamine-induced (10 mg/mL) cutaneous wheal and 87% inhibition of the flare 12 hours after administration of the last dose. The clinical relevance of this suppression of histamine-induced wheal and flare response on skin testing is unknown.

The effects of intradermal injection of various other mediators or histamine releasers were also inhibited by cetirizine, as was 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 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 in combination. ZYRTEC caused a mean increase in QTc of 9.1 msec from baseline after 10 days of therapy. Ketoconazole also increased QTc by 8.3 msec. The combination caused an increase of 17.4 msec, equal to the sum of the individual effects. Thus, there was no significant drug interaction 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 four-week clinical trial in pediatric patients aged 6 to 11 years, results of randomly obtained ECG measurements before treatment and after 2 weeks of treatment showed that ZYRTEC 5 or 10 mg did not increase QTc versus placebo. In a one week clinical trial (N=86) of ZYRTEC syrup (0.25 mg/kg bid) compared with placebo in pediatric patients 6 to 11 months of age, ECG measurements taken within 3 hours of the last dose did not show any ECG abnormalities or increases in QTc interval in either group compared to baseline assessments. Data from other studies where ZYRTEC was administered to patients 6-23 months of age were consistent with the findings in this study.

The effects of ZYRTEC on the QTc interval at doses higher than 10 mg have not been studied in children less than 12 years of age.

In a six-week, placebo-controlled study of 186 patients (aged 12 to 64 years) with allergic rhinitis and mild to moderate asthma, ZYRTEC 10 mg once daily improved rhinitis symptoms and did not alter pulmonary function. In a two-week, placebo-controlled clinical trial, a subset analysis of 65 pediatric (aged 6 to 11 years) allergic rhinitis patients with asthma showed ZYRTEC did not

alter pulmonary function. These studies support the safety of administering ZYRTEC to pediatric and adult 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 12 years and older 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 aged 12 to 16 years. In addition, four multicenter, randomized, placebo-controlled, double-blind 2-4 week trials in 534 pediatric patients aged 6 to 11 years with seasonal allergic rhinitis were conducted in the United States at doses up to 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 in adults and children 2 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 6 months of age and older. Symptoms treated effectively include sneezing, rhinorrhea, postnasal 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 6 months 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 effect.

**Carcinogenesis, Mutagenesis and Impairment of Fertility:** In a 2-year carcinogenicity study in rats, cetirizine was not carcinogenic at dietary doses up to 20 mg/kg (approximately 15 times the maximum recommended daily oral dose in adults on a mg/m<sup>2</sup> basis, or approximately 7 times the maximum recommended daily oral dose in infants on a mg/m<sup>2</sup> basis). In a 2-year carcinogenicity study in mice, cetirizine caused an increased incidence of benign liver tumors in males at a dietary dose of 16 mg/kg (approximately 6 times the maximum recommended daily oral dose in adults on a mg/m<sup>2</sup> basis, or approximately 3 times the maximum recommended daily oral dose in infants on a mg/m<sup>2</sup> basis). No increase in the incidence of liver tumors was observed in mice at a dietary dose of 4 mg/kg (approximately 2 times the maximum recommended daily oral dose in adults on a mg/m<sup>2</sup> basis, or approximately equivalent to the maximum recommended daily oral dose in infants on a mg/m<sup>2</sup> 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 *in vivo* micronucleus test in rats.

In a fertility and general reproductive performance study in mice, cetirizine did not impair fertility at an oral dose of 64 mg/kg (approximately 25 times the maximum recommended daily oral dose in adults on a mg/m<sup>2</sup> basis).

**Pregnancy Category B:** In mice, rats, and rabbits, cetirizine was not teratogenic at oral doses up to 96, 225, and 135 mg/kg, respectively (approximately 40, 180 and 220 times the maximum recommended daily oral dose in adults on a mg/m<sup>2</sup> basis). 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:** In mice, cetirizine caused retarded pup weight gain during lactation at an oral dose in dams of 96 mg/kg (approximately 40 times the maximum recommended daily oral dose in adults on a mg/m<sup>2</sup> basis). Studies in beagle dogs indicated that approximately 3% of the dose was excreted in milk. Cetirizine has been reported to be excreted in human breast milk. Because many drugs are excreted in human milk, use of ZYRTEC in nursing mothers is not recommended.

**Geriatric Use:** Of the total number of patients in clinical studies of ZYRTEC, 186 patients were 65 years and older, and 39 patients were 75 years and older. No overall differences in safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. With regard to efficacy, clinical studies of ZYRTEC for each approved indication did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently than younger patients.

ZYRTEC is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See Geriatric Patients and Renal Impairment subsections in CLINICAL PHARMACOLOGY).

**Pediatric Use:** The safety of ZYRTEC has been demonstrated in pediatric patients aged 6 months to 11 years. The safety of ZYRTEC, at daily doses of 5 or 10 mg, has been demonstrated in 376 pediatric patients aged 6 to 11 years in placebo-controlled trials lasting up to four weeks and in 254 patients in a non-placebo-controlled 12-week trial. The safety of cetirizine has been demonstrated in 168 patients aged 2 to 5 years in placebo-controlled trials of up to 4 weeks duration. On a mg/kg basis, most of the 168 patients received between 0.2 and 0.4 mg/kg of cetirizine HCl. The safety of cetirizine in 399 patients aged 12 to 24 months has been demonstrated in a placebo-controlled 18-month trial, in which the average dose was 0.25 mg/kg bid, corresponding to a range of 4 to 11 mg/day. The safety of ZYRTEC syrup has been demonstrated in 42 patients aged 6 to 11 months in a placebo-controlled 7-day trial. The prescribed dose was 0.25 mg/kg bid, which corresponded to a mean of 4.5 mg/day, with a range of 3.4 to 6.2 mg/day.

The effectiveness of ZYRTEC for the treatment of allergic rhinitis and chronic idiopathic urticaria in pediatric patients aged 6 months to 11 years is based on an extrapolation of the demonstrated efficacy of ZYRTEC in adults inwith these conditions and the likelihood that the disease course, pathophysiology and the drug's effect are substantially similar between these two populations. Efficacy is extrapolated down to 6 months of age for perennial allergic rhinitis and down to 2 years of age for seasonal allergic rhinitis because these sediseases are thought to occur down to these ages in children. The recommended doses for the pediatric population are based on cross-study comparisons of the pharmacokinetics and pharmacodynamics of cetirizine in adult and pediatric subjects and on the safety profile of cetirizine in both adult and pediatric patients at doses equal to or higher than the recommended doses. The cetirizine AUC and C<sub>max</sub> in pediatric subjects aged 6 to 23 months who received a mean of 2.3 mg in a single dose, and in subjects aged 2 to 5 years who received a single dose of 5 mg of cetirizine syrup and in pediatric subjects aged 6 to 11 years who received a single dose of 10 mg of cetirizine syrup were estimated to be intermediate between that observed in adults who received a single dose of 10 mg of cetirizine tablets and those who received a single dose of 20 mg of cetirizine tablets.

The safety and effectiveness of cetirizine in pediatric patients under the age of 6 months have not been established.

#### ADVERSE REACTIONS

Controlled and uncontrolled clinical trials conducted in the United States and Canada included more than 6000 patients aged 12 years and older, 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 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 or 10 mg was not significantly different from placebo (2.9% vs. 2.4%, respectively).

The most common adverse reaction in patients aged 12 years and older that occurred more frequently on ZYRTEC 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 no differences by age, race, gender or by body weight with regard to the incidence of adverse reactions.

Table 1 lists adverse experiences in patients aged 12 years and older 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 Patients Aged 12 Years and Older in**  
**Placebo-Controlled United States ZYRTEC Trials (Maximum Dose of 10 mg)**  
**at Rates of 2% or Greater (Percent Incidence)**

<b>Adverse Experience</b>	<b>ZYRTEC (N=2034)</b>	<b>Placebo (N=1612)</b>
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.

Pediatric studies were also conducted with ZYRTEC. More than 1300 pediatric patients aged 6 to 11 years with more than 900 treated with ZYRTEC at doses of 1.25 to 10 mg per day were

included in controlled and uncontrolled clinical trials conducted in the United States. The duration of treatment ranged from 2 to 12 weeks. Placebo-controlled trials up to 4 weeks duration included 168 pediatric patients aged 2 to 5 years who received cetirizine, the majority of whom received single daily doses of 5 mg. A placebo-controlled trial 18 months in duration included 399 patients aged 12 to 24 months treated with cetirizine (0.25 mg/kg bid), and another placebo-controlled trial of 7 days duration included 42 patients aged 6 to 11 months who were treated with cetirizine (0.25 mg/kg bid).

The majority of adverse reactions reported in pediatric patients aged 2 to 11 years with ZYRTEC were mild or moderate. In placebo-controlled trials, the incidence of discontinuations due to adverse reactions in pediatric patients receiving up to 10 mg of ZYRTEC was uncommon (0.4% on ZYRTEC vs. 1.0% on placebo).

Table 2 lists adverse experiences which were reported for ZYRTEC 5 and 10 mg in pediatric patients aged 6 to 11 years in placebo-controlled clinical trials in the United States and were more common with ZYRTEC than placebo. Of these, abdominal pain was considered treatment-related and somnolence appeared to be dose-related, 1.3% in placebo, 1.9% at 5 mg and 4.2% at 10 mg. The adverse experiences reported in pediatric patients aged 2 to 5 years in placebo-controlled trials were qualitatively similar in nature and generally similar in frequency to those reported in trials with children aged 6 to 11 years.

In the placebo-controlled trials of pediatric patients 6 to 24 months of age, the incidences of adverse experiences, were similar in the cetirizine and placebo treatment groups in each study. Somnolence occurred with essentially the same frequency in patients who received cetirizine and patients who received placebo. In a study of 1 week duration in children 6-11 months of age, patients who received cetirizine exhibited greater irritability/fussiness than patients on placebo. In a study of 18 months duration in patients 12 months and older, insomnia occurred more frequently in patients who received cetirizine compared to patients who received placebo (9.0% v. 5.3%). In those patients who received 5 mg or more per day of cetirizine as compared to patients who received placebo, fatigue (3.6% v. 1.3%) and malaise (3.6% v. 1.8%) occurred more frequently.

**Table 2.**  
**Adverse Experiences Reported in Pediatric Patients Aged 6 to 11 Years in**  
**Placebo-Controlled United States ZYRTEC Trials (5 or 10 mg Dose) Which Occurred at a**  
**Frequency of  $\geq 2\%$  in Either the 5-mg or the 10-mg ZYRTEC Group, and More Frequently**  
**Than in the Placebo Group**

Adverse Experiences	Placebo (N=309)	ZYRTEC	
		5 mg (N=161)	10 mg (N=215)
Headache	12.3%	11.0%	14.0%
Pharyngitis	2.9%	6.2%	2.8%
Abdominal pain	1.9%	4.4%	5.6%
Coughing	3.9%	4.4%	2.8%
Somnolence	1.3%	1.9%	4.2%
Diarrhea	1.3%	3.1%	1.9%
Epistaxis	2.9%	3.7%	1.9%
Bronchospasm	1.9%	3.1%	1.9%
Nausea	1.9%	1.9%	2.8%
Vomiting	1.0%	2.5%	2.3%

The following events were observed infrequently (less than 2%), in either 3982 adults and children 12 years and older or in 659 pediatric patients aged 6 to 11 years who received ZYRTEC in U.S. trials, including an open adult study of six months duration. A causal relationship of these infrequent events with ZYRTEC administration has not been established.

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

**Cardiovascular:** cardiac failure, hypertension, palpitation, tachycardia.

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

**Gastrointestinal:** abnormal hepatic function, aggravated tooth caries, constipation, dyspepsia, eructation, flatulence, gastritis, hemorrhoids, increased appetite, melena, rectal hemorrhage, stomatitis including ulcerative stomatitis, tongue discoloration, tongue edema.

**Genitourinary:** cystitis, dysuria, hematuria, micturition frequency, polyuria, urinary incontinence, urinary tract infection.

**Hearing and Vestibular:** deafness, earache, ototoxicity, tinnitus.

**Metabolic/Nutritional:** dehydration, diabetes mellitus, thirst.

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

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

**Respiratory System:** bronchitis, dyspnea, hyperventilation, increased sputum, pneumonia, respiratory disorder, rhinitis, sinusitis, upper respiratory tract infection.

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

**Reticuloendothelial:** lymphadenopathy.

**Skin:** acne, alopecia, angioedema, bullous eruption, dermatitis, dry skin, eczema, erythematous rash, furunculosis, hyperkeratosis, hypertrichosis, increased sweating, maculopapular rash, photosensitivity reaction, photosensitivity toxic reaction, pruritus, purpura, rash, seborrhea, skin disorder, skin nodule, urticaria.

**Special Senses:** parosmia, taste loss, taste perversion.

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

**Body as a Whole:** accidental injury, asthenia, back pain, chest pain, enlarged abdomen, face edema, fever, generalized edema, hot flashes, increased weight, leg edema, malaise, nasal polyp, pain, pallor, periorbital edema, peripheral edema, rigors.

Occasional instances of transient, reversible hepatic transaminase elevations have occurred during cetirizine therapy. Hepatitis with significant transaminase elevation and elevated bilirubin in association with the use of ZYRTEC has been reported.

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

#### **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 adult 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. In an 18 month old pediatric patient who took an

overdose of ZYRTEC (approximately 180 mg), restlessness and irritability were observed initially; this was followed by drowsiness. 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 acute minimal lethal oral doses were 237 mg/kg in mice (approximately 95 times the maximum recommended daily oral dose in adults on a mg/m<sup>2</sup> basis, or approximately 40 times the maximum recommended daily oral dose in infants on a mg/m<sup>2</sup> basis) and 562 mg/kg in rats (approximately 460 times the maximum recommended daily oral dose in adults on a mg/m<sup>2</sup> basis, or approximately 190 times the maximum recommended daily oral dose in infants on a mg/m<sup>2</sup> basis). In rodents, the target of acute toxicity was the central nervous system, and the target of multiple-dose toxicity was the liver.

### **DOSAGE AND ADMINISTRATION**

**Adults and Children 12 Years and Older:** 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.

**Children 6 to 11 Years:** The recommended initial dose of ZYRTEC in children aged 6 to 11 years is 5 or 10 mg (1 or 2 teaspoons) once daily depending on symptom severity. The time of administration may be varied to suit individual patient needs.

**Children 2 to 5 Years:** The recommended initial dose of ZYRTEC syrup in children aged 2 to 5 years is 2.5 mg (½ teaspoon) once daily. The dosage in this age group can be increased to a maximum dose of 5 mg per day given as 1 teaspoon (5 mg) once daily, or as ½ teaspoon (2.5 mg) given every 12 hours.

**Children 6 months to < 2 years:** The recommended dose of ZYRTEC syrup in children 6 months to 23 months of age is 2.5 mg (½ teaspoon) once daily. The dose in children 12 to 23 months of age can be increased to a maximum dose of 5 mg per day, given as ½ teaspoonful (2.5 mg) every 12 hours.

**Dose Adjustment for Renal and Hepatic Impairment:** In patients 12 years of age and older 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 is recommended. Similarly, pediatric patients aged 6 to 11 years with impaired renal or hepatic function should use the lower recommended dose. Because of the difficulty in reliably administering doses of less than 2.5 mg (½ teaspoon) of ZYRTEC syrup and in the absence of pharmacokinetic and safety information for cetirizine in children below the age of 6 years with impaired renal or hepatic function, its use in this impaired patient population is not recommended.

#### **HOW SUPPLIED**

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

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

Bottles of 100: NDC 0069-5500-66

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

Bottles of 100: NDC 0069-5510-66

**STORAGE:** Store at 20°-25°C (68°-77°F) excursions permitted to 15°-30°C (59°-86°F)[see USP Controlled Room Temperature].

ZYRTEC® syrup is colorless to slightly yellow with a banana-grape flavor. Each teaspoonful (5 mL) contains 5 mg cetirizine hydrochloride. ZYRTEC® syrup is supplied as follows:

120 mL amber glass bottles

NDC 0069-5530-47

1 pint amber glass bottles

NDC 0069-5530-93

**STORAGE:** Store at 20°-25°C (68°-77°F) excursions permitted to 15°-30°C (59°-86°F)[see USP Controlled Room Temperature]; or Store refrigerated, 2°-8°C (36°-46°F).

Cetirizine is licensed from UCB Pharma, Inc.

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**CENTER FOR DRUG EVALUATION AND RESEARCH**

***APPLICATION NUMBER:***

**NDA 19-835/S-015**

**NDA 20-346/S-008**

**Division Director's Summary Review**

**DIVISION DIRECTOR'S MEMORANDUM**

DATE: October 21, 2002

TO: NDA 19-835/S-015  
NDA 20-346/S-008

FROM: Badrul A. Chowdhury, MD, PhD  
Acting Director, Division of Pulmonary and Allergy Drug Products

PRODUCT: Zyrtec (cetirizine hydrochloride) Tablets and Syrup

APPLICANT: Pfizer Pharmaceuticals Group, New York, New York

**Introduction**

Pfizer submitted a supplement to NDA 19-835 and NDA 20-346 for Zyrtec (cetirizine hydrochloride) Tablets and Syrup on December 21, 2001, for treatment of \_\_\_\_\_ perennial allergic rhinitis and chronic idiopathic urticaria in patients 6 months to <24 months of age. Cetirizine is currently approved down to 2 years of age for the same indications. Cetirizine was developed by UCB Pharma of Belgium. UCB Pharma markets the drug outside North America. Pfizer licenses and markets cetirizine in North America under the trade name Zyrtec.

Pfizer submitted the results of one pharmacokinetic study and ten safety studies in support of this application. One safety study submitted with this application was the Agency's pediatric written request for cetirizine. The study was deemed adequate and satisfied the conditions of the written request. On the basis of this submission pediatric exclusivity for cetirizine was granted on March 13, 2002.

**Chemistry, Manufacturing, and Controls**

Zyrtec (cetirizine hydrochloride) Tablets and Syrup are approved formulations and are marketed in the United States. There are no new chemistry, manufacturing, and controls issues with this application. The CMC reviewer has suggested changes to the storage temperature statement in the label for the purpose of consistency across labels.

**Establishment Evaluation**

The drug substance and the drug product are manufactured in establishments that have an acceptable establishment evaluation status.

**Clinical Pharmacology and Biopharmaceutics**

The applicant submitted results from one pharmacokinetic study to support the proposed dose of 2.5 mg once-daily to twice-daily for ages 6 months to <24 months of age. Office of Clinical Pharmacology and Biopharmaceutics (OCBP) reviewer Dr. Suarez reviewed the study in detail and concluded that this study provides adequate pharmacokinetic data to support the approval of Zyrtec syrup at the proposed doses for children 6 to <24 months of age and I concur with that recommendation. The submitted study showed that the clearance of cetirizine was more rapid in children <24 months of age than in older children and adults. However, mean systemic exposure was similar in children <24 months of age receiving 2.5 mg once-daily and adults receiving 10 mg cetirizine once-daily, presumably because the weight-adjusted doses are greater in children <24 months of age. By implication the mean systemic exposure in children <24 months of age receiving 2.5 mg cetirizine twice-daily will be double the mean systemic exposure in adults receiving 10 mg cetirizine once-daily.

**Clinical and Statistical**

The applicant submitted results from ten studies to support the safety of cetirizine in children between the ages of 6 and <24 months. One study (study 1010) was conducted in the United States in response to the Agency's pediatric written request, and the other studies were international. The safety database in younger children for cetirizine is quite large. A total of 544 subjects between the ages of 6 and <24 months received cetirizine in these studies, of which 479 received cetirizine for at least 7 days. The dose administered in these studies was 0.25-0.75 mg/kg per day, which translates to total daily dose of 4-11 mg. These studies support the safety of cetirizine down to 6 months of age. These studies are reviewed in depth in Dr. Nicklas's medical review. Brief comments are made on three studies in this memorandum. These three were placebo-controlled studies.

Study 1010 was a multi-center, double-blind, placebo-controlled study conducted in the United States. A total of 96 subjects between the ages of 6 and <12 months were randomized to treatment with either cetirizine (n=42) or placebo (n=44) for 7 days. Study subjects had a diagnosis of allergic rhinitis, urticaria, or other conditions that required use of antihistamines. Safety assessment included recording of adverse events, vital signs, physical examination, ECG, and evaluation of sleep, irritability, and tremor. Treatment with cetirizine was well tolerated by the study subjects. There were no clinically relevant changes in vital signs, physical examination, or ECG reading. QTc values corrected by both Fridericia's and Bazett's correction did not show any changes between treatment groups. On adverse event recording, subjects on cetirizine treatment reported higher frequency of irritability or fussiness compared to subjects on placebo.

Study 9322 was a multi-country European study to assess the effectiveness of early treatment of atopic children on the prevention of later development of asthma. A total of 822 subjects between the ages of 10 and 28 months were randomized to treatment with cetirizine at a dose of 0.25 mg/kg twice-daily or placebo for 18 months. Safety assessment was based on 795 subjects, 399 on cetirizine, and 396 on placebo. Safety assessment included recording of adverse events, vital signs, physical examination, and ECG. Treatment with cetirizine was

well tolerated by the study subjects. There were no clinically relevant changes in vital signs, physical examination, or ECG reading including QTc values corrected by Bazett's method.

Study 9708 was also a multi-country European study. The primary objective of this study was to evaluate the efficacy of cetirizine in the treatment of atopic dermatitis. A total of 223 subjects between the ages of 11 to 71 months were randomized to treatment with cetirizine at doses of 0.25 mg/kg, 0.50 mg/kg, or 0.75 mg/day twice-daily, or placebo for 8 weeks. Safety assessment was based on 222 subjects, 54 on cetirizine 0.25 mg/day, 56 on cetirizine 0.50 mg/day, 57 on cetirizine 0.75 mg/day, and 55 on placebo. Safety assessment included recording of adverse events and physical examination. Treatment with cetirizine was well tolerated by the study subjects. Subjects on cetirizine appeared to have more adverse events related to the gastrointestinal tract such as gastroenteritis, and related to the upper respiratory tract, such as rhinitis and otitis, but there was no consistent pattern or dose-ordering for these adverse events.

#### **Pharmacology and Toxicology**

There are no outstanding preclinical issues. No preclinical pharmacology or toxicology studies were conducted in support of this application. Preclinical data support the use of cetirizine down to 6 months of age in humans. Dr. Shah has concluded that the proposed drug product is safe and I concur with that conclusion.

#### **Data Quality and Integrity**

No DSI audit of clinical study sites was requested or conducted for this application. Cetirizine is not a new molecular entity, and during the review of this application no irregularities that would raise questions about the data integrity were found. The studies submitted with this application were conducted in accordance with accepted ethical standards. There is no apparent conflict of interest of investigators involved in the studies submitted with this application based on financial disclosure information submitted by the applicant.

#### **Pediatric Consideration**

On September 3, 1999, and November 7, 2000, the Agency issued pediatric written requests to Pfizer on cetirizine asking for a clinical safety study down to the age of 6 months. Pfizer submitted results of that study to this NDA with this supplemental application. On the basis of the submitted study, pediatric exclusivity was granted for cetirizine on March 13, 2002. The Agency's determination that cetirizine should be studied down to 6 months of age has therefore been satisfied.

#### **Product Name**

The proprietary name of Zyrtec is approved and used by Pfizer for the line of products containing cetirizine. There are no outstanding issues with nomenclature.

**Labeling**

The applicant has proposed labeling changes and additions to various sections of the label, including the clinical pharmacology section, indication and usage section, pediatric use subsection, adverse reaction section, and dosage and administration section to incorporate the data submitted in this application. These changes and additions were reviewed by various disciplines, and the Division and Pfizer have agreed on the final version of the label. The age of approval is lowered to 6 months for the indications of perennial allergic rhinitis and chronic idiopathic urticaria. The rationale for the approval is described in the pediatric use subsection. The dosage and administration section states that the recommended dose for children 6 to <24 months of age is 2.5 mg once-daily, with an additional statement that in children 12 to <24 months of age the total daily dose can be 5 mg. The proposed dose-range is based on demonstrated safety and not on efficacy. The applicant's proposal of \_\_\_\_\_ has been removed for all ages, because there are no data to support such \_\_\_\_\_.

**Recommendation**

The applicant has submitted adequate rationale and data to support the approval of Zyrtec (cetirizine hydrochloride) at doses of 2.5 mg once-daily or twice-daily for the treatment of perennial allergic rhinitis and chronic idiopathic urticaria down to the age of 6 months. The action on this application is therefore an APPROVAL down to the age of 6 months for perennial allergic rhinitis and chronic idiopathic urticaria. The seasonal allergic rhinitis indication is limited to 2 years and above, because it is unlikely that a child younger than 2 years will develop atopic sensitization to seasonal allergens and develop classic seasonal allergic rhinitis. For systemically active drugs such as oral antihistamines, the Division relies on pharmacokinetic data to support the proposed dose or doses, and clinical studies to support safety of the proposed dose, provided that the disease exists down to the proposed age, and the course of the disease and the effects of the drug is expected to be similar. The applicant has submitted data that support the proposed dose, and has submitted adequate clinical data to support safety of cetirizine down to the age of 6 months.

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# **CENTER FOR DRUG EVALUATION AND RESEARCH**

***APPLICATION NUMBER:***

**NDA 19-835/S-015**

**NDA 20-346/S-008**

**LABELING REVIEW**



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*APPLICATION NUMBER:*

**NDA 19-835/S-015**

**NDA 20-346/S-008**

**MEDICAL REVIEWS**

# MEDICAL OFFICER REVIEW

## Division of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION #: NDA 19,835/20,346

APPLICATION TYPE: Supplemental NDA

SPONSOR: Pfizer

PRODUCT/PROPRIETARY NAME: Zyrtec

USAN Established Name: Cetirizine

CATEGORY OF DRUG: Antihistamine

ROUTE OF ADMINISTRATION: Oral tablet/syrup

MEDICAL REVIEWER: Nicklas

REVIEW DATE: 20 February 2002

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
21 December 2001	21 December 2001	Supplemental NDA and pediatric exclusivity	see overview below

**Overview of Application/Review:** In response to the Division's Written Requests of 3 September 1999 and 17 November 2000, the sponsor in this submission has submitted a full study report for study 1010, a multicenter, randomized, double-blind, placebo-controlled, parallel safety study in patients 6 months to 11 months of age. Moreover, the sponsor has submitted other reports of PK and multiple dose studies in this patient population. This data has been submitted for the purpose of obtaining pediatric exclusivity. In addition, however, the sponsor has submitted proposed labeling changes for the use of this drug product in children 6 months to 2 years of age. The 45 day filing meeting for this supplemental NDA was held on 13 February 2002.

The sponsor has submitted data from a sufficient number of patients evaluated at the appropriate dose in acceptable studies to allow filing of this supplemental NDA for safety of Zyrtec in children 6 months to 2 years of age. This includes study 1010, a study performed in the US, where patients 6-11 months of age received a dose of 0.25 mg/kg bid for 7 days of the syrup formulation. It also includes study 9322 in which approximately 400 patients 10-28 months of age received 0.25 mg/kg bid for 18 months with the oral solution formulation. Data from 8 other studies were also submitted. There were no major filing issues and no clinical filing issues. This NDA does not need to be discussed at an advisory committee meeting. No DSI audit is needed. The clinical review of the pivotal studies will be completed by 1 April 2002. The data is provided in electronic form and is satisfactory.

Outstanding Issues: none

Recommended Regulatory Action: none at this time

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Signed: Medical Reviewer: \_\_\_\_\_

Date: \_\_\_\_\_

Medical Team Leader: \_\_\_\_\_

Date: \_\_\_\_\_

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Badrul Chowdhury  
2/20/02 03:59:39 PM  
MEDICAL OFFICER  
I concur

**CLINICAL REVIEW**

# **Clinical Review Cover Sheet**

# CLINICAL REVIEW

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## CLINICAL REVIEW

### Executive Summary Section

# Clinical Review for NDAs 19,835 and 20,346

## Executive Summary

### I. Recommendations

- A. **Recommendation on Approvability: The efficacy of this drug product (ceterizine) for this patient population (patients 6-24 months of age with allergic rhinitis) can be extrapolated from data that demonstrates the efficacy of this drug product for this condition in older patients. In this submission, the sponsor has adequately demonstrated the safety of ceterizine in patients 6-24 months of age and has proposed an appropriate dose for administration. Therefore, ceterizine is approvable for patients 6-24 months of age with allergic rhinitis.**
- B. **Recommendation on Phase 4 Studies and/or Risk Management Steps: None is necessary at this time.**

### II. Summary of Clinical Findings

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## CLINICAL REVIEW

### Executive Summary Section

- A. Brief Overview of Clinical Program.** Two large non-US, randomized, double-blind, placebo-controlled parallel studies (9322 and 9708) were performed with administration of ceterizine at a dose of 0.50-0.75 mg/kg/day over a period of 8 weeks (n = 204) and 18 months (n = 795), respectively, using the oral solution formulation. There was one US study (1010) that evaluated 0.25 mg bid of ceterizine syrup in a randomized, double-blind, placebo-controlled parallel study of 7 days duration in 85 patients. In addition, the safety of cetirizine was evaluated in 724 patients in open repetitive dose studies of 14 days to 48 months duration where patients received either 0.25 mg/kg bid, 5 mg or 10 mg of ceterizine. Safety parameters included assessment for adverse events and in some studies laboratory tests and/or ECGs.
- B. Efficacy:** Ceterizine is efficacious for patients with allergic rhinitis who are 6-24 months of age, based on extrapolation from data in older children. The dosage proposed by the sponsor is a dosage that, based on pharmacokinetic parameters in patients 6-24 months of age, would be expected to provide efficacy.
- C. Safety:** Ceterizine was demonstrated to be safe for administration to patients 6-24 years of age at the recommended dose of 2.5-5 mg/day.
- D. Dosing:** The safety of ceterizine was demonstrated at a dosage of 0.25-0.75 mg/kg/day in patients 6-24 months of age. This weight-adjusted dose produced a dosage range of 4-11 mg/day. The sponsor's recommended dose of 2.5 mg/day (1 teaspoonful of ceterizine syrup), with the option of increasing the dose to 2.5 mg bid (5 mg/day) is appropriate and supported by the data for children 12 months of age and older, in terms of safety. Because of the variability of response in terms of PK parameters in children less than 12 months of age, only a dose of 2.5 mg per day should be administered to children less than 12 months of age. A single dose of 2.5 mg does not produce a plasma level that is consistent with efficacy throughout the 24 hour dosing interval. At steady state, however, the AUC after a dose of 2.5 mg once a day is similar to the AUC after a dose of 2.5 mg bid, at steady state. Moreover, in a patient 12 months of age or older, there is the option of increasing the dose to 2.5 mg bid. Therefore, the dose and dosing interval proposed by the sponsor is acceptable, provided the labeling is changed to indicate that only a dose of 2.5 mg per day is appropriate in children less than 12 months of age.

## CLINICAL REVIEW

### Executive Summary Section

- E. Special Populations: There was no significant difference in the safety profile for patients < 12 months of age and patients 12 months and older. There were no safety differences based on gender or race.**

**\* On 30 August 2002, at the Division's request, the sponsor submitted safety data on all patients 5 years of age and older who received a dose of 5 mg or more of cetirizine in the studies submitted in the supplemental NDA (see review below).**

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# CLINICAL REVIEW

## Clinical Review Section

### Clinical Review

#### I. Introduction and Background

- A. **Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups:** The established name for this drug product is cetirizine. Pfizer licenses and markets cetirizine in North America under the trade name, Zyrtec. Ceterizine was developed by UCB Pharma of Belgium which markets the drug outside North America.

Ceterizine is an orally active racemic mixture and selective H<sub>2</sub> receptor antagonist. In humans, 70% of the drug is recovered from the urine and 10% in the feces. Ceterizine is metabolized to a limited extent by oxidative O-dealkylation to a metabolite with negligible antihistaminic activity. The mean plasma protein binding of cetirizine is 93%.

Cetirizine syrup is proposed for administration at a dose of 2.5 mg (1/2 teaspoon) once a day, with the option of increasing the dose to 2.5 mg bid every 12 hours (5 mg per day or 1 teaspoonful per day).

- B. **State of Art/Armamentarium for Indication(s) :** Treatment of allergic rhinitis consists of avoidance measures, pharmacotherapy, and/or allergen immunotherapy. The pharmacotherapeutic management of allergic rhinitis revolves around the use of antihistamines, decongestants and intranasal corticosteroids. Nasally inhaled anticholinergics are effective in the management of rhinorrhea in many patients. Only decongestants are approved for treatment of patients 6-24 months of age. Neither Allegra (fexofenadine) nor Claritin (loratadine) are approved for use in patients less than 6 years of age. Intranasal corticosteroids are not approved for use in patients less than 2 years of age. Avoidance measures and immunotherapy are more complex and more likely to be ineffective in patients less than 2 years of age.
- C. **Important Milestones in Product Development:** Ceterizine was initially approved in a tablet formulation for patients 12 years of age and older. On September 1995, it was approved in the syrup formulation (1 mg/ml) for patients 6-11 years of age with seasonal and perennial allergic rhinitis at a dose of 5 or 10 mg as a single daily dose. On 15 May and 29 May 1997, a supplemental NDA was submitted by the sponsor for the syrup and the tablet formulation, respectively, for administration to patients 2-5 years of age. After review of the data submitted by the sponsor for this age group, which

## CLINICAL REVIEW

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was based on cross-study comparison of pharmacokinetic data in patients 2-5 years of age who received the 10 mg/ml oral solution formulation compared with pharmacokinetic data from studies of older children and adults, it was determined that the initial dosage for patients 2-5 years of age should be 2.5 mg once a day. It was considered acceptable to increase the dose to 2.5 mg bid or 5 mg once a day if the patient's symptoms were not controlled with a dose of 2.5 mg given once daily and no adverse event had occurred with administration of the lower dose. Data on the syrup formulation for children 2-5 and 6-11 years of age was linked to data on the tablet formulation in adults. The tablet formulation and the 1 mg/ml syrup formulation were linked to the 1 mg/ml solution formulation by data showing bioequivalence of these formulations.

D. Other Relevant Information: none

E. Important Issues with Pharmacologically Related Agents: none

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews: See Chemistry and Pharmtox reviews. There are no issues related to chemistry or pharmtox that would mitigate against approval of the ceterizine syrup formulation, which is already approved for patients 2-5 years of age.

### III. Human Pharmacokinetics and Pharmacodynamics:

A. Pharmacokinetics: The clearance of ceterizine is approximately three times more rapid in patients *less than 2 years of age* than in older children and adults. However, mean AUC is similar in patients less than 2 years of age and older children and adults, presumably because the weight-adjusted dose is greater in the former group.

The pharmacokinetic data submitted to the NDA supplement for the purpose of extending the indication for ceterizine to patients *2-5 years of age* indicated that ceterizine acted differently from a pharmacokinetic standpoint in children 2-5 years of age compared to older children and was more consistent

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with the pharmacokinetic profile in adults. For a given milligram dose, the C<sub>max</sub> and AUC were greater in children 2-5 years of age than in children 6-24 months, while the half-life was shorter and clearance more rapid, even when normalized for a body surface of 1.73 m<sup>2</sup>. The AUC was essentially the same as that seen in children 6-12 years of age but only about ½ of the AUC seen in children 2-5 years of age (see table below for cross-study comparison of mean pharmacokinetic parameters in different age groups)(v4,p22,23). About 70% of a ceterizine dose is excreted by the kidney unchanged, while a minor fraction is eliminated through the gastrointestinal tract as an inactive dealkylated metabolite.

Patient population	C <sub>max</sub> (ng/ml)	T <sub>max</sub> (hrs)	t <sub>½</sub> (hrs)	Cl (ml/min/kg)	AUC (ng.hr/ml)
6-24 months; 0.25 mg/kg (about 10 mg/1.73 m <sup>2</sup> )	390	2.0	3.1	2.1	2704
2-6 years 5 mg; study 120 *	606	1.9	5.5	1.3	4772
2-4 years 5 mg; study 122 *	660	1.1	4.9	1.4	4009
6-12 years 5 mg	275	1.1	6.0	0.9	2201
Adults 10 mg	350	1.1	9.4	0.6	-
Adults 20 mg	890	0.7	10.6	0.8	-
Elderly 10 mg	360	1.3	11.8	0.6	-

\* Studies — and — were submitted with the supplemental NDA for children 2-5 years of age.

References:

1. Lefebvre RA et al. Single dose pharmacokinetics of cetirizine in young and elderly volunteers. Int J Clin Pharma Res 1988; 8:463.
2. Horsmans Y et al. Single dose pharmacokinetics of cetirizine in patients with chronic liver disease. J Clin Pharmacol 1993; 33:929.
3. Matzke GR. Pharmacokinetics of cetirizine in the elderly and patients with renal insufficiency. Ann Allergy 1987; 59:25

- B. Pharmacodynamics:** In study 123, the sponsor altered the design of the study after the pharmacokinetic data from the first 8 patients showed that the half-life was shorter and the clearance more rapid in patients 6-24 months of age compared to older children and adults, to include an assessment of suppression of histamine-induced wheal and flare reaction in the skin. There was 90% inhibition of wheal formation and 87% inhibition of flare formation 12 hours after cetirizine administration. This data can not be used to support the sponsor's contention that the shorter half-life and more rapid clearance in patients 6-24 months of age than in older patients is not

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C = completed

- C. Postmarketing Experience:** none submitted with this application. A review of the post-marketing database in preparation for the Advisory Committee Meeting on OTC switch of second generation antihistamines revealed that 39% of adverse reaction reports included one or more nervous or psychiatric terms, most often in patients 17-60 years of age. Four of the events reported – convulsions, abnormal dreams, loss of consciousness and hallucinations are not included in the current labeling for cetirizine and about 50% of these reports were in pediatric patients. Because abnormal dreams and hallucinations began shortly after treatment with cetirizine was started, stopped occurring when treatment with cetirizine was stopped and because there was no other likely explanation for the event in most cases, it was considered probable that cetirizine produced the majority of these events. The age range in the reports of convulsions was 3-57 years of age, the age range for hallucinations and abnormal dreams was 3-80 years of age, and the age range for ventricular arrhythmias, sudden cardiac death or QT prolongation was 3-80 years of age. A review of the database for thrombocytopenia in 2001 produced one patient who was 3 years of age, with other reports being in older patients. As of 6 January 2000, there were 2111 AE reports in the AERS database associated with the use of cetirizine. Of these, 144 (7%) were in children 6 years of age and younger. There were 31 reports of psychiatric disorders and 49 reports of nervous system disorders in this age group, of which 8 of the reports of psychiatric disorders and 7 of the reports of nervous system disorders were in children less than 2 years of age. The total number of adverse event reports for psychiatric disorders and nervous system disorders was 380 and 768, respectively. Therefore, 2% and 1% of these events, respectively were in patients less than 2 years of age.
- D. Literature Review:** The sponsor has submitted a number of published articles on the pharmacokinetics of ceterizine, including the pharmacokinetics of ceterizine syrup in infants. This data was reviewed in regard to its relevance to the approvability of ceterizine syrup for the treatment of allergic rhinitis in patients 6-24 months of age. There is no data in the medical literature that would make this drug product non-approvable.

## V. Clinical Review Methods

- A. How the Review was Conducted:** The integrated summary of safety was reviewed first. Following this, each of the key studies was reviewed. The

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pharmacokinetic studies were also reviewed at this time. Finally, this data was evaluated in terms of the labeling proposed by the sponsor.

- B. Overview of Materials Consulted in Review:** In review of this supplemental NDA, the MOR for the supplemental NDA for ceterizine syrup in children 2-5 years was reviewed, in terms of the pharmacokinetic data in this age group and the review process in linking the pharmacokinetic data for the 2-5 year old age group with the pharmacokinetic data in older children and adults. No other database outside of the material submitted by the sponsor in this supplemental NDA was reviewed.
- C. Overview of Methods Used to Evaluate Data Quality and Integrity:** The data provided in different parts of the submission, e.g. the integrated summary of safety, individual study reports, literature references were compared for accuracy of data and appropriateness of conclusions. Based on such comparisons, there was no reason to doubt the quality or integrity of the database in general.
- E. Were Trials Conducted in Accordance with Accepted Ethical Standards:** The studies submitted by the sponsor were conducted in accordance with accepted ethical standards.
- E. Evaluation of Financial Disclosure:** There was no apparent conflict of interest of investigators involved in the study of ceterizine under this supplemental NDA, based on financial disclosure information submitted by the sponsor.

### VI. Integrated Review of Efficacy

- A. Brief Statement of Conclusions:** No efficacy data relating to the use of ceterizine for allergic rhinitis in patients 6-24 months of age was submitted. This drug product is efficacious for patients 6 months to 2 years of age, based on the fact that the drug product has been shown to be efficacious in older children and adults and there is no reason to believe that patients 6 months to 2 years of age have a different disease than was studied in older patients or would react differently to this drug product than would older patients.

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- B. General Approach to Review of the Efficacy of the Drug:** The sponsor provided no data on the efficacy of the ceterizine syrup formulation in children 6-24 months of age with allergic rhinitis. Based on the efficacy of ceterizine syrup in older children with allergic rhinitis, it is reasonable to conclude that ceterizine syrup is efficacious for children 6-24 months of age for this indication.
- C. Detailed Review of Trials by Indication:** not applicable for the reasons noted above.
- D. Efficacy Conclusions:** Ceterizine is efficacious for patients 6 months to 2 years of age because it is efficacious for older patients and since patients 6 months to 2 years of age do not have a different disease than older patients and would not be expected to respond differently to ceterizine than older patients.

### VII. Integrated Review of Safety

- A. Brief Statement of Conclusions:** A review of the safety database submitted by the sponsor supports the safety of cetirizine syrup at a dose of 2.5-5 mg per day in patients 6-24 months of age.
- B. Description of Patient Exposure:** Data generated in one US and 10 non-US clinical studies in patients 2 weeks to 17 years of age. Two of these studies were single dose studies and the others were repetitive dose studies with treatment from 7 days to 4 years. There were 541 children < 24 months of age who received ceterizine in these studies, 508 in placebo controlled studies. There were 447 patients who received placebo. Of the patients who received ceterizine, 74 were less than 12 months of age, 39 of whom received ceterizine for 7 days or longer. Of the 544 patients who received ceterizine, there were 307 males and 201 females. The mean duration of treatment was 326 days for patients < 12 months of age, 446 days for patients 12 months of age and 430 days for patients > 12 months of age but less than 24 months of age.
- C. Methods and Specific Findings of Safety Review:** The Safety Overview submitted by the sponsor was reviewed first, followed by a review of the safety data in each of the individual studies submitted in the NDA by the sponsor. Finally, the pharmacokinetic studies were reviewed in regard to the safety and efficacy of the dosing regimen proposed by the sponsor. The specific findings in regard to safety are discussed below under VII E and in the review of each individual study.

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- D. Adequacy of Safety Testing:** The safety database submitted by the sponsor to assess the safety of the ceterizine syrup formulation at the dose recommended for treatment in patients 6-24 months of age was adequate.
- E. Summary of Critical Safety Findings and Limitations of Data**

One database submitted by the sponsor includes 7 placebo-controlled European studies that included 927 patients, of whom 794 were from study 9322. In this database, 508 patients were treated with cetirizine and 447 were treated with placebo. Of the 508 patients who received cetirizine, 55 (11%) were < 12 months of age, compared with 37 (8%) of placebo patients who were in this age range.

#### 1. Adverse events: all patients

	cetirizine	placebo
<b>All studies</b>	N = 544	-
<b>All AEs – number patients</b>	448 (82%)	-
<b>Drug-related AEs - # pts</b>	75 (14%)	-
<b>All AEs – occurrence</b>	6440	-
<b>Severe adverse events</b>	119 (22%)	-
<b>Serious adverse events</b>	41 (8%)	-
<b>Drug-related serious AEs</b>	3 (1%)	-
<b>Placebo-controlled studies</b>	N = 508	N = 447
<b>All AEs – number patients</b>	425 (84%)	397 (89%)
<b>Drug-related AEs - # pts</b>	67 (13%)	64 (14%)
<b>All AEs – occurrence</b>	5959	5891
<b>Severe adverse events</b>	111 (22%)	96 (22%)
<b>Serious adverse events</b>	38 (8%)	55 (12%)
<b>Drug-related serious AEs</b>	3 (1%)	10 (2%)
<b>Studies at least 7 days</b>	N = 479	N = 419
<b>All AEs – number patients</b>	422 (88%)	394 (94%)
<b>Drug-related AEs - # pts</b>	66 (14%)	63 (15%)
<b>All AEs – occurrence</b>	5956	5887
<b>Severe adverse events</b>	111 (23%)	96 (23%)
<b>Serious adverse events</b>	38 (8%)	55 (13%)
<b>Drug-related serious AEs</b>	3 (1%)	10 (2%)

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#### 2. Adverse events stratified by age

	all studies cetirizine	placebo-controlled studies cetirizine	placebo	studies of at least 7 days cetirizine	placebo
<b>&lt; 12 months</b>	<b>N = 74</b>	<b>N = 55</b>	<b>N = 37</b>	<b>N = 39</b>	<b>N = 21</b>
<b>All AEs #</b>	<b>45 (61%)</b>	<b>34 (62%)</b>	<b>20 (54%)</b>	<b>33 (85%)</b>	<b>19 (91%)</b>
<b># Drug-related-AEs</b>	<b>9 (21%)</b>	<b>8 (15%)</b>	<b>2 (5%)</b>	<b>8 (21%)</b>	<b>1 (5%)</b>
<b>All AEs – occurrence</b>	<b>724</b>	<b>455</b>	<b>196</b>	<b>454</b>	<b>194</b>
<b>Severe AEs</b>	<b>14 (19%)</b>	<b>13 (24%)</b>	<b>9 (24%)</b>	<b>13 (33%)</b>	<b>9 (43%)</b>
<b>Serious AEs</b>	<b>6 (8%)</b>	<b>6 (11%)</b>	<b>3 (8%)</b>	<b>6 (15%)</b>	<b>3 (14%)</b>
<b>Drug-related serious AEs</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>
<b>12 months</b>	<b>N = 96</b>	<b>N = 94</b>	<b>N = 74</b>	<b>N = 90</b>	<b>N = 70</b>
<b>All AEs #</b>	<b>87 (91%)</b>	<b>85 (90%)</b>	<b>68 (92%)</b>	<b>84 (93%)</b>	<b>67 (96%)</b>
<b># drug-related AEs</b>	<b>17 (18%)</b>	<b>17 (18%)</b>	<b>10 (14%)</b>	<b>16 (18%)</b>	<b>10 (14%)</b>
<b>All AEs – occurrence</b>	<b>1317</b>	<b>1270</b>	<b>1105</b>	<b>1269</b>	<b>1104</b>
<b>Severe AEs</b>	<b>20 (21%)</b>	<b>19 (20%)</b>	<b>16 (22%)</b>	<b>19 (21%)</b>	<b>16 (23%)</b>
<b>Serious AEs</b>	<b>10 (10%)</b>	<b>9 (10%)</b>	<b>12 (16%)</b>	<b>9 (10%)</b>	<b>12 (17%)</b>
<b>Drug-related serious AEs</b>	<b>2 (2%)</b>	<b>2 (2%)</b>	<b>3 (4%)</b>	<b>2 (2%)</b>	<b>3 (4%)</b>
<b>&gt; 12 months</b>	<b>N = 374</b>	<b>N = 359</b>	<b>N = 336</b>	<b>N = 350</b>	<b>N = 328</b>
<b>All AEs #</b>	<b>316 (85%)</b>	<b>306 (85%)</b>	<b>309 (92%)</b>	<b>305 (87%)</b>	<b>308 (94%)</b>
<b># drug-related AEs</b>	<b>49 (13%)</b>	<b>42 (12%)</b>	<b>52 (16%)</b>	<b>42 (12%)</b>	<b>52 (16%)</b>
<b>All AEs – occurrence</b>	<b>4399</b>	<b>4234</b>	<b>4590</b>	<b>4233</b>	<b>4589</b>
<b>Severe AEs</b>	<b>85 (23%)</b>	<b>79 (22%)</b>	<b>71 (21%)</b>	<b>79 (23%)</b>	<b>71 (22%)</b>
<b>Serious AEs</b>	<b>25 (7%)</b>	<b>23 (6%)</b>	<b>40 (12%)</b>	<b>23 (7%)</b>	<b>40 (12%)</b>
<b>Drug-related serious AEs</b>	<b>1 (0.3%)</b>	<b>1 (0.3%)</b>	<b>7 (2%)</b>	<b>1 (0.3%)</b>	<b>7 (2%)</b>

**3. There was an incidence of 16% for vomiting, 22% for diarrhea and 24% for gastroenteritis in patients receiving cetirizine. The**

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highest percentage was found in the 12 month age group and the lowest percentage in the < 12 month age group. The incidence of these adverse events was essentially the same or greater in the group that received placebo. This may reflect irritation of the GI tract from this drug formulation rather than the active drug component.

4. There was an incidence of 32% for bronchitis, 46% for coughing, 20% for pharyngitis, 62% for rhinitis, 24% for otitis media, 32% for fever and 47% for upper respiratory infection in patients receiving cetirizine. The highest percentage was found in the 12 month age group while the lowest percentage was generally in the < 12 month age group. Bronchospasm and pharyngitis occurred more frequently in the < 12 month age group. The incidence of these adverse events was essentially the same or greater in the group that received placebo, except for c-reactive protein being positive in 4% of 12 month olds who received cetirizine compared to none to 0.6% in patients who received placebo. Somnolence occurred in 1.8% of both the cetirizine and the placebo groups.

One patient, a one year old male, developed an increase in liver enzymes with an increase in SGOT to 1100 IU/L SGPT to 1300 IU/L and alkaline phosphatase to 532 IU/L (upper limit 266 IU/L), 34 days after starting cetirizine that persisted and was considered highly likely to be related to the study drug. One week after discontinuing cetirizine, SGOT was 146 and SGPT was 594 and 3 weeks after discontinuing cetirizine SGOT was 61 and SGPT was 67. COMMENT: The fall in LFTs after discontinuing cetirizine strongly suggests a causal relationship between the study drug and the changes in liver function.

There were 3 patients who developed serious lymphadenopathy while receiving cetirizine and one patient who developed serious lymphadenopathy while receiving placebo. Overall, the adverse events reported are a reflection, in all probability, of the study of a pediatric patient population with airway disease.

5. Only insomnia occurred with 2% greater incidence in patients who received cetirizine compared to patients who received placebo. Cetirizine has been reported to produce CNS effects.

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6. Based on the UCB data from placebo-controlled European studies (v3, p68-75, t4b-6b), there were 11 cetirizine and 13 placebo patients who discontinued because of an adverse event. Using this database, 84% of the cetirizine patients and 89% of the placebo patients developed treatment-emergent adverse events, 22% of the cetirizine patients and 22% of the placebo patients developed severe treatment-emergent adverse events, 13% of the cetirizine patients and 14% of the placebo patients developed drug-related adverse events and 1% of the cetirizine patients and 2% of the placebo patients developed serious drug-related adverse events. There was no substantive difference between the frequency of adverse reactions overall in the patient group < 12 months of age and the patient group > 12 months of age. Individually, adverse events such as rhinitis, cough, otitis media, vomiting, conjunctivitis, and viral infection were more frequent in patients 12 months of age and older while bronchospasm was more frequent in patients < 12 years of age who received cetirizine. The frequency of such adverse events was comparable or greater in patients who received placebo (v3, p96-126). The only frequently reported adverse events that were greater in an age group that received ceterizine as compared to any age group that received placebo were: 1) pruritis (7% in patients 12 months of age who received cetirizine compared to 3% in placebo groups); 2) positive C-reactive protein (4% in patients 12 months of age who received cetirizine compared to 0-1% in placebo groups); 3) conjunctivitis (22% in patients 12 months of age who received cetirizine compared to 17% in placebo patients 13-23 months of age); and 4) bronchitis (51% in patients < 12 months in placebo controlled studies of at least 7 days duration compared to 39% in 12 month placebo patients).

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Serious adverse events in patients < 2 years of age per the UCB database can be seen in the table below (v3, p308-343).

Adverse event	cetirizine likely	cetirizine unlikely	placebo	comment
Asthma	0	5	11	None
Convulsions	0	2	1	Due to fever
Lymphadenopat	0	3	1	None
Syncope	0	1	0	None
Allergic reactio	0	1	2	None
Diarrhia	0	2	0	None
Gastroenteritis	0	5	3	None
Vomiting	0	1	1	None
Abdominal pain	0	1	1	None
Surgery	0	4	4	None
Pyleonephritis	0	1	0	None
Glomeruloneph	0	0	1	None
Urinary infectio	0	1	1	None
Hernia	0	1	1	None
Cough	0	1	0	None
Bronchitis	0	2	2	None
Pneumonia	0	1	1	None
Viral infection	0	0	3	None
Laryngitis	0	0	1	None
Eczema	0	2	3	None
Increased LFTs	1	0	0	Potential to increase LFTs
Wound infectio	0	0	1	None
Fever	0	0	1	None
URI	0	0	1	None
Dehydration	0	0	1	None
Food poisoning	0	0	1	None
Animal bite	0	0	1	None
Ataxia	0	0	1	None
Testicular disor	0	0	1	None
Angioedema	0	0	1	None
Concussion	0	0	1	None
Rhinitis	0	1	0	None

3. ECG findings: ECGs were performed in studies 1010, 9322, and 123 (single dose PK study). No clinically significant changes in ECGs were noted in these studies. Specifically, there were no clinically significant change in the

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**QTc interval after treatment with cetirizine. As requested by the Division, the sponsor submitted on 9 October 2002 an analysis of the ECG data from study 1010 with QTc intervals corrected using Bazett's correction. The original analysis of the QTc data had used Fridericia's correction. After review of the QTc data using Bazett's correction, there was no significant change in QTc interval after administration of cetirizine, consistent with the original submission of the data using Fridericia's correction.**

**VIII. Dosing, Regimen, and Administration Issues: The dosage proposed by the sponsor is 2.5 mg (1/2 teaspoon of the syrup formulation) once a day with the option of increasing the dose to 2.5 mg bid every 12 hours (5 mg [1 teaspoonful] per day) if the lower dose is not effective. This dosage is acceptable from a safety standpoint for children 12 months of age and older, but is not acceptable for children less than 12 months of age because of the marked variability in pharmacokinetic parameters in this younger age group. Plasma levels after administration of a single dose of ceterizine are very low over the last 12 hours of the 24 hour dosing interval after drug administration. On the other hand, at steady state, the AUC when ceterizine is given at a dose of 2.5 mg once a day is very similar to the AUC when ceterizine is given at a dosage of 2.5 mg bid, suggesting that patients will experience efficacy throughout the 24 hour dosing interval. Moreover, it is acceptable in patients 12 months of age and older to increase the dose to 2.5 mg bid (5 mg per day).**

### **IX. Use in Special Populations**

- A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation: The sponsor's gender effects analysis was adequate.**
  
- B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy: The sponsor categorized adverse events based on age. The sponsor's analysis of race and ethnicity effects was adequate.**

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- C. **Evaluation of Pediatric Program:** With this supplemental application, the sponsor has now evaluated the safety of this drug product in patients down to 6 months of age.
- D. **Comments on Data Available or Needed in Other Populations:** The diagnosis of allergic rhinitis is very difficult to make in patients less than 6 months of age. Therefore, there is compelling reason for requesting that the sponsor evaluate the safety and efficacy of this dosage formulation in patients less than 6 months of age.

\* On 30 August 2002, at the request of the Division, the sponsor submitted safety data for patients who received 5mg of cetirizine or more in the database submitted with the supplemental NDA (see review below)

### X. Conclusions and Recommendations

- A. **Conclusions:** Ceterizine syrup formulation has been shown to be efficacious and safe for administration with some modification of the dose proposed for patients 6-24 months with allergic rhinitis (see below under labeling)
- B. **Recommendations:** That ceterizine syrup formulation be approved for the treatment of allergic rhinitis in patients 6-24 months of age with some modification of the dose proposed by the sponsor (see below under labeling),

### XI. Appendix

- A. **Other Relevant Materials**

#### 1. Labeling:

- a. **Clinical Pharmacology section: Special Populations subsection: Pediatric Patients subsection:** the sponsor has added the statement, "In pediatric patients aged 6 to 23 months who received a single dose of 0.25 mg/kg cetirizine oral solution (mean dose 2.3 mg), the mean C<sub>max</sub> was 390 ng/ml. Based on cross-study comparisons, the weight-normalized, apparent total body clearance was 304%

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greater and the elimination half-life was 63% shorter in this pediatric population than in adults. —” This section of the labeling was discussed with Biopharm. Since the dose given to patients in this age group was proportionally higher than was given to adults and older children, the AUC is basically the same in patients 6-23 months of age as compared to older patients, despite the more rapid clearance of the drug in this younger patient population. Biopharm has recommended that the following additional sentence be added to the labeling; “The average AUC<sub>t</sub> in children 6 months to < 2 years of age receiving the maximum dose of cetirizine solution (2.5 mg twice a day) is expected to be two-fold higher than that observed in adults receiving a dose of 10 mg cetirizine tablets once a day.” With the addition of this sentence, this part of the labeling is acceptable.

- b. **Clinical Pharmacology section: Pharmacodynamics subsection:** the sponsor has added, “In 10 infants aged 7-25 months who received 4 to 9 days of cetirizine in an oral solution (0.25 mg/kg bid), there was a 90% inhibition of histamine-induced (10 mg/mL ) cutaneous wheal and 87% inhibition of the flare 12 hours after administration of the last dose (1).” Since the Division does not believe that suppression of wheal and flare response in the skin is a good pharmacodynamic marker of clinical effectiveness, an additional sentence should be added that states, “However, the clinical relevance of this suppression of histamine-induced wheal and flare response on skin testing is unknown.” Without this addition, the statement implies effectiveness that has not been directly demonstrated in patients 6-23 months of age.

- c. **Clinical Pharmacology section: Pharmacodynamics subsection:** the sponsor states that “



In a one week clinical trial (N = 86) of ZYRTEC syrup (0.25 mg/kg

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bid) versus placebo in pediatric patients aged 6 to 11 months, ECG measurements taken within 3 hours of the last dose did not show any ECG abnormalities or increases in QTc interval in either group compared to baseline assessments.

The age range of patients in the 18 month study (study 9322) was 10-28 months. The comments on the one week study (study 1010) and the single dose study (study 123) are accurate and appropriate. In regard to the total ECG database, the conclusions that there were no significant changes from baseline after administration of cetirizine and no significant prolongation of the QTc interval are accurate. We recommend, however, that the first sentence be deleted. In the second sentence "versus" should be replaced with "compared with" and "pediatric patients 6-11 months of age". The third sentence should be deleted and replaced with the following: "Data from other studies where ZYRTEC was administered to patients 6-23 months of age were consistent with the findings in this study."

d. Indications and Usage section:

for [ ] the claim [ ]  
can not be made. Note, however, that under the Pediatric Use subsection, the statement that the effectiveness of Zyrtec for the treatment of allergic rhinitis in general has been allowed.

c. Precautions section: Pediatric Use subsection: The sponsor has added the following statements: "The safety of ZYRTEC has been demonstrated in pediatric patients aged 6 months to 11 years of age. —" and "The safety of cetirizine in 399 patients aged 12 to 24 months has been demonstrated in a placebo-controlled trial 18 months in

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duration, in which the average dose was 0.25 mg/kg bid, corresponding to a range of 4 to 11 mg per day. The safety of ZYRTEC syrup has been demonstrated in 42 patients aged 6 to 11 months in a placebo-controlled trial of 7 days \_\_\_\_\_ . The prescribed dose was 0.25 mg/kg bid, which corresponded to a mean of 4.5 mg/day, with a range of 3.4 to 6.2 mg/day. — ” This section has also been changed to indicate the cetirizine AUC and Cmax in patients 6 to 23 months of age, that the safety of cetirizine has been demonstrated in patients 6 months of age and older, and that effectiveness has been demonstrated in patients 6 months of age and older. These statement are accurate and acceptable.

- f. Adverse Reactions section: The sponsor has added the following statements: 1) “A \_\_\_\_\_ placebo-controlled trial 18 months in duration included 399 patients aged 12 to 24 months treated with cetirizine (0.25 mg/kg bid), and another placebo-controlled trial of 7 days duration included 42 patients aged 6 to 11 months who were treated with cetirizine (0.25 mg/kg bid). — ”; and 2) “

[ ]

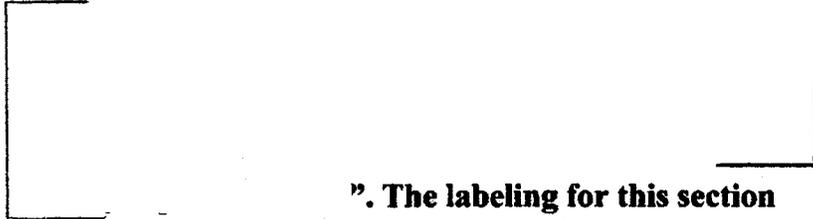
The second statement should be changed to read, “In the placebo controlled studies of pediatric patients 6-24 months of age, the incidence of adverse experiences were similar in the cetirizine and the placebo treatment groups in each study. Somnolence occurred with essentially the same frequency in patients who received cetirizine and patients who received placebo.

[ ]

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- g. Dosage and Administration section: the sponsor has added the following: “



”. The labeling for this section should be changed to read, “Children 6 months to < 2 years: The recommended dose of ZYRTEC syrup in children 6 months to 23 months of age is 2.5 mg (1/2 teaspoonful) once daily. The dose in children 12 to 23 months of age can be increased to a maximum dose of 5 mg per day, given as 1/2 teaspoonful (2.5 mg) every 12 hours.”

2. Submission of 30 August 2002: In this submission, the sponsor has responded to the request of the Division for evaluation of the safety database in patients who received 5 mg or more of cetirizine.

#### Comparison of selected safety parameters based on dose of cetirizine in study 1010

parameter	< 5 mg/day (n = 32)	≥ 5 mg/day (n = 10)	placebo (n = 43)
Patients with AEs	26 (81%)	5 (50%)	38 (84%)
Somnolence	7 (22%)	2 (20%)	13 (31%)
Treatment-related AEs	16 (50%)	3 (30%)	27 (63%)
Irritability/restless	10-33%	10-40%	8-24%
Patients D/C AEs	3	0	3
Change QT interval	- 2 msec	-10 msec	4 msec
Change QTc interval	2 msec	- 3 msec	- 1 msec

**COMMENT:** There was no clinically significant difference, in terms of specific adverse events, between patients who received < 5 mg and patients who received 5 mg or more of cetirizine in either study 1010 or study 9322 (see below). It should be noted that the patient in study 9322 who had a significant increase in liver enzymes received a dose of 3.2 mg of cetirizine and should not have been included in the category of 5 mg or more of cetirizine.

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#### Comparison of selected safety parameters based on dose of cetirizine in study 9322

parameter	< 5 mg/day	≥ 5 mg/day	placebo
Number of patients	37	362	396
Adverse events %	100%	98%	99%
Insomnia	6 Patients (16%)	29 patients (8%)	21 patients (6%)
Somnolence	2 patients (5%)	7 patients (2%)	8 patients (2%)
Fatigue	None	13 patients (4%)	5 patients (1%)
Malaise	None	13 patients (4%)	7 patients (2%)
Hepatic enzymes ↑	None	5 patients (1%)	6 patients (1%)
Platelets mean change	45.8 giga/L	- 11.6 giga/L	3.6 giga/L
SGOT mean change	- 5.6 IU/L	- 3.5 IU/L	- 3.6 IU/L
SGPT mean change	- 5.4 IU/L	- 2.9 IU/L	- 3.8 IU/L
QTc mean last visit (Bazetts)	387 msec	387 msec	388 msec
QTc > 500 msec	None	None	1
QTc mean change (Bazetts)	26 msec	11 msec	11 msec

There was no clinically significant difference between adverse events seen in patients who received < 5 mg of cetirizine and patients who received 5 mg or more of cetirizine in study 9708.

#### B. Individual More Detailed Study Reviews

##### 1. Repetitive dose studies:

##### a. Study 1010: volumes 6,7

- 1) number of patients: 86 patients randomized (44 placebo and 42 cetirizine); 76 patients completed study (39

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- placebo and 37 cetirizine); 85 patients were assessable for safety (43 placebo and 42 cetirizine)
- 2) **age range:** 6-11 months
  - 3) **patient population:** patients with rhinitis, urticaria or any condition for which use of antihistamines was appropriate
  - 4) **study design:** multicenter, randomized, double-blind, placebo-controlled, parallel study
  - 5) **drug administration:** cetirizine syrup 0.25 mg/kg bid; 1 mg/ml formulation of cetirizine HCl
  - 6) **periods of study:** 7 days of randomized treatment
  - 7) **parameters evaluated:** this was a safety study; no efficacy assessments were made; safety parameters included adverse events, vital signs, ECGs, evaluation of sleep, irritability and tremor on a daily basis, physical examination
  - 8) **study results:**
    - a) **adverse events (v6, p4):**

1) There were no **serious adverse events.**

2) Three patients in each treatment group **discontinued** the study because of an adverse event. One of the cetirizine patients and 2 of the placebo patients that were discontinued had an adverse event that was considered related to the study drug. The ceterizine patient developed moderate diarrhea that cleared (v6, p 379).

3) There were no patients in the cetirizine group that experienced unusual, unexpected or severe adverse events (v6, pgs 372-380). The most common treatment emergent adverse events in both treatment groups were nervousness, insomnia, and somnolence.

4) The incidence of significant decrease in sleep, abnormal restlessness during sleep and abnormal irritability were not significantly different in the group that received cetirizine and the group that received placebo (v7, pgs 510-540).

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**Decreased sleep – 5 cetirizine, 8 placebo**

**Sleep restlessness – 7 cetirizine, 11 placebo**

**Irritability – 10 cetirizine, 9 placebo**

- b) **vital signs**: There were no clinically significant changes in blood pressure or heart rate in patients who received cetirizine (v7, pgs490-495).
- c) **ECGs**: Digital measurements were used to derive and record ECG data that was obtained on all patients at baseline and on visit 2 (after one week of treatment). A 12 lead ECG was obtained approximately 2 hours ( $\pm 1$  hour) after the administration of the study medication. (v6 p13,14) All ECGs were read and interpreted by a pediatric cardiologist. QT interval was corrected using the Fridericia correction. There were no clinically significant changes in the QTc interval or other ECG parameters in patients who received cetirizine (v7. pgs496-503). At the request of the Division, the sponsor submitted on 9 October 2002 data on the QTc interval of patients in this study using Bazett's correction. An evaluation of this data shows no clinically significant change in QTc interval after administration after using this correction.
- b. **Study 9322** (volumes 8-20)(multi-country study to evaluate cetirizine in preventing the onset of asthma)(unbalanced sites in Austria, Belgium, Canada, Czech Republic, France, Germany, Italy, Luxembourg, Netherlands, Norway, Spain, Sweden, UK and Switzerland. The study objective was to assess the effect of cetirizine in preventing the onset of asthma in young children at risk of developing asthma but without a diagnosis of asthma to be determined by counting the number of patients who developed asthma during the study with the expected cumulative incidence of asthma being 40% after 18 months and a 30% reduction in the incidence of asthma being considered clinically significant.

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- 1) **Number of patients:** 830 screened, 822 randomized, 817 treated, 696 completed study; 795 ITT population (safety population) (399 children received cetirizine and 396 children received placebo)
- 2) **Age range:** 10-28 months
- 3) **Patient population:** atopic dermatitis
- 4) **Study design:** double-blind, randomized, parallel, placebo-controlled repetitive dose study
- 5) **Drug administration:** 0.25 mg/kg bid oral 10 mg/ml solution; one ml contained 20 drops and one drop contained 0.5 mg; 0.22-0.31 mg/kg per dose; 4 – 11 mg per dose
- 6) **Periods of study:** a screening period of 1-6 weeks; randomized treatment for 78 weeks (18 months); a 26 week blinded follow-up period; and a 52 week extended follow-up period; follow-up visits were conducted after one month, after 3 months and thereafter every 13 weeks during the randomized treatment period; visit 1 was the baseline evaluation prior to starting treatment; visit 2 was after 4 weeks of treatment; visit 3 was after 13 weeks of treatment; visit 4 was after 26 weeks of treatment; visit 5 was after 39 weeks of treatment; visit 6 was after 52 weeks of treatment; visit 7 was after 65 days of treatment; and visit 8 was after 78 days of treatment
- 7) **Parameters evaluated:** the primary endpoint was the time to the diagnosis of asthma;

from a safety standpoint, vital signs at each visit, physical examination at each visit, adverse events, ECGs at each visit if applicable (definitely performed at baseline and after 1 and 18 months of treatment) and laboratory values at baseline, and after 13, 26, 39, 52, 65, and 78 weeks of treatment.

QTc was evaluated using Bazett's correction with a central blinded reader (he/she did not have access to the study code) experienced in cardiac rhythmology reviewing all ECG recordings. An analysis of QTc was performed in 4 classes which were increase in QTc from baseline: 1) > 30

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msec (class 1); 2) 30- <60 msec (class 2); 3) 60- <90 msec (class 3); and 4) 90 msec or greater (class 4). There were 8 children and 7 receiving placebo who were concomitantly taking macrolide antibiotics.

#### 8) Adverse Events:

a) The percentage of patients with no adverse event during the study was 17% for the placebo group and 16% for the cetirizine group (v9, p838)

b) Overall, the following adverse events occurred with a 2% or greater frequency in the cetirizine group than was seen in the placebo group: 1) pruritis (6%); 2) conjunctivitis (20%); 3) insomnia (9%); 4) gastroenteritis (29%); 5) stomatitis (3%); 6) bronchitis (40%); 7) fatigue (3%); 8) viral infection (15%); 9) otitis media (31%); and 10) varicella (23%). There was no more than a 2% difference between the two treatment groups for any of these adverse events (v9, pgs 839-848).

#### c) Severe adverse events:

Severe adverse events where the number of patients experiencing the adverse event was 2 or greater in the cetirizine group than in the placebo group (v9, pgs849-860).

Adverse event	N = 396 placebo (# patients)	n = 399 cetirizine (# patients)
<b>Somnolence</b>	None	2
<b>Diarrhea</b>	2	8
<b>Gastroenteritis</b>	6	10
<b>Rhinitis</b>	13	16
<b>Condition aggravated</b>	1	6
<b>Otitis media</b>	4	13
<b>Rhinitis</b>	13	16
<b>Varicella</b>	4	10

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- d) **Related adverse events:** There was one patient in the cetirizine group who developed somnolence considered very likely related to the study drug, compared to none in the placebo group. There were 2 patients in the cetirizine group who developed vomiting, one considered likely related and the other considered definitely related to the study drug, compared to none in the placebo group (v9, pgs861-872).
- e) **Serious adverse events:** A 13 month old male (#758) developed a serious elevation of liver enzymes that was considered related to the study drug 34 days after beginning treatment with cetirizine. At baseline, his SGOT was 48 IU/l and his SGPT was 54 IU/l. On day 34, his SGOT was 1100 IU/l and his SGPT was 1300 IU/l. Study medication was discontinued and the patient was hospitalized. On day 7 of hospitalization, his SGOT was 146 IU/l and his SGPT was 594 IU/l and 2 weeks later, after ceterizine was discontinued, his SGOT was 61 IU/l and his SGPT was 67 IU/l. No other definitive etiology for the elevation in liver enzymes could be demonstrated. No rechallenge was done in this patient.

Serious adverse events were reported in 9% of the children taking cetirizine and 14% of the children taking placebo. There was one ceterizine patient and 5 placebo patients in whom the serious adverse event was considered related to the study drug (v8, p 108-110). There were 2 overdoses in the ceterizine group (up to single dose of 180 mg) without any serious adverse event (v8, p122).

There were 3 patients who received cetirizine who developed lymphadenopathy due to lymphadenitis compared with one patient who developed this finding in the placebo group (v10, pgs1026-1037).

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f) There were 11 dropouts in the ceterizine group (23%) because of an adverse event compared to 15 patients in the placebo group (29%). Discontinuations in patients receiving cetirizine were for: 1) asthma and diarrhea; 2) diarrhea; 3) asthenia and loss of balance; 4) fatigue and loss of hair; 5) "toxiderma"; 6) flu; 7) eczema; 8) increased LFTs; 9) vomiting; 10) nocturnal cough; and 11) constipation (v10, pgs 978-980)

### 9) laboratory tests:

a) There was a mean decrease in SGOT of 3.68 IU/l in the cetirizine group and 3.59 IU/l in the placebo group at the end of the study. There was a mean decrease in SGPT of 3.13 IU/l in the cetirizine group and 3.84 IU/l in the placebo group.

b) At the final visit, there were 8% of the cetirizine patients and 7% of the placebo patients who had an SGOT value above the upper limit of the normal reference range, but more placebo than cetirizine patients who had an elevated SGOT or SGPT at the final visit who had normal values for these parameters at baseline (v10, p1151). On the other hand, there were more placebo patients who had an elevation of SGPT above the upper limit of the normal reference range at the last visit (v10, p1152). There were no patients in the cetirizine group that had what was considered to be a clinically significant abnormality in either SGOT or SGPT at the end of the study. There were a few patients who received cetirizine who had a clinically significant elevation of either SGOT or SGPT during the study, but these tests returned to normal while they continued on cetirizine. There were patients with similar findings in the placebo group. One patient in the cetirizine group had an increase in bilirubin from 12 at baseline

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to 39 at the end of treatment (v10, p1173), but this patient had no increase in either SGOT or SGPT.

- c) One patient who received cetirizine had a WBC of 6290 at baseline and 2970 after treatment.
  - d) The mean platelet count decreased at the end of the study in the group that received cetirizine compared to an increase in the group that received placebo, although the changes were small and there was greater decrease in the platelet count in the placebo group at visit 6 and minimum levels were lower in the placebo group than in the cetirizine group (v10, 1090). There were 2 patients in the cetirizine group who had platelet counts below the NRR at baseline and 2 patients who had such a finding at the end of treatment (v10, p1116), one of which had a normal platelet value at baseline (v10, p1147), platelet count 58,000 at visit 3 (v10, p1307). On the other hand, one placebo patient had a decrease in platelets from 463,000 at baseline to 41,000 at visit 3 (v10, p1173).
  - e) There were 23 patients in the cetirizine group (18 of whom had a normal baseline creatinine level (v10, p1149) and 11 patients in the placebo group who had a creatinine level at the end of treatment that was above the upper limit of the NRR (v10, p1119). On the other hand, there was a greater mean change from baseline in terms of creatinine in the placebo group than in the cetirizine group (v10, p1092). None of these changes was considered clinically significant (v10, p1167).
  - f) One patient who received ceterizine had a fall in WBC from 6290 at baseline to 2970 after 78 days of treatment (v10, p1171).
- 10) ECGs:

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- a) **The mean QTc (Bazetts correction) in the cetirizine group went from 374 msec at baseline to 387 msec at the end of treatment. The mean QTc in the placebo group went from 376 msec at baseline to 388 msec at the end of treatment. No patient in the cetirizine group had a QTc interval > 500 msec. There were 6 patients in the cetirizine group (1.6%) who had an increase in QTc interval of 90- msec or more, compared with 5 patients in the placebo group (1.3%). There was one cetirizine patient who had an increase from baseline in QTc interval from 407 to 480 msec, but there was one placebo patient who had in increase from baseline in QTc interval from 327 to 1086 msec (v10, p1346). There was no significant gender difference in change from baseline in QTc interval in patients who received either ceterizine or placebo.**
- b) **There was no increase in the QTc interval in patients who received ceterizine or placebo concomitantly with macrolide antibiotics (v8, p113) in 8 children taking ceterizine and 7 children taking placebo.**
- c) **There was a mean change in heart rate from 115 bpm at baseline to 103 bpm after placebo which was identical to the mean change seen after treatment with cetirizine (v10, p1365).**

#### 11. vital signs:

- a) **There were no significant differences between the ceterizine and the placebo groups.**

12. **Efficacy: There was no difference between the percentage of children developing asthma in the placebo group (38%) and in the ceterizine group (38%)(v8, p116). However, in subgroups sensitized to grass pollen and house dust mite (but not cat allergen), ceterizine significantly decreased the incidence of asthma compared to placebo (v8, p118). There was no difference between the two treatment groups in regard**

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to episodes of wheezing or nocturnal cough (v8, p119). Sensitization to major allergens was not influenced by ceterizine.

**COMMENT:** This is interesting and important information that further enhances the benefit: risk assessment from the administration of ceterizine to this patient population.

- c. **Study 9708 (v21-28):** The primary objective was to evaluate the efficacy of ceterizine in the treatment of atopic dermatitis. Secondary objectives were to evaluate the safety of ceterizine at different doses and to compare the amount of corticosteroids used with different doses of ceterizine. Centers included Belgium (2), France (10), Great Britain (1), Germany (4), The Netherlands (1) and Russia (8).
- 1) number of patients: 250 patients screened; 223 randomized; 205 completed study; 222 were evaluated for efficacy and safety in the ITT population; 91 females and 131 males in the ITT population (v21, p116).
  - 2) age range: 11-71 months (< 1-5 yrs 11 months)
  - 3) patient population: atopic dermatitis; there were 7 patients receiving systemic corticosteroids (1,2,3,1 in the placebo, 0.25, 0.50 and 0.75 mg/kg/day groups, respectively (v21, p158).
  - 4) study design: multicenter, multicountry, double-blind, placebo-controlled, randomized, parallel, repetitive dose study
  - 5) drug administration: ceterizine drops 0.25, 0.50, and 0.75 mg/kg per day given bid; oral drops containing 5, 10 or 15 mg/mL
  - 6) periods of study: a run-in period of 4 weeks with patients stabilized on appropriate topical treatment; 8 weeks of randomized treatment; a 4 week double-blind follow-up after discontinuation of the study medication
  - 7) parameters evaluated: The primary efficacy variable was change from baseline to end of treatment in modified SCORAD index. Secondary efficacy variable

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was the quantity of CS cream used. Safety evaluation included adverse events and physical examination.

#### 8) results:

- a) **safety: adverse events:** Adverse events occurred in 56% of the patients in the 0.25 mg/kg/day group, 57% of the patients in the 0.50 mg/kg/day group, 53% of the patients in the 0.75 mg/kg/day group and 56% of the placebo group. The most common type of adverse events was related to the respiratory system, 48%, 45%, 33% and 31% in the 0.25 mg/kg/day group, 0.50 mg/kg/day group, 0.75 mg/kg/day group, and placebo group, respectively (v21, p76).
- b) There were 6 patients who had serious adverse events, 5 of whom were in the placebo group. The one patient in the 0.25 mg/kg/day ceterizine group developed angioneuotic edema, urticaria and asthma which was considered unlikely to be related to the treatment drug (v21, p85). There were 4 patients who were discontinued from the study because of an adverse event - one placebo patient, one 0.50 mg/kg/day ceterizine patient (diarrhea) and two 0.75 mg/kg/day ceterizine patients (URI and allergic rash). Only the allergic rash was considered related to the study drug (v21, p82). One patient, a 4 year old male, who received 0.25 mg/kg/day of ceterizine had an increase in hepatic transaminases (SGOT, SGPT) and laboratory tests for viral hepatitis were negative. The child was hospitalized, liver function tests returned to normal and the patient was discharged and continued in the study without any apparent recurrence (v21, p256)(v21, pgs 280-283)(CRF 212). One patient, a one year old male, who received 0.50 mg/kg/day of ceterizine developed cyanosis and circulatory failure, was hospitalized for one night without recurrence (v21, pgs 287-289).

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- c) See table below for adverse events which occurred with a greater frequency (4% or more) in patients receiving one of the doses of ceterizine than in the group that received placebo. There were 6 serious adverse events, 5 in the group that received placebo and one in the group that received 0.25 mg of cetirizine. The most common types of adverse events can be seen in the second table below (v21 p8).

adverse event	placebo	cetirizine 0.25	cetirizine 0.50	cetirizine 0.75
	N = 55	N = 54	N = 56	N = 57
Conjunctivitis	1 (2%)	None	4 (7%)	2 (4%)
Gastroenteritis	1 (2%)	4 (7%)	6 (11%)	3 (5%)
Otitis media	3 (5%)	5 (9%)	4 (7%)	2 (4%)
Rhinitis	6 (11%)	16 (30%)	11(20%)	8 (14%)
Skin disorder	1 (2%)	2 (4%)	4 (7%)	3 (5%)
Tracheitis	1 (2%)	3 (6%)	1 (2%)	None
Resp disorder	1 (2%)	1 (2%)	5 (9%)	None

adverse event	placebo	cetirizine 0.25	cetirizine 0.50	cetirizine 0.75
Gastroenteritis	2%	7%	11%	5%
Rhinitis	11%	30%	20%	14%
URI	18%	11%	18%	12%
Psychiatric *	5%	2%	2%	4%
Fever	13%	9%	9%	7%

\* agitation, anorexia, increased appetite, insomnia and nervousness

- d) efficacy: No additional beneficial effect of ceterizine was seen on the symptoms of atopic dermatitis in children stabilized on topical corticosteroids.

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**8) study results: no interim study results were supplied by the sponsor.**

**COMMENT: No data have been submitted for this study.**

#### **2. single dose studies:**

##### **a. study 123 (v4):**

- 1) number of patients: 15 (10 males, 5 females)(11 in Prague and 4 in Brussels)**
- 2) age range: 6-23.4 months**
- 3) patient population: infants hospitalized for respiratory problems including chronic respiratory infections and "other hypersensitivity related pathologies"**
- 4) study design: open 2 center (Prague and Brussels) PK single dose (note that the study was amended to evaluate inhibition of histamine-induced wheal and flare response in 10 infants after 0.25 mg/kg bid for at least 4 days) study**
- 5) drug administration: cetirizine 0.25 mg/kg using a 10 mg/ml solution as a single dose for pharmacokinetic measurements and 0.25 mg/kg bid for at least 4 days for the pharmacodynamic measurements**
- 6) periods of study: follow-up for at least 24 hours after drug administration and after at least 4 days for inhibition of histamine-induced wheal and flare response**
- 7) parameters evaluated: blood samples at 0.5, 1, 1.5, 2, 4, 6, 8, 12 and 24 hours after drug administration to measure C<sub>max</sub>, T<sub>max</sub>, half-life and AUC; ECGs were done at baseline and 24 hours after the last dose of cetirizine; in 10 patients inhibition of histamine-induced wheal and flare was measured after administration of**

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0.25 mg/kg for at least 4 days and compared with baseline determination of such inhibition.

8) study results: Patients received 2-3 mg of ceterizine.

a) mean pharmacokinetic parameters (v4, p10,20)

$C_{max} = 390 \pm 135$  ng/ml (range of 205-603)(v4 p30)

$T_{max} = 2 \pm 1.3$  hours (range of 0.5-4)(v4, p30)

elimination  $\frac{1}{2}$  life =  $3.1 \pm 1.8$  hours (range 0.8-6.8)

clearance =  $2.13 \pm 1.15$  ml/min/kg (range 0.57-4.96)

renal clearance was 2/3 of the Cl/F

volume of distribution =  $0.44 \pm 0.19$  l/kg

AUC  $2704 \pm 1829$  ng/ml (range 747-7730)(v4, p30)

Infants have a shorter half-life and faster clearance of cetirizine than older children and adults, and therefore the risk of accumulation after repeated doses is likely to be low. See table above for comparison of pharmacokinetic data in patients 6-24 years of age with older children and adults. The AUC in children 2-5 years of age is about twice that seen in patients 6-24 months of age in this study. However, there was significant variation in the AUC seen in this study with some infants having an AUC of almost twice that seen in patients 2-5 years of age.

The mean plasma ceterizine concentration time curve (v4, p35) shows that by 12 hours after drug administration in infants, the plasma level is about 60 ng/ml and decreases further over the next 12 hours, raising questions about the efficacy of ceterizine over the last 12 hours of the 24 hour dosing interval.

b) All ECGs were normal without prolongation of the QTc interval. The maximum increase in the QTc interval was 8% and the greatest decrease in the QTc interval was 12% (v4, p21)(v4, p33).

c) adverse events were reported in 3 infants; 1) moderate somnolence associated with anorexia and

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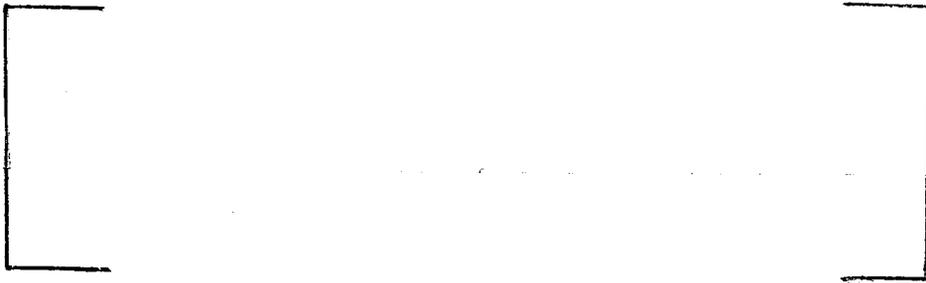
### Clinical Review Section

**asthenia from 30 minutes to 24 hours after drug administration considered possibly related to study drug; 2) mild vomiting 1 hour and 30 minutes after drug administration considered unlikely to be related to study drug; and 3) marked nervousness from 45 minutes to 11 hours after drug administration considered possibly related to the study drug (v4,p21).**

- d) Wheal and flare inhibition was high (87-90% 12 hours after administration of cetirizine) despite the short half-life suggesting that pharmacodynamic assessment at a cutaneous level is longer than could be inferred from the PK data in infants(v4, p10)**

**COMMENT: The PD portion of this study, i.e. evaluation of wheal and flare response was not part of the original design of the study but the protocol was amended because of the shorter  $\frac{1}{2}$  life and more rapid clearance noted in the first 8 patients analyzed. The Division does not accept inhibition of histamine-induced wheal and flare as a validated marker of clinical effectiveness. Clinical effectiveness of ceterizine in patients 6-24 months of age could be questioned on the basis of the data from this study, because of the suggested decrease in bioavailability of ceterizine in this age group. However, cross-study comparison of pharmacokinetic data from studies in adults show that the Cmax and AUC are comparable in adults and in patients 6-24 months of age at a dose in adults that has been shown to be efficacious.**

**b.**



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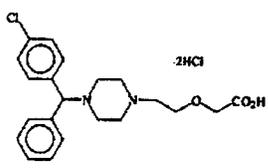
**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**NDA 19-835/S-015**

**NDA 20-346/S-008**

**CHEMISTRY REVIEW**

<b>CHEMIST'S REVIEW #1</b>		<b>1. ORGANIZATION</b> HFD-570 DPDP	<b>2. NDA NUMBER</b> 19-835 20-346
<b>3. NAME AND ADDRESS OF APPLICANT (City and State)</b> Pfizer Inc. 235 East 42 <sup>nd</sup> Street New York, NY 10017-5755		<b>4. AF NUMBER</b>	
<b>6. NAME OF DRUG</b> Zyrtec® Tablets (N19-835) Zyrtec® Syrup (N20-346)		<b>5. SUPPLEMENT(S) NUMBER(S) DATES(S)</b> SE5-015 (N19-835) 12/21/01 SE5-008 (N20-346) 12/21/01	
<b>7. NONPROPRIETARY NAME</b> cetirizine hydrochloride		<b>9. AMENDMENT(S), REPORT(S), ETC.</b> SE5-015 (AZ) 1/30/02 SE5-008 (AZ) 1/30/02	
<b>8. SUPPLEMENT PROVIDES FOR:</b> The addition of an indication for _____ allergic rhinitis for patients >6 months to 24 months.		<b>12. RELATED IND/NDA/DMF</b>	
<b>10. PHARMACOLOGICAL CATEGORY</b> antihistamine	<b>11. HOW DISPENSED</b> RX <u>X</u> OTC	<b>16. RECORDS AND REPORTS</b> CURRENT YES_NO REVIEWED YES_NO	
<b>13. DOSAGE FORM(S)</b> tablet and syrup	<b>14. POTENCY</b> 5 mg and 10 mg/tablet 5mg/5 mL (syrup)		
<b>CHEMICAL NAME AND STRUCTURE</b>  (±)-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]acetic acid or (±)-[2-[4-(p-Chlorophenylbenzyl)-1-piperazinyl]ethoxy]acetic acid			
<b>17. COMMENTS:</b> The applicant claims a categorical exclusion under 21CFR 25.31(b), i.e., it is estimated that the additional indication and larger age range will not increase the expected concentration in the aquatic environment of > 1 ppb. cc: Orig. NDA 19-835 Orig. NDA 20-346 HFD-570/div. File HFD-570/CBertha/2/1/02 HFD-570/GPoochikian HFD-570/COstroff R/D Init. by: _____ F/T by: CBertha/2/1/02 doc # 02-01-30.rev.doc			
<b>18. CONCLUSIONS AND RECOMMENDATIONS:</b> Based on the information provided, it is recommended from the CMC perspective, that the supplements be approved (AP).			
<b>19. REVIEWER NAME:</b> Craig M. Bertha, Ph.D.		<b>SIGNATURE</b>	<b>DATE COMPLETED</b> 2/2/02

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this page is the manifestation of the electronic signature.**

/s/

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Craig Bertha  
2/4/02 06:29:51 AM  
CHEMIST

Guiragos Poochikian  
2/5/02 05:20:43 PM  
CHEMIST

# **CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**NDA 19-835/S-015**

**NDA 20-346/S-008**

**ENVIRONMENTAL ASSESSMENT**

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**The Environmental Assessment is addressed in the  
Chemistry Review dated 2-2-02**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

***APPLICATION NUMBER:***

**NDA 19-835/S-015**

**NDA 20-346/S-008**

**Pharmacology / Toxicology Review**

## PHARMACOLOGY/TOXICOLOGY COVER SHEET

**NDA number:** NDA 19-835  
**Review number:** 1  
**Sequence number/date/type of submission:** SE5-015PS/12-21-01  
**Information to sponsor:** Yes  
**Sponsor and/or agent:** Pfizer, Inc.  
**Manufacturer for drug substance :** UCB S.A., Chemin du Foriest, 1420 Braine-L'Alleud, Belgium.

[ ]

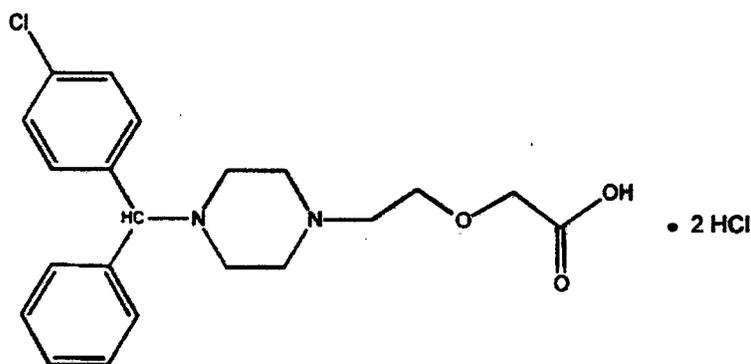
**Reviewer Name:** Jui R. Shah, Ph.D.  
**Division Name:** Division of Pulmonary and Allergy Drug Products  
**HFD #:** 570  
**Review Completion Date:** September, 2002

### Drug:

**Trade name:** Zyrtec  
**Code Name:** N/A  
**Generic Name:** Cetirizine  
**Chemical Name:** Cetirizine: (+/-)- [2-[4-[(4-chlorophenyl) phenylmethyl]-1-piperaziny] ethoxy] acetic acid, dihydrochloride. Pseudo-ephedrine: (1S,2S)-2-methylamino-1-phenyl-1-propanol hydrochloride.

**Molecular Formula/ Molecular Weight:** Cetirizine Dihydrochloride:  
C<sub>21</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>3</sub>·2HCl, 461.82

### Structure:



**Relevant INDs/NDAs/DMFs:** IND 41,365 also NDA 21-150, NDA 20-346.

**Drug class:** Antihistamine (H<sub>1</sub> histamine receptor antagonist)

**Indication:** \_\_\_\_\_ perennial allergic rhinitis and chronic urticaria.

**Clinical formulation:** Tablets (10 mg & 5 mg strengths) and syrup (1 mg/ml) for oral use.

**Route of administration:** Oral

**Proposed use:** ZYRTEC (doses below) is indicated for the relief of symptoms associated with \_\_\_\_\_ perennial allergic rhinitis and for the treatment of uncomplicated skin manifestations of chronic idiopathic urticaria in patients 6 months of age and older.

<b>Age</b>	<b>Maximum daily dose (mg)</b>
<b>6 months - 2 years</b>	<b>5</b>
<b>2 - 5 years</b>	<b>5</b>
<b>6-11 years</b>	<b>10</b>
<b>Adult</b>	<b>10</b>

**Disclaimer:** Tabular and graphical information is from sponsor's submission unless stated otherwise.

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## ***Executive Summary***

### **I. Recommendations**

#### **A. Recommendation on Approvability**

This is a supplement to the original NDA. The supplement contains labeling changes since the age for administration is being decreased from 2 years to 6 months.

#### **B. Recommendation for Nonclinical Studies**

Not applicable.

#### **C. Recommendations on Labeling**

The sponsor submitted proposed labeling for the use of cetirizine hydrochloride in pediatric patients from 6 months to 24 months in age. Previously, cetirizine was used only in pediatric patients 2 years old and above. It was noted upon reviewing the proposed labeling text that the ratios for the carcinogenicity and overdosage sections had not been recalculated to account for the lower body weights of pediatric patients 6 months to 2-years of age.

The reviewer used data from the Centers for Disease Control ([www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical\\_chart.htm](http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical_chart.htm)) which were last updated in November 2000, and determined that the average weight (50<sup>th</sup> percentile) of a 6 month old infant was between 7-8 kg. Therefore, the weight used for calculation of a mg/kg dose was 7 kg.

The following sections of the label should read as follows. The only changes made to the dose ratios to children.

#### **Carcinogenesis, Mutagenesis and Impairment of Fertility:**

In a 2-year study in rats, cetirizine was not carcinogenic at dietary doses up to 20 mg/kg (approximately 15 times the maximum recommended daily oral dose in adults on a mg/m<sup>2</sup> basis, or approximately 7 times the maximum recommended daily oral dose in \_\_\_\_\_ on a mg/m<sup>2</sup> basis). In a 2-year study in mice, cetirizine caused an increased incidence of benign liver tumors in males at a dietary dose of 16 mg/kg (approximately 6 times the maximum recommended daily oral dose in adults on a mg/m<sup>2</sup> basis, or approximately 3 times the maximum recommended daily oral dose in \_\_\_\_\_ on a mg/m<sup>2</sup> basis). No increase in the incidence of liver tumors was observed in mice at a dietary dose of 4 mg/kg (approximately 2 times the maximum recommended daily oral dose in adults on a mg/m<sup>2</sup> basis, or approximately equivalent to the maximum recommended daily oral dose in \_\_\_\_\_ on a mg/m<sup>2</sup> 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 \_\_\_\_\_

In a fertility and general reproductive study in mice, cetirizine did not impair fertility \_\_\_\_\_ 64 mg/kg (approximately 25 times the maximum recommended daily oral dose in adults on a mg/m<sup>2</sup> basis).

## OVERDOSAGE

Overdosage has been reported with cetirizine. In one adult patient who took 150 mg of cetirizine, the patient was somnolent but did not display any other clinical signs or abnormal blood chemistry or hematology results. In an 18-month-old pediatric patient who took an overdose of cetirizine (approximately 180 mg), restlessness and irritability were observed initially; this was followed by drowsiness. 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 acute minimal lethal oral doses were 237 mg/kg in mice (approximately 95 times the maximum recommended daily oral dose in adults on a mg/m<sup>2</sup> basis, or approximately 40 times the maximum recommended daily oral dose in \_\_\_\_\_ on a mg/m<sup>2</sup> basis) and 562 mg/kg in rats (approximately 460 times the maximum recommended daily oral dose in adults on a mg/m<sup>2</sup> basis, or approximately 190 times the maximum recommended daily oral dose in \_\_\_\_\_ on a mg/m<sup>2</sup> basis). In rodents, the target of acute toxicity was the central nervous system, and the target of multiple-dose toxicity was the liver.

## II. Summary of Nonclinical Findings

### A. Brief Overview of Nonclinical Findings

Not applicable.

### B. Pharmacologic Activity

Not applicable.

### C. Nonclinical Safety Issues Relevant to Clinical Use

Not applicable.

## III. Administrative

A. Reviewer signature: \_\_\_\_\_

Reviewer: \_\_\_\_\_

NDA No. \_\_\_\_\_

B. Supervisor signature: Concurrence - \_\_\_\_\_  
\_\_\_\_\_

Non-Concurrence - \_\_\_\_\_  
(see memo attached)

C.  
cc: HFD 570/Division file  
HFD 570/ShahJ  
HFD 570/HuffR  
HFD 570/NicklausR  
HFD 570/OstroffC

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Jui Shah  
10/16/02 01:12:05 PM  
PHARMACOLOGIST

Robin Huff  
10/16/02 02:17:29 PM  
PHARMACOLOGIST  
I concur.

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**NDA 19-835/S-015**

**NDA 20-346/S-008**

**STATISTICAL REVIEW**

**STATISTICAL REVIEW AND EVALUATION  
CLINICAL STUDIES**

**Date**  
**NDA #** 20-346  
**Applicant** Pfizer  
**Name of Drug** Zyrtec (cetirizine HCl) Syrup 0.25mg/kg (NDA 20-346)  
**Indication** Treatment of patients aged 6-11 months with rhinitis  
**Document Reviewed**  
 Study Report: Zyrtec (Cetirizine HCl) Protocol A143-1010  
 Data sets:  
 Safety Data set: ADVERS  
 Safety Data set: AE VAT  
 Safety Data set: FINAL  
**Statistical Reviewer** Ted J. Guo, Ph.D., Div II/OEB, HFD-715  
**Medical Input** Richard Nicklas, MD  
Division of Pulmonary Drug Products (ODE II, HFD-570)  
**Key Words** NDA, Clinical Studies

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## **Summary**

This reviewer performed a preliminary exploration of the safety data from Study A143-1010, based on three data files, named ADVERS, AE\_VAT, and FINAL. The data show some adverse events, such as NERVOUSNESS, had high frequencies of occurrences and recurrences, compared with others. However, the reported adverse events did not appear to be strongly linked to the treatments. Considering the young ages of the patients (6-11 months), the relatively small number of patients (86), and the relatively short follow-up time (4 months), this study, alone, does not provide strong quantitative evidence for a safety claim.

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## Introduction

Zyrtec (cetirizine) syrup, orally taken at 0.25mg/kg bid, is indicated for patients with allergic rhinitis. To support the safety claim, Pfizer submitted Study Report: ZYRTEC (CETIRIZINE) HYDROCHLORIDE PROTOCOL A143-1010: *A multi-center, randomized, double-blind, placebo-controlled, parallel group study of the safety of Zyrtec (cetirizine hydrochloride) syrup in pediatric subject 6 months to 11 months of age (vols. 6-40).*

Table 1 summarizes the characteristics of this study.

**Table 1. Study A134-1010**

Study	General Feature	Specific Characteristics
Protocol A143-1010	7-day treatment and 15-day follow-up	<b>Visit 1 (Study Day 1):</b> Pretreatment screening—collects medical history, performs physical examination, and dispenses study medication. <b>Visit 2 (Study Day 8):</b> The visit of parents with their patients—collects treatment diary and performs physical examination. <b>Follow-up (Study Day 15):</b> Telephone interview of parents for assessing concomitant medication use and adverse events. (See p.13, vol. 6.)
	Study time line	Study dates: 4/9/01-8/23/01 Report date: 11/15/01
	Randomized	
	Double-blind	
	Parallel-group	<ul style="list-style-type: none"> <li>• Zyrtec (cetirizine) syrup, orally taken at 0.25mg/kg bid</li> <li>• Placebo</li> </ul>
	Multi-center	15 centers
	Efficacy variables	No efficacy data were collected
	Safety variables	Adverse events and other safety variables

The objective of this study was to evaluate the safety of Zyrtec. The patients in this study were aged 6-11 months, having allergic rhinitis (p.5, vol.6). Out of 86 participating patients, 69 were reported (by parents) to have at least one episode of an adverse event over the 15-day study period. No efficacy evaluation was planned and performed for this study.

To assist the medical reviewer in the safety evaluation, this reviewer tabulated the reported adverse events by grouping and subsetting based on the characteristics of the patients and adverse-events. This approach was used in an attempt to uncover possible associations between the treatment and the adverse events. Having taken into consideration the characteristics of the sponsor's study—the number of the patients participated, the ages of the patients, and the length of the study period—inferential statistical analysis (often concluded with p-values) was not attempted. It is the descriptive statistics that play a proper role in this safety evaluation. In this reviewer's viewpoint, it is mainly the medical judgment that decides the safety of this drug.

This reviewer's safety analyses comprises two parts:

1. Analyses of patient distributions based mainly on status of adverse events. In this analysis, a patient is identified as one with or without adverse events. Hence, a patient is counted only once when numbers and percentages are calculated.
2. Analyses of AE episodes. Here we count a patient multiple times if he had more than one type of AE. These analyses were used to expose possible links between the treatments and adverse events.

The data sets mostly used in this reviewer's safety evaluation were ADVERS, AE\_VAT, and FINAL, submitted by the sponsor as part of the NDA. The first two were labeled as the data sets of adverse events, and FINAL was utilized to obtain information about patient demographics and final status.

The sponsor's main conclusions regarding the safety is highlighted as follows:

- The safety data do not reveal any unexpected safety concerns.
- No serious or unexpected treatment-emergent adverse events were reported during this study.
- There was no apparent difference in the incidence and severity of the treatment-emergent adverse events by age group between the two treatment groups.

The complete safety conclusions can be found starting on page 4, vol. 6 of the Study Report. Many of the sponsor's computations were verified. Any discrepancies between the sponsor's data and report will be noted.

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**Analysis of Patient Distributions**

Table 2 shows the numbers of patients by treatment. The numbers and percentages of those who ever had at least one episode of adverse event are also listed. Overall, 80% of the patients had at least one episode of adverse event. Note: 44 patients received placebo. According to the sponsor's report, only 43 of them were included in the safety assessment, decided by the inclusion and exclusion criteria (p.3, 15, vol.6). The percentage of those with AEs was slightly higher in the placebo group than in the cetirizine group.

**Table 2. Numbers and percentages of patients by treatment and AE status**

	86	69	80%
	42	31	74%
	44	38	86%

Source: Reviewer's analysis safety data set, AEDATA

Patients listed in Table 3 did not have any adverse events.

**Table 3. Patients with no AE reported**

Study ID	AE	AE	AE	AE	AE	AE	AE	AE	AE
CETIRIZINE	000049	1002	35180	04/18/01	04/25/01	COMPLETED	10	WHITE	MALE
	000027	1007	34353	05/10/01	05/17/01	COMPLETED	6	WHITE	MALE
	000080	1011	34841	07/18/01	07/28/01	COMPLETED	10	OTHER	FEMALE
	000123	1011	34841	07/23/01	07/30/01	COMPLETED	8	WHITE	FEMALE
	000014	1012	35918	04/19/01	04/28/01	COMPLETED	6	WHITE	MALE
	000059	1013	15507	05/17/01	05/24/01	COMPLETED	10	WHITE	FEMALE
	000099	1013	15507	06/13/01	08/13/01	WITHDRAWN CONSENT	10	WHITE	FEMALE
	000020	1014	36047	06/26/01	07/05/01	COMPLETED	11	WHITE	MALE
	000034	1015	36058	06/04/01	06/11/01	COMPLETED	10	WHITE	MALE
	000085	1017	26843	06/18/01	06/25/01	COMPLETED	8	OTHER	MALE
	000067	1018	35809	05/11/01	05/18/01	COMPLETED	11	WHITE	FEMALE
	000050	1002	35180	04/18/01	04/25/01	COMPLETED	10	WHITE	FEMALE
	000028	1007	34353	06/28/01	07/05/01	COMPLETED	6	WHITE	MALE
	000015	1012	35918	04/27/01	05/04/01	COMPLETED	6	WHITE	MALE
	000060	1013	15507			OTHER	7	WHITE	FEMALE
	000146	1015	36058	07/30/01	08/06/01	COMPLETED	9	WHITE	MALE
	000068	1018	35809	05/25/01	06/01/01	COMPLETED	11	WHITE	MALE

Source: Reviewer's analysis safety data set, AEDATA

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Table 4 shows the number of patients with AEs among 15 centers by treatment. Centers 1005, 1012, and 1017 appear to have more patients with AEs. Note that the sponsor's report included 19 centers. However, no data were provided for the following three centers, Centers 1003, 1010, and 1019.

**Table 4. Centers where adverse events were reported**

	1001	1002	1004	1005	1006	1007	1008	1009	1011	1012	1013	1014	1015	1016	1017	1018	Total
Placebo	1	1	1	8	1	2	1	2	1	5	3	1	2		4		31
Cetirizine	2	1	1	6	1	2		2	3	5	3	3	2	1	6		38
Total	3	2	2	12	2	4	1	4	4	10	6	4	4	1	10		69

Source: Reviewer's analysis safety data set, AEDATA

The tables below indicate that the patient population had a fairly balanced arrangement in terms of age and sex. Table 5 shows that, on average, patients with AEs were slightly older in the cetirizine group than in the placebo group.

**Table 5. Patients' ages by treatment**

	Mean	SD	Min	Max
Placebo	8.0	8.0	6.0	11.0
Cetirizine	7.4	7.0	5.0	10.0

Source: Reviewer's analysis safety data set, AEDATA

Table 6 shows that the number of patients by sex.

**Table 6. Number of patients by sex and treatment**

	Male	Female	Total
Placebo	15	16	31
Cetirizine	16	22	38
Total	31	38	69

Source: Reviewer's analysis safety data set, AEDATA

Table 7 describes the patient distributions. We treat patients' final status as complete and dropouts which fall into one of these three groups: dropout due to adverse event, dropout due to protocol violation, or dropout due to other reasons. Overall, 88.4% of the patients with at least one AE episode had complete follow-ups. This reviewer, in the next section of this report, further examined those withdrawn due to adverse events. The percent of follow-ups is acceptable to this reviewer.

**Table 7. Final status of patient with adverse events**

	Complete	%	Dropout due to adverse event	%	Dropout due to protocol violation	%	Dropout due to other reasons	%	Total	%
Placebo	27	87.1	3	9.7	1	3.2	0	0	31	100.0
Cetirizine	34	89.5	3	7.9	0	0	1	2.6	38	100.0
Total	61	88.4	6	8.7	1	1.4	1	1.4	69	100.0

Source: Reviewer's analysis safety data set, AEDATA

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**Analysis of Adverse Events**

This section is focused on the analysis of episodes of adverse events. Note that a patient could have multiple occurrences of the same adverse event at different times. More commonly, a patient could have more than one kind of adverse event during the treatment. Taken these facts into consideration, we analyze the adverse events and then trace back to patients who had these adverse events.

The main source of reported adverse events was the sponsor's data set, ADVERS. In this data set, AECODE and AENAME describe the codes and names of adverse events. However, by examining the AE names, this reviewer found that the descriptions of adverse events using AENAME was crude, inaccurate, and sometimes redundant. This situation is demonstrated in Table 8, below. This reviewer used another variable, called preferred name of adverse event by the sponsor, AENAMEALT (in data set AE\_VAT) that consolidated AENAME. In this report, this reviewer describes and counts adverse events solely based on the "preferred" adverse-event name, AENAMEALT (labeled as AE name Alt.). The medical reviewer may need to decide the appropriateness of the adverse-event names.

**Table 8. Example of variable names of adverse events--AENAME and AENAMEALT compared**

DECREASE IN SLEEP	INSOMNIA
DECREASED SLEEP	INSOMNIA
RESTLESS DURING SLEEP	INSOMNIA
RESTLESSNESS DURING SLEEP	INSOMNIA
SLEEPLESSNESS	INSOMNIA

Source: Sponsor's data sets, ADVERS and AE\_VAT

Table 9 gives the entire list of reported adverse events in the data as a starting point for further data exploration and analysis. Please note that NERVOUSNESS was the one having the highest frequency of all.

**Table 9. All reported adverse events**

AE Name	AE Code	Frequency					Total
		1	2	3	4	5	
ADVERSE	ADVERSE						
ADVERSE	ADVERSE	2					2
ADVERSE	ADVERSE	1			1		1
ADVERSE	ADVERSE	6	2		1		8
ADVERSE	ADVERSE	1				1	1
ADVERSE	ADVERSE	1				1	1
ADVERSE	ADVERSE	1				1	1
ADVERSE	ADVERSE		1		1		1
ADVERSE	ADVERSE	1	1		2		2
ADVERSE	ADVERSE			1	1		1
ADVERSE	ADVERSE	1				1	1
ADVERSE	ADVERSE	4	2		1		6
ADVERSE	ADVERSE	1			1		1
ADVERSE	ADVERSE		1		1		1

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		Zyrtec Syrup		Placebo	
		Number of Patients	Percentage of Patients	Number of Patients	Percentage of Patients
HEADACHE	ALL PATIENTS	1	1	1	1
	PLACEBO	2	1	1	2
DIZZINESS	ALL PATIENTS	1	1	1	1
	PLACEBO	10	10	10	10
TREMOR	ALL PATIENTS	2	1	3	3
	PLACEBO	1		1	1
INSOMNIA	ALL PATIENTS	1		1	1
	PLACEBO	1		1	1
VOMITING	ALL PATIENTS	1		1	1
	PLACEBO	1		1	1

Source: Reviewer's analysis safety data set, AEDATA

Table 10 shows the number of patients who had repeated occurrences of certain adverse events during the study. Note that NERVOUSNESS had the highest recurrences among other adverse events, INSOMNIA being the next. Please also note that the recurrences of adverse events had a higher frequency in the placebo group than in the cetirizine group.

**Table 10. Number of patients who had repeated occurrences of certain adverse events**

Adverse Event	Number of Patients	
	Placebo	Zyrtec Syrup
NERVOUSNESS	15	8
INSOMNIA	9	4
SOMNOLENCE	1	1
AGITATION	1	1
TREMOR	1	1

Source: Reviewer's analysis safety data set, AEDATA

Table 11 shows the number of patients in either group with adverse events. Here the preferred name of adverse event, AENAMEALT is used. One needs to pay special attention to NERVOUSNESS, INSOMNIA, SOMNOLENCE, AGITATION and other adverse events with high frequency and high recurrence.

**Table 11. Number of patients with adverse events**

Adverse Event	Number of Patients
HEADACHE	31
DIZZINESS	29
SOMNOLENCE	22
AGITATION	9
NERVOUSNESS	8
INSOMNIA	7
CONSTIPATION	5
UPPER RESPIRATORY INFECTION	4
DIARRHEA	4
EAR, MIDDLE, WITH EFFUSION	4
EAR, MIDDLE, WITHOUT EFFUSION	4
ENTRAPPED AIR IN MIDDLE EAR	3
EAR, MIDDLE, WITH EFFUSION	3



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	1		1	1.0	1.0	1.0				
	12	19	20	1.0	4.5	8.0	42	1.0	3.3	13.0
	1		1	6.0	6.0	6.0				
	3	2	3	8.0	10.3	12.0	2	8.0	8.0	8.0
	2		2	11.0	11.0	11.0				
	1		1							
	1	2	1	5.0	5.0	5.0	2	1.0	1.0	1.0
	3	1	3	4.0	8.0	12.0	1			
	2	2	2				2	2.0	2.0	2.0
	9	13	10	1.0	2.4	5.0	14	1.0	3.6	10.0
	1		1							
	4	4	5	1.0	4.0	10.0	5	2.0	2.0	2.0
	2	2	2	3.0	3.5	4.0	3	2.0	4.0	8.0
		1					1	3.0	3.0	3.0
	1	1	1	7.0	7.0	7.0	1	2.0	2.0	2.0

Source: Reviewer's analysis safety data set, AEDATA

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Table 14 summarizes the severity of adverse events by treatment group. The numbers in the table are the number of episodes of the adverse events.

Table 14. Severity of the adverse events by treatment group

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Adverse Event	Group 1		Group 2		Group 3	
	Number	Percentage	Number	Percentage	Number	Percentage
ASTHMA	3		3	7	2	9
BRONCHITIS				1		1
ASTHMA EXACERBATION			1			1
BRONCHOPULMONARY ASPIRATION					1	1
BRONCHOSPASM		1	1	1		2
BRONCHITIS ACUTE	2	1	3	3	1	4
BRONCHITIS CHRONIC	1		1			
BRONCHITIS EXACERBATION					1	1
BRONCHITIS OBSTRUCTIVE	2		2	2		2
BRONCHITIS VESICULAR	1		1			
BRONCHOPULMONARY ASPIRATION	1		1			
BRONCHOPULMONARY ASPIRATION	14		14	32	2	34
BRONCHOPULMONARY ASPIRATION	1		1			
BRONCHOPULMONARY ASPIRATION	20		20	40	2	42
BRONCHOPULMONARY ASPIRATION	1		1			
BRONCHOPULMONARY ASPIRATION		3	3	1	1	2
BRONCHOPULMONARY ASPIRATION	2		2			
BRONCHOPULMONARY ASPIRATION		1	1			
BRONCHOPULMONARY ASPIRATION	1		1	1	1	2
BRONCHOPULMONARY ASPIRATION	1	2	3	1		1
BRONCHOPULMONARY ASPIRATION	2		2	2		2
BRONCHOPULMONARY ASPIRATION	9	1	10	11	3	14
BRONCHOPULMONARY ASPIRATION		1	1			
BRONCHOPULMONARY ASPIRATION	5		5	5		5
BRONCHOPULMONARY ASPIRATION	1	1	2	3		3
BRONCHOPULMONARY ASPIRATION				1		1
BRONCHOPULMONARY ASPIRATION	1		1	1		1

Source: Reviewer's analysis safety data set, AEDATA

***Reviewer's Recommendations***

This reviewer performed a preliminary exploration of the safety data from Study A143-1010, based on three data files, named ADVERS, AE\_VAT, and FINAL. The data show some adverse events, such as NERVOUSNESS, had high frequencies of occurrences and recurrences, compared with others. However, the reported adverse events did not appear to be strongly linked to the treatments. Considering the young ages of the patients (6-11 months), the relatively small number of patients (86), and the relatively short follow-up time (4 months), this study, alone, does not provide strong quantitative evidence for a safety claim.

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## **Appendix**

A web-based review tool is available, allowing a preview of all adverse events patient-by-patient. This site was created using SAS/IntrNet v.8.2, accessible for CDER reviewers.

- Preview AE data

You must have a CDER FDA Intranet connection to while reading this report.

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## Concurrence

Reviewer:  
Concur:

Ted Guo, Ph.D.  
Lisa Kammerman, Ph.D.  
Steve Wilson, Dr.P.H.

CC:  
Archival  
NDA 19-835  
NDA 20-346

HFD-570/Division file  
HFD-570/RNicklas

HFD-715/Division file  
HFD-715/LKammerman  
HFD-715/SWilson  
HFD-715/TGuo

HFD-700/Canello

TG/N20346AE1.doc

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**

/s/

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Ted Guo  
10/17/02 04:48:56 PM  
BIOMETRICS

Steve Wilson  
10/17/02 05:02:08 PM  
BIOMETRICS

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**NDA 19-835/S-015**

**NDA 20-346/S-008**

**CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS**  
**REVIEW**

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

---

<b>NDA:</b>	19-835 (Pediatric Exclusivity Supplement)
<b>Proprietary Drug Name:</b>	Zyrtec Oral Solution
<b>Generic Name:</b>	Cetirizine HCL
<b>Indication:</b>	Perennial Allergic Rhinitis, Chronic Idiopathic Urticaria
<b>Dosage Form:</b>	Syrup
<b>Strength:</b>	1 mg/mL
<b>Route of Administration:</b>	Oral
<b>Dosage and administration:</b>	Children 6 months to <2 years of age: 2.5 mg QD or 2.5 mg BID depending on symptom severity
<b>Applicant:</b>	Pfizer Laboratories
<b>Clinical Division:</b>	DPADP (HFD-570)
<b>Submission Date:</b>	December 21, 2001
<b>Reviewer:</b>	Sandra Suarcz-Sharp, Ph.D.
<b>Team Leader:</b>	Emmanuel Fadiran, Ph. D.

---

## 1. EXECUTIVE SUMMARY

Cetirizine, an active metabolite of hydroxyzine, is an orally active and selective H<sub>1</sub>-receptor antagonist. Zyrtec (cetirizine) 5 and 10 mg tablets (NDA 19-835) and Zyrtec syrup 1 mg/mL (NDA 20-346) were approved by the Agency on 12/08/95 and 09/27/96, respectively.

In the present supplemental NDA (19-835) the sponsor, Pfizer, is seeking FDA's concurrence to the information submitted, pursuant to the Pediatric Rule, which support the use of Zyrtec (cetirizine HCL) at the dose of 2.5 mg QD or 2.5 mg BID in pediatric patients down to 6 months of age for the treatment of \_\_\_\_\_ Perennial Allergic Rhinitis and Chronic Idiopathic Urticaria.

A total of eleven clinical trials were conducted in children under 2 years of age receiving cetirizine 0.25 mg/kg BID and were submitted to the Agency in support of this NDA. None of these controlled studies assessed efficacy in children under 2 years of age with allergic rhinitis or urticaria.

In addition, included in this submission were data from one pharmacokinetic / pharmacodynamic study from a non-US clinical trial of cetirizine in children aged 6-23 months to support the dosing recommendations in this patient population.

Children 6 months to 2 years of age receiving a single dose of cetirizine 0.25 mg/kg had apparent oral clearance (normalized for body weight) and half-life values, which were 3-fold faster and 2.5-fold shorter, respectively than those observed in adults receiving a single dose of 10 mg cetirizine tablet. Despite of this discrepancy, the mean systemic exposure (AUC<sub>t</sub> and C<sub>max</sub>) in this children population was similar to that observed in adults. The mean AUC<sub>t</sub> and C<sub>max</sub> in these children were 15% lower and 24% higher, respectively, compared to those in adults. However, computer simulations performed by this reviewer showed, as expected, that the systemic exposure in this children population receiving 2.5 mg BID (proposed dosing regimen) was twice the exposure observed in adults receiving a single 10 mg dose of cetirizine.

A 90 ± 12% inhibition of the wheal and 87 ± 17% inhibition of the flare was observed 12 h after last dose of a multiple dosing regimen of cetirizine 0.25 mg/kg to children 6 months to 2 years of age. However, the clinical relevance of histamine wheal skin testing is unknown, and therefore, these data should be interpreted with caution.

### 1.1 COMMENTS TO THE MEDICAL OFFICER

1. Although the 0.25 mg/kg (approximately 2.5 mg) BID dosing regimen for cetirizine was used in the clinical trials for this young population, the medical reviewer should be aware of the following:
  - The pharmacokinetic data presented in this NDA indicated similar mean systemic exposure (AUC and C<sub>max</sub>) of Zyrtec in children 6 months to < 2 years of age receiving single dose of cetirizine 0.25 mg/kg (10 mg/mL) and adults receiving a dose of 10 mg. However, these findings should be interpreted with caution because of the higher variability in the AUC observed in children compared to that in adults and the fact that the dose used is half the proposed daily dose in this children population. Therefore, assuming linear pharmacokinetics in the dosing range the exposure to cetirizine in children receiving 2.5 mg BID will double that of adults receiving 10 mg cetirizine

once daily.

- No comparative bioavailability study has been conducted to determine if the 10 mg/mL oral solution used in the Europe pediatric pharmacokinetic studies is bioequivalent to the 1 mg/mL formulation approved in US and used in the US pediatric clinical trials. Based on cross-study comparisons between the 10 mg/mL solution and the 1 mg/mL syrup (data obtained from healthy adults) the mean AUC and mean Cmax were 14% and 30% higher for the former formulation. The difference in systemic exposure may not be clinically relevant.
2. The AUCt and Cmax for children 6 months to < 2 of age receiving cetirizine solution 2.5 mg BID is expected to be 22% and 18% higher, respectively than that observed in children 2-5 years of age receiving cetirizine solution 5 mg QD. This difference in systemic exposure may not be clinically relevant.

## 1.2 RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceuticals / Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed NDA 19-835 submitted on December 21, 2001. The NDA's Human Pharmacokinetics and Bioavailability Section is acceptable to OCPB. The labeling comments should be conveyed to the sponsor.

Reviewer

Sandra Suarez-Sharp, Ph.D. \_\_\_\_\_

Office of Clinical Pharmacology and Biopharmaceutics

Division of Pharmaceutical Evaluation II

Final version signed by Emmanuel Fadiran, Ph.D., Team leader \_\_\_\_\_

cc

NDA 19-835 : Division File

HFD-870: Malinowski, Hunt

HFD-570: Fadiran, Nicklas, Chowdhury, Ostroff, Suarez-Sharp

## 2. TABLE OF CONTENTS

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### **3. SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS**

Cetirizine, an active metabolite of hydroxyzine, is an orally active and selective H<sub>1</sub>-receptor antagonist. Zyrtec (cetirizine) 5 and 10 mg tablets (NDA 19-835) and Zyrtec syrup 1 mg/mL (NDA 20-346) have been approved by the agency on 12/08/95 and 09/27/96, respectively.

Zyrtec is indicated for the relief of symptoms associated with seasonal or perennial allergic rhinitis (SAR or PAR) and for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria (CIU). The recommended initial dose of Zyrtec for adults and children 12 years and older is 5- or 10 mg per day, for children 6-11 years old is 5- or 10 mg (1 or 2 teaspoons) QD, and for children 2-5 years of age is 2.5- or 5 mg, depending on symptoms severity.

In the present supplemental NDA (19-835) the sponsor, Pfizer, is seeking FDA's concurrence to the information generated, pursuant to the pediatric Rule, which supports the use of Zyrtec (cetirizine HCl) at the dose of 2.5 mg QD or 2.5 mg BID in pediatric patients down to 6 months of age for the treatment — PAR, and CIU.

This submission included information from clinical experts and from the medical literature, that according to the sponsor, supports the conclusion that the course of disease of allergic rhinitis and chronic idiopathic urticaria in pediatric patients down to 6 months of age and adult patients are similar and the effects of cetirizine in children and adults are also similar.

A total of eleven (11) clinical trials were conducted by Pfizer and UCB Pharma in children under 2 years of age and were included in the overview of safety of the present NDA; none of these controlled studies assessed efficacy in children under 2 years of age with allergic rhinitis or urticaria.

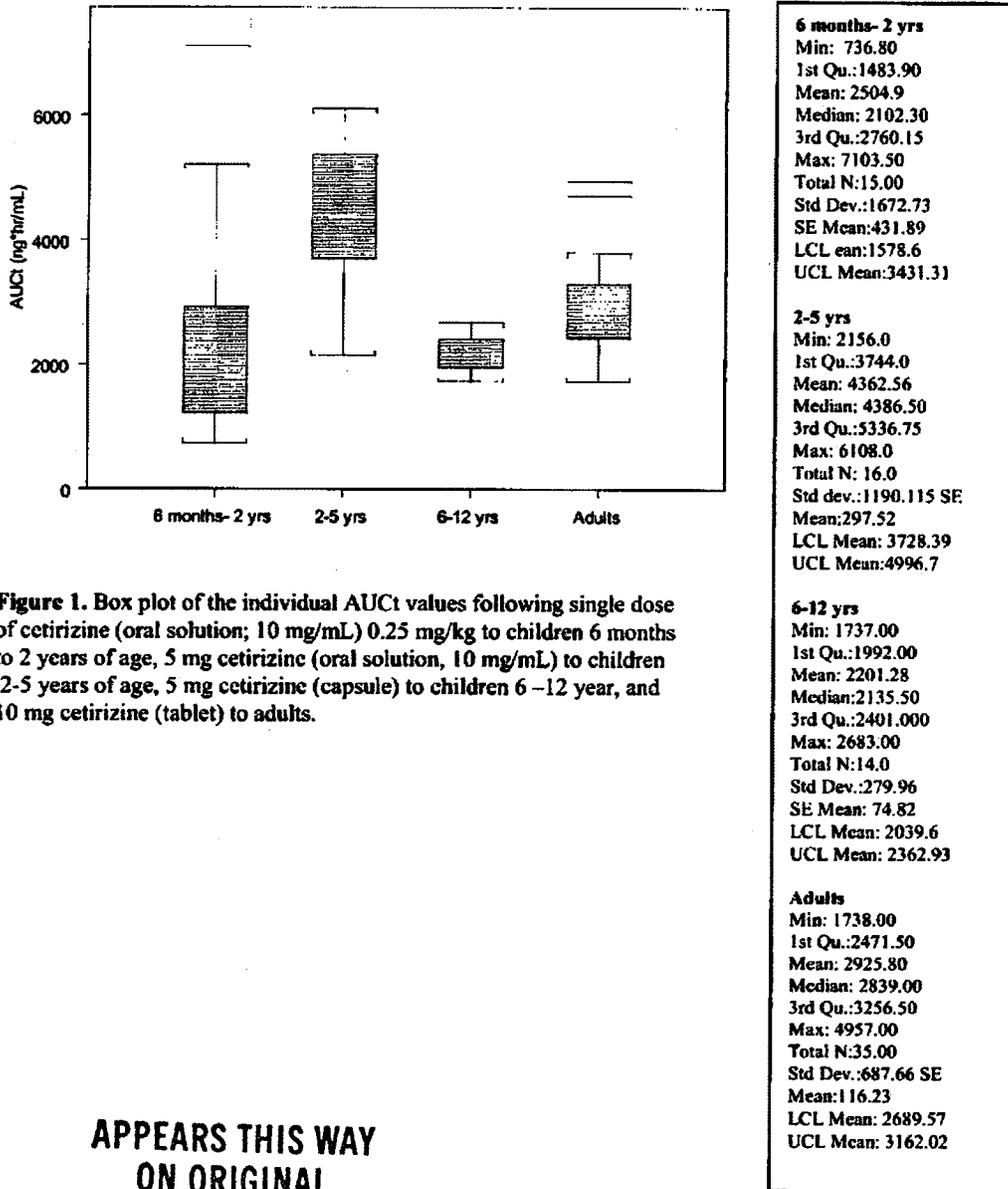
In addition, included in this submission were data from one pharmacokinetic / pharmacodynamic from a non-US clinical trial of cetirizine in children aged 6-23 months to support the dosing recommendations in this patient population.

Children 6 months to 2 years of age had apparent oral clearance (normalized for body weight) and half-life values, which were 3-fold faster and 2.5 shorter, respectively than those observed in adults. Despite of this discrepancy, the systemic exposure (AUC and C<sub>max</sub>) in children 6 months to < 2 years of age receiving a single dose of cetirizine 0.25 mg/kg was similar to that observed in adult receiving a single dose of cetirizine 10 mg tablets. The mean AUC and C<sub>max</sub> in children 6 months to 2 years of age were 15% lower and 24% higher, respectively, compared to those in adults (Table 1). These findings should be interpreted with caution since higher variability in the individual AUC was observed compared to that in adults (Figure 1). In addition, this data is based on a single dose study, which used half the maximum dose proposed in this children population and included 15 subjects from 2 different centers in Europe.

Computer simulations performed by this reviewer considering a multiple dose regimen of cetirizine 2.5 mg BID at steady-state to children 6 months to < 2 years of age resulted, as expected, in AUC values which were 2-fold higher than those observed in adults (Table 1). The AUC and C<sub>max</sub> for children 6m-2y of age receiving cetirizine solution 2.5 mg BID is expected to be 22% and 18% higher, respectively than that observed in children 2-5 years of age children receiving cetirizine solution 5 mg QD (Table 1). However, the difference in systemic exposure observed between the 6m-2y

olds and the 2-5 years old or the adult population may not be clinically relevant considering the large safety database generated for the children population.

A  $90 \pm 12\%$  inhibition of the wheal and  $87 \pm 17\%$  inhibition of the flare was observed 12 h after last dose of a multiple dosing regimen of cetirizine 0.25 mg/kg to children 6 months to 2 years of age. However, the clinical relevance of histamine wheal skin testing is unknown, and therefore, these data should be interpreted with caution.



**Figure 1.** Box plot of the individual AUCt values following single dose of cetirizine (oral solution; 10 mg/mL) 0.25 mg/kg to children 6 months to 2 years of age, 5 mg cetirizine (oral solution, 10 mg/mL) to children 2-5 years of age, 5 mg cetirizine (capsule) to children 6-12 year, and 10 mg cetirizine (tablet) to adults.

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**Table 1. Mean (SD) PK parameters in different subject populations receiving cetirizine**

	PK parameters						
	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	AUC <sub>t</sub> (ng*hr/mL)	AUC <sub>inf</sub> (ng*hr/mL)	V/F (L/kg)	CL/F (mL/min/kg)
<sup>a</sup> Children 6m-2y (0.25mg/kg)	390.2 ±135	1.8 ±1.3	3.06 ±1.4	2505 ±1673	2699 ±1796	0.44 ±0.19	2.05 ±1.15
<sup>b</sup> Children 6m-2y (0.25mg/kg)	390.2 ±135	2 ±1.3	3.1 ±1.8	2523 ±1676	2704 ±1839	0.44 ±19	2.13 ±1.15
Children 2-5 y (5 mg sol)	660 ±231	1.44 ±1.39	4.91 ±0.98	4130 ±1251	4772 ±1318	0.63 ±0.38	1.38 ±0.8
Children 6-12y (5 mg capsule)	275 ±58	1.1 ±0.4	5.6 ±1.1	2201 ±286	-	0.58	1.01 ±0.2
Adults (10 mg tablet)	315 ±85	1.0 ±0.6	8.2 ±1.15	2915 ±729	-	0.58	0.70 ±0.16
<sup>c</sup> Children 6m-2y (2.5mg bid)	444.7	1.25	3.1	6048	-	-	2.13
<sup>d,e</sup> Children 6m-2y (2.5mg QD)	373.6	1.33	3.1	3024.8	-	-	2.13

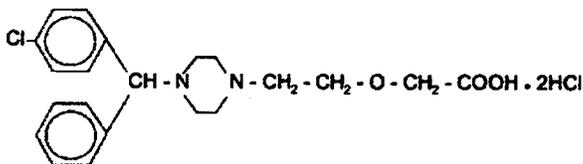
<sup>a</sup>Data calculated by this reviewer using non-compartmental methods; <sup>b</sup>Data reported by the sponsor based on compartmental methods (1CBM with first order absorption); <sup>c,d</sup>Data generated from computer simulations assuming multiple dose of cetirizine. <sup>e</sup>PK values at steady state.

#### 4. QUESTION BASED REVIEW

##### Q1. What are the general attributes of Cetirizine HCL Oral Solution?

**Chemical name:** The chemical name is (±) - [2- [4- [(4-chlorophenyl)phenylmethyl] -1-piperazinyl] ethoxy]acetic acid, dihydrochloride. Cetirizine hydrochloride is a racemic compound.

**Structural formula:**



**Molecular formula:** C<sub>21</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>3</sub>•2HCl

**Molecular weight:** 461.82

**Solubility:** Cetirizine hydrochloride is a white, crystalline powder and is water soluble.

#### FORMULATION

##### Zyrtec Tablets

Tablets are formulated as white, film-coated, rounded-off rectangular shaped tablets for oral administration and are available in 5 and 10 mg strengths. Inactive ingredients are: lactose; magnesium stearate; povidone; titanium dioxide; hydroxypropyl methylcellulose; polyethylene glycol; and corn starch.

**Zyrtec Syrup**

Syrup is a colorless to slightly yellow syrup containing cetirizine HCL at a concentration of 1mg/mL. The pH is between 4 and 5. The inactive ingredients of the syrup are: banana flavor; glacial acetic acid; glycerin; grape flavor; methylparaben; propylene glycol; propylparaben; sodium acetate; sugar syrup; and water.

**ZYRTEC Oral Solution**

Oral solution contains cetirizine HCl at a concentration of 10 mg/mL for oral administration. The components and composition are described in Table below:

**INDICATION (as per proposed label)**

**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 2 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 2 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, postnasal 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 2 years of age and older. It significantly reduces the occurrence, severity, and duration of hives and significantly reduces pruritus.

**DOSAGE AND ADMINISTRATION (as per proposed label)**

**Adults and Children 12 Years and Older:** The recommended initial dose of ZYRTEC is 5 or 10mg per day in adults and children 12 years and older, depending on symptom severity

**Children 6 to 11 Years:** The recommended initial dose of ZYRTEC in children aged 6 to 11 years is 5 or 10 mg (1 or 2 teaspoons) once daily depending on symptom severity

**Children 2 to 5 Years:** The recommended initial dose of ZYRTEC syrup in children aged 2 to 5 years is 2.5 mg (½ teaspoon) once daily. The dosage in this age group can be increased to a maximum dose of 5 mg per day given as 1 teaspoon (5 mg) once daily, or as ½ teaspoon (2.5 mg) given every 12 hours, \_\_\_\_\_

**Children 6 months to < 2 years:** The recommended initial dose of ZYRTEC syrup in children aged 6 months to <24 months is 2.5 mg (½ teaspoon) once daily. The dosage in this age group can be increased to a maximum dose of 5 mg per day given as ½ teaspoon (2.5 mg) every 12 hours, \_\_\_\_\_

**Q1. Was the to-be marketed formulation used in the pharmacokinetic studies?**

The sponsor used the following formulation in the pharmacokinetic Study UBU-123:

This formulation has a concentration of 10 mg/mL and has not been approved by the Agency, but is approved in Europe where the PK studies were conducted. The sponsor mentioned in the present submission that this formulation is bioequivalent to previous approved formulations; however no data was submitted to support such a claim. The same formulation was used in the PK studies in children 2-5 years of age. The reviewer at that time asked for information to link this formulation (oral solution 10mg/mL) to the already approved 1 mg/mL oral solution. The reviewer at that time concluded that since no 90% confidence were calculated no decision could be made in terms of declaring bioequivalence between these 2 formulations. However, an inter-study comparison between the 10 mg/mL solution and the 1 mg/mL syrup (data obtained from healthy adults) showed that the mean AUC and mean Cmax were 14% and 30% higher for the former formulation. The clinical relevance of these findings should be evaluated by the medical reviewer in light of the safety data available.

**Q2. What is known about the pharmacokinetics of cetirizine?**

The pharmacokinetics of cetirizine have been previously reported in NDAs 19-835 and 20-346.

**Absorption:** Cetirizine was rapidly absorbed with a time to maximum concentration (T<sub>max</sub>) of approximately 1 hour following oral administration of tablets or syrup in adults. Comparable bioavailability was found between the tablet and syrup dosage forms. When healthy volunteers were administered multiple doses of cetirizine (10 mg tablets once daily for 10 days), a mean peak plasma concentration (C<sub>max</sub>) of 311 ng/mL was observed. No accumulation was observed. Cetirizine pharmacokinetics were linear for oral doses ranging from 5 to 60 mg. Food had no effect on the extent of cetirizine exposure (AUC) but T<sub>max</sub> was delayed by 1.7 hours and C<sub>max</sub> was decreased by 23% in the presence of food.

**Distribution:** The mean plasma protein binding of cetirizine is 93%, independent of concentration in the range of 25-1000 ng/mL, which includes the therapeutic plasma levels observed.

**Metabolism:** A mass balance study in 6 healthy male volunteers indicated that 70% of the administered radioactivity was recovered in the urine and 10% in the feces. Approximately 50% of the radioactivity was identified in the urine as unchanged drug. Most of the rapid increase in peak plasma radioactivity was associated with parent drug, suggesting a low degree of first-pass metabolism. Cetirizine is metabolized to a limited extent by oxidative O-dealkylation to a metabolite with negligible antihistaminic activity. The enzyme or enzymes responsible for this metabolism have not been identified.

**Elimination:** The mean elimination half-life in 146 healthy volunteers across multiple pharmacokinetic studies was 8.3 hours and the apparent total body clearance for cetirizine was approximately 53 mL/min.

**Interaction Studies**

Pharmacokinetic interaction studies with cetirizine in adults were conducted with pseudoephedrine, antipyrine, ketoconazole, erythromycin and azithromycin. No interactions were observed. In a multiple dose study of theophylline and cetirizine (20 mg once daily for 3 days), a 16% decrease in the clearance of cetirizine was observed. The disposition of theophylline was not altered by concomitant cetirizine administration.

**Special Populations**

**Pediatric Patients:** When pediatric patients aged 7 to 12 years received a single, 5 mg oral cetirizine capsule, the mean C<sub>max</sub> was 275 ng/mL. Based on cross-study comparisons, the weight-normalized, apparent total body clearance was 33% greater and the elimination half-life was 33% shorter in this pediatric population than in adults. In pediatric patients aged 2 to 5 years who received 5 mg of cetirizine, the mean C<sub>max</sub> was 660 ng/mL. Based on cross-study comparisons, the weight-normalized apparent total

body clearance was 81 to 111% greater and the elimination half-life was 33 to 41% shorter in this pediatric population than in adults.

**Geriatric Patients:** Following a single, 10 mg oral dose, the elimination half-life was prolonged by 50% and the apparent total body clearance was 40% lower in 16 geriatric subjects with a mean age of 77 years compared to 14 adult subjects with a mean age of 53 years. The decrease in cetirizine clearance in these elderly volunteers may be related to 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 in the kinetics of cetirizine have been observed.

**Renal Impairment:** The kinetics of cetirizine were studied following multiple, oral, 10 mg daily doses of cetirizine for 7 days in normal volunteers, patients with mild renal function impairment, and patients with moderate renal function impairment. The pharmacokinetics of cetirizine were similar in patients with mild impairment and normal volunteers. Moderately impaired patients had a 3-fold increase in half-life and a 70% decrease in clearance compared to normal volunteers.

Patients on hemodialysis (n=5) given a single, 10 mg dose of cetirizine had a 3-fold increase in half-life and a 70% decrease in clearance compared to normal volunteers. Less than 10% of the administered dose was removed during the single dialysis session. Dosing adjustment is necessary in patients with moderate or severe renal impairment and in patients on dialysis.

**Hepatic Impairment:** Sixteen patients with chronic liver diseases, given 10 or 20 mg of cetirizine as a single, oral dose had a 50% increase in half-life along with a corresponding 40% decrease in clearance compared to 16 healthy subjects. Dosing adjustment may be necessary in patients with hepatic impairment.

**Pharmacodynamics:** Studies in 69 adult normal volunteers (aged 20 to 61 years) showed that ZYRTEC at doses of 5 and 10 mg strongly inhibited the skin wheal and flare caused by the intradermal injection of histamine. The onset of this activity after a single 10-mg dose occurred within 20 minutes in 50% of subjects and within one hour in 95% of subjects; this activity persisted for at least 24 hours. ZYRTEC at doses of 5 and 10 mg also strongly inhibited the wheal and flare caused by intradermal injection of histamine in 19 pediatric volunteers (aged 5 to 12 years) and the activity persisted for at least 24 hours. In a 35-day study in children aged 5 to 12, no tolerance to the antihistaminic (suppression of wheal and flare response) effects of ZYRTEC was found.

**Q3. Does the pharmacokinetic data generated in children 6 months to < 2 years of age support the proposed dosing regimen in this children population?**

Study UCB-123 was a pharmacokinetic study of a single oral administration of cetirizine (0.25 mg/kg) in infants aged from 6 to 24 months. The objectives of this study were to determine the pharmacokinetic parameters of cetirizine in infants and to compare these parameters to those for older children and adults. The sponsor also conducted an additional pharmacodynamic study (wheal and flare) in the same infants after repeated cetirizine administration, in order to investigate whether cetirizine is still active at the tissue level at the dose interval (every 12 hours).

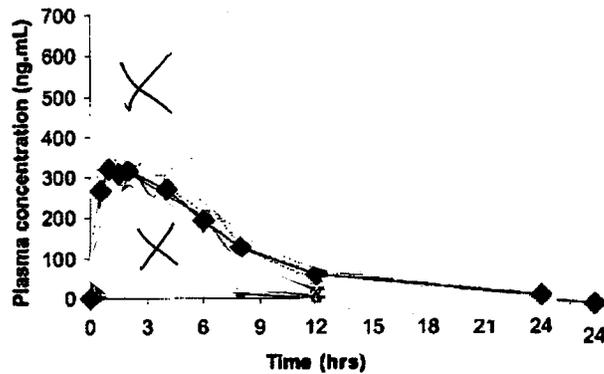
Fifteen infants were included in the study. This study was conducted in two different centers in Europe: Prague center (11 subjects); Brussels center (4 subjects). There were 10 boys and 5 girls, aged 6 to 23.5 months (mean  $\pm$  SD: 12.3  $\pm$  5.4), weighing 7.30 to 11.30 kg (mean  $\pm$  SD: 9.03  $\pm$  1.1) and with a height of 65 to 84 cm (mean  $\pm$  SD: 73.2  $\pm$  5.2).

The individual and mean plasma concentration-time profiles for cetirizine in children 6m-2y of age receiving a single dose of 0.25 mg/kg (average) of cetirizine (10 mg/mL oral solution) are shown in Figure Q1. Table Q1 summarizes the pharmacokinetics of cetirizine reported by the sponsor and those calculated by this reviewer. Figure Q2 represents computer simulations in children 6 months to 2 years receiving a multiple dose of cetirizine 2.5 mg BID at steady state.

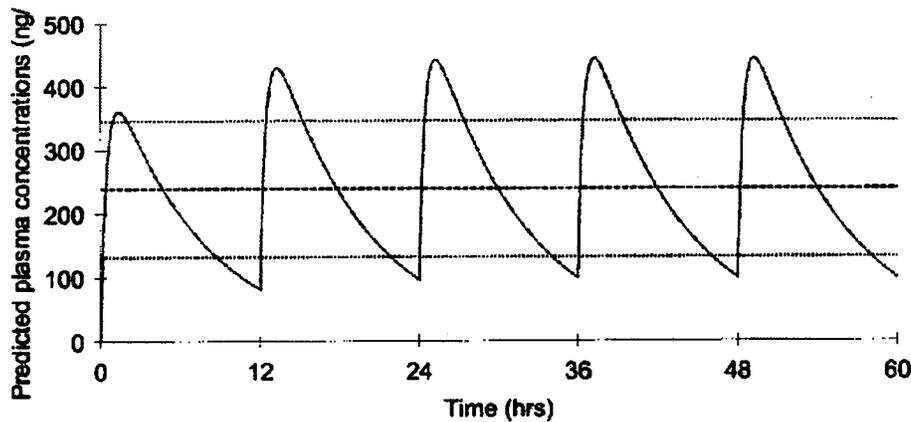
**Table Q1. Mean (SD) PK parameters in different subject populations receiving cetirizine**

	PK parameters						
	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	AUC <sub>t</sub> (ng*hr/mL)	AUC <sub>inf</sub> (ng*hr/mL)	V/F (L/kg)	CL/F (mL/min/kg)
<sup>a</sup> Children 6m-2y (0.25mg/kg)	390.2 $\pm$ 135	1.8 $\pm$ 1.3	3.06 $\pm$ 1.4	2505 $\pm$ 1673	2699 $\pm$ 1796	0.44 $\pm$ 0.19	2.05 $\pm$ 1.15
<sup>b</sup> Children 6m-2y (0.25mg/kg)	390.2 $\pm$ 135	2 $\pm$ 1.3	3.1 $\pm$ 1.8	2523 $\pm$ 1676	2704 $\pm$ 1839	0.44 $\pm$ 19	2.13 $\pm$ 1.15
Children 2-5 y (5 mg sol)	660 $\pm$ 231	1.44 $\pm$ 1.39	4.91 $\pm$ 0.98	4130 $\pm$ 1251	4772 $\pm$ 1318	0.63 $\pm$ 0.38	1.38 $\pm$ 0.8
Children 6-12y (5 mg capsule)	275 $\pm$ 58	1.1 $\pm$ 0.4	5.6 $\pm$ 1.1	2201 $\pm$ 286		0.58	1.01 $\pm$ 0.2
Adults (10 mg tablet)	315 $\pm$ 85	1.0 $\pm$ 0.6	8.2 $\pm$ 1.15	2915 $\pm$ 729		0.58	0.70 $\pm$ 0.16
<sup>c,e</sup> Children 6m-2y (2.5mg bid)	444.7	1.25	3.1	6048	-	-	2.13
<sup>d,e</sup> Children 6m-2y (2.5mg QD)	373.6	1.33	3.1	3024.8	-	-	2.13

<sup>a</sup>Data calculated by this reviewer using non-compartmental methods; <sup>b</sup>Data reported by the sponsor based on compartmental methods (ICBM with first order absorption); <sup>c,d</sup>Data generated from computer simulations assuming multiple dose of cetirizine at steady state. <sup>e</sup>PK values at steady state.



**Figure Q1.** Individual concentration-time profiles following single dose of cetirizine 0.25 mg/kg to children 6 months to 2 years of age. Diamond represent average values of n=15.



**Figure Q2.** Simulation done assuming 1CBM for cetirizine 2.5 mg BID x 5 given to children 6 months to < 2 yrs of age. Lines represent mean  $\pm$ SD.

From this study the following conclusions were drawn:

1. The mean AUCt and Cmax in children 6 months to 2 years of age receiving a single dose of cetirizine solution 0.25 mg/kg were 15% lower and 24% higher, respectively, compared to those in adults receiving a single dose of cetirizine 10 mg. However, it should be noted that higher variability in the individual AUC was observed compared to that in adults. In addition, this data is based on a single dose study which included 15 subjects from 2 different centers in Europe and the formulation used (cetirizine oral solution 10 mg/mL) has not been approved by the Agency.
2. Children 6 months to 2 years of age had apparent oral clearance (normalized for body weight) and half-life values, which were 3-fold faster and 2.5-fold shorter,

respectively than those observed in adults.

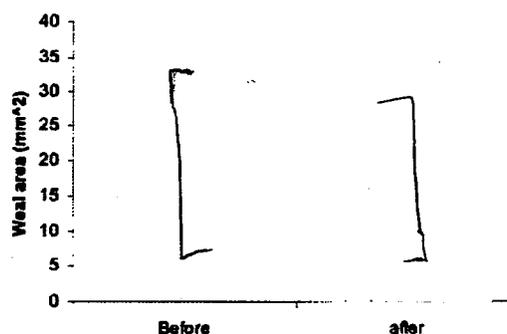
3. In the 6 infants whose urinary collection was considered complete,  $62.70 \pm 13.15\%$  of the administered dose was recovered. However, these findings should be interpreted with caution since the sponsor noted that for some subjects the calculated percentage of administered dose was abnormally high in 3 out of the other 9 infants, most likely due to an error of transcription of the urinary volume.
4. Computer simulations performed by this reviewer considering a multiple dose regimen of 2.5 mg BID at steady state to children 6 months to < 2 years of age resulted in AUC and  $C_{max}$  values which are two-fold higher than those observed in adults receiving cetirizine 10 mg QD. However, since the AUC and  $C_{max}$  for children 6m-2y of age receiving cetirizine solution 2.5 mg BID is expected to be 22% and 18% higher, respectively than that observed in children 2-5 years of age children receiving cetirizine solution 5 mg QD (approved dose), the difference in systemic exposure among populations may not be clinically relevant.

**Q3. Is cetirizine effective in reducing the induced histamine wheal and flare reaction in children 6 months receiving a multiple dose of cetirizine 0.25 mg/kg BID?**

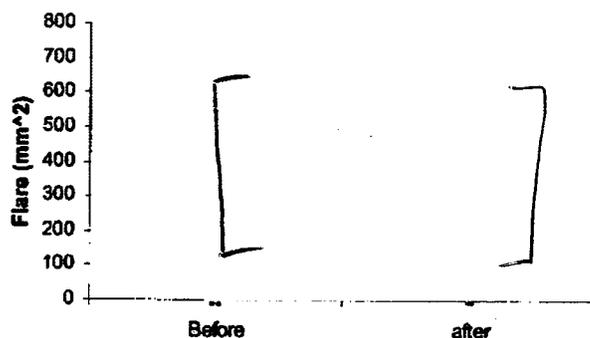
An additional pharmacodynamic study was done, after the pharmacokinetic part of the trial. A cutaneous prick test (wheal and flare) was performed with stimulation by histamine 10 mg/mL. The wheal and flare areas were recorded on a transparency with a fine water resistant marker. Thereafter 0.25 mg/kg cetirizine was administered BID to the infant for a minimum of 3 days. Twelve hours after the last cetirizine intake, a new histamine-induced wheal and flare test was performed by the same investigator.

The individual wheal and flare areas for the 10 children submitted to the histamine-induced wheal and flare pharmacodynamic evaluation are shown in Figures Q3.1 and Q3.2, respectively.

There was a delay of several months between the pharmacokinetic and pharmacodynamic studies in the 8 of the infants in whom the pharmacodynamic study could be performed. At the moment of the pharmacodynamic testing, the infants were aged  $15.2 \pm 6.2$  months (range:7-25).



**Figure Q3.1.** Individual data for the inhibition of the histamine-induced wheal areas recorded 12 hr after the last dose in a multiple dose regimen of cetirizine 0.25mg/kg bid for 4 to 9 days to children 6 months to 2 years of age.



**Figure Q3.1.** Individual data for the inhibition of the histamine-induced flare areas recorded 12 hr after the last dose in a multiple dose regimen of cetirizine 0.25mg/kg bid for 4 to 9 days to children 6 months to 2 years of age.

From this study the following conclusions were drawn:

1. A  $90 \pm 12\%$  inhibition of the wheal and  $87 \pm 17\%$  inhibition of the flare was observed 12 h after last dose of a multiple dosing regimen of cetirizine 0.25 mg/kg to children 6 months to 2 years of age. However, the clinical relevance of histamine wheal skin testing is unknown, and therefore, this data should be interpreted with caution.

**Q. Was the suitability of the analytical method supported by the submitted information?**

Yes, the sponsor provided in-study validation data that supports the suitability of the method. However, no samples of chromatograms were submitted.

The limit of quantitation was 2 ng/mL. The CV% and % bias were less than 15% for the two Quality Control samples used. The calibration curve was linear in the range of 20-1000 ng/mL, with a correlation coefficient of 0.992

**3. LABELING COMMENTS**

The following changes are recommended for the Clinical Pharmacology section of the label:

**Special Populations**

**Pediatric Patients:** When pediatric patients aged 7 to 12 years received a single, 5-mg oral cetirizine capsule, the mean C<sub>max</sub> was 275 ng/mL. Based on cross-study comparisons, the weight-normalized, apparent total body clearance was 33% greater and the elimination half-life was 33% shorter in this pediatric population than in adults. In pediatric patients aged 2 to 5 years who received 5 mg of cetirizine, the mean C<sub>max</sub> was 660 ng/mL. Based on cross-study comparisons, the weight-normalized apparent total body clearance was 81 to 111% greater and the elimination half-life was 33 to 41% shorter in this pediatric population than in adults. In pediatric patients aged 6 to 23 months who received a single dose of 0.25 mg/kg cetirizine oral solution (mean dose 2.3

mg), the mean C<sub>max</sub> was 390 ng/mL. Based on cross-study comparisons, the weight-normalized, apparent total body clearance was 304% greater and the elimination half-life was 63% shorter in this pediatric population compared to adults.           in children 6 months to < 2 years of age receiving the maximum dose of cetirizine solution           twice a day) is expected to be two-fold higher than that observed in adults receiving a dose of 10 mg cetirizine tablets once a day.

**Pharmacodynamics:** Studies in 69 adult normal volunteers (aged 20 to 61 years) showed that ZYRTEC at doses of 5 and 10 mg strongly inhibited the skin wheal and flare caused by the intradermal injection of histamine. The onset of this activity after a single 10-mg dose occurred within 20 minutes in 50% of subjects and within one hour in 95% of subjects; this activity persisted for at least 24 hours. ZYRTEC at doses of 5 and 10 mg also strongly inhibited the wheal and flare caused by intradermal injection of histamine in 19 pediatric volunteers (aged 5 to 12 years) and the activity persisted for at least 24 hours. In a 35-day study in children aged 5 to 12, no tolerance to the antihistaminic (suppression of wheal and flare response) effects of ZYRTEC was found. In 10 infants aged 7 to 25 months who received 4 to 9 days of cetirizine in an oral solution (0.25 mg/kg bid), there was a 90% inhibition of histamine-induced (10 mg/mL) cutaneous wheal and 87% inhibition of the flare 12 hours after administration of the last dose. However, the clinical relevance of histamine wheal skin testing is unknown.

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11 pages of draft labeling have been removed from this portion of the document.

## 6.2 INDIVIDUAL REPORTS

### Clinical Pharmacology and Biopharmaceutics Review

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*"Pharmacokinetic study of a single oral administration of cetirizine (0.25 mg/kg) in infants aged from 6 to 24 months"*

Clinical Report: **MRCE95H2102/IV**  
Date: **September 18, 1997**  
Investigator: **Prof. Dr. \_\_\_\_\_**

#### OBJECTIVES

- to determine the pharmacokinetic parameters of a single dose (0.25 mg/kg) of cetirizine in infants aged 6-24 months.
- to compare these parameters to the references existing for older children.
- to perform, when possible, an additional pharmacodynamic study (wheal and flare) in the same infants after repeated cetirizine administration, in order to investigate whether cetirizine is still active at the tissue level at the dose interval (every 12 hours).

#### STUDY DESIGN AND REGIMEN

The study was an open 2 center study of the pharmacokinetics of a single oral dose of cetirizine (average=0.25 mg/kg), delivered in the form of a 10 mg/mL solution (Batch number 71). According to the sponsor, the bioequivalence of this solution compared to tablet form has already been established.

#### Population

Fifteen infants were included into the study between October 27, 1993 and September 27, 1994. Infants from the Prague center were numbered from 001 to 011, infants from Brussels from 101 to 104.

There were 10 boys and 5 girls, aged 6 to 23.5 months (mean  $\pm$  SD: 12.3  $\pm$  5.4), weighing 7.30 to 11.30 kg (mean  $\pm$  SD: 9.03  $\pm$  1.1) and with a height of 65 to 84 cm (mean  $\pm$  SD: 73.2  $\pm$  5.2). Infant #003 was an Eurasian, infant #104 was black. The others were Caucasians.

Most infants were hospitalized for respiratory problems. Allergy or atopy was documented in 14 of the 15 infants by the medical history, the clinical signs and/or elevated IgE.

#### Pharmacokinetic assessments

##### Blood sample collection:

Serial blood samples (3-4 mL each) were collected at 30 min, 1 h, 1.5 h, 2 h, 4 h, 6 h, 8 h, 12 h and 24 h post ingestion. These samples were obtained via the IV line, after wash-out of the infusion line with a small amount of blood.

##### Urine Sample Collection

Urine samples were retrieved during the whole 24 hr of the trial.

##### Analytical Method



**Limit of Quantitation:** 2 ng/mL

**Stability:** not reported in this submission

**Statistical Analysis:**

The sponsor provided in-study validation data that supports the suitability of the method. However, no samples of chromatograms were submitted.

The limit of quantitation was 2 ng/mL. The CV% and % bias were less than 15% for the two Quality Control samples used. The calibration curve was linear in the range of 20-1000 ng/mL, with a correlation coefficient of 0.992

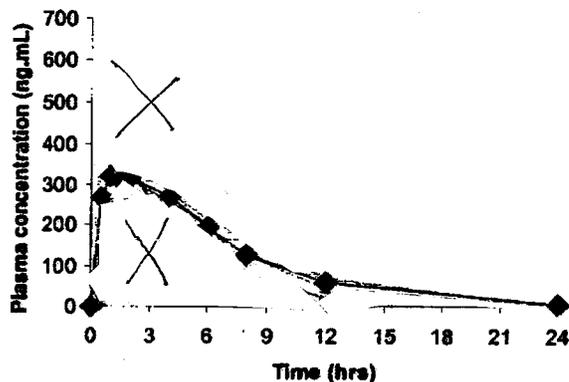
**Pharmacokinetic Results**

**Plasma Concentrations**

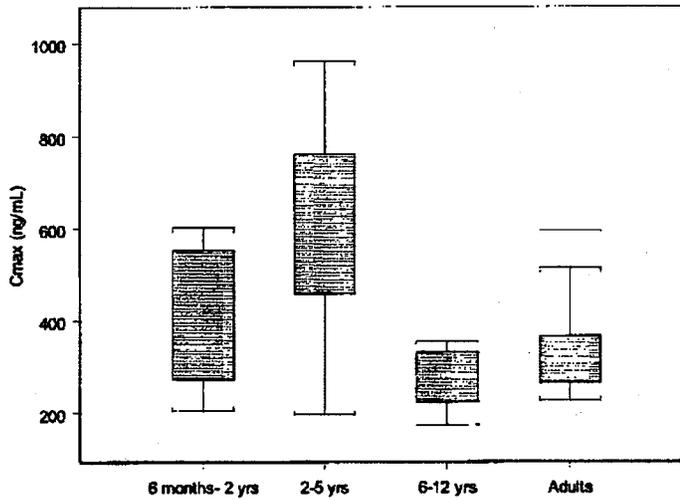
All fifteen infants were assessable for pharmacokinetic analysis. Infant #001 received a dose of 2.3 mg instead of the foreseen dose of 2.5 mg. The other children received the foreseen dose of 2, 2.5 or 3 mg. The dose per kg body weight ranged from 0.22 to 0.27 mg/kg (mean  $\pm$  SD: 0.25  $\pm$  0.02).

Cetirizine plasma level was below the limit of quantification (<2 ng/mL) in most of 24 h samples. In infant #009, there was a "double Cmax" at 0.5 and 4 h respectively. In infants #008 and 010, the pre-study sample contained a cetirizine peak of the same order of magnitude as the first study sample.

The individual and mean plasma concentration-time profiles for cetirizine in children 6m-2y of age receiving a single dose of 0.25 mg/kg (average) of cetirizine 10 mg/mL solution are shown in Figure 1. Table 1 summarizes the pharmacokinetics of cetirizine reported by the sponsor and calculated by this reviewer. Box plots for individual Cmax, CL/F and AUC0-inf are presented in Figures 2, 3 and 4, respectively. Figures 5 and 6 represent computer simulations performed for children receiving a multiple dose of cetirizine 2.5 mg QD and BID at steady state, respectively.



**Figure 1.** Individual concentration-time profiles following single dose of cetirizine 0.25 mg/kg to children 6 months to 2 years of age. Diamond represent average values of n=15.



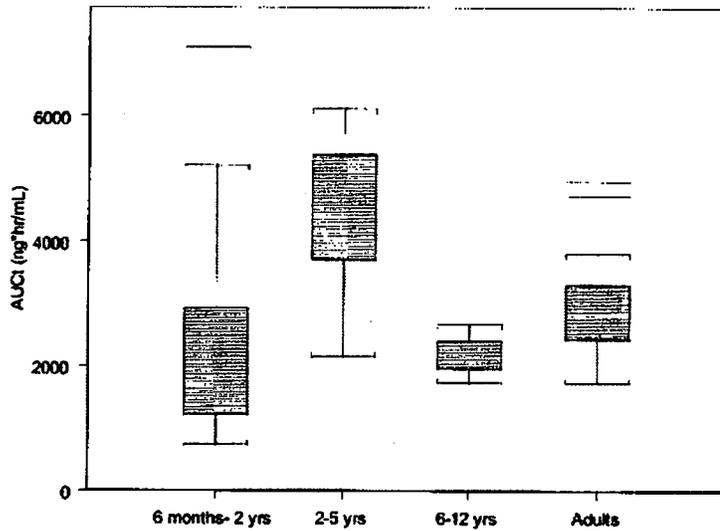
**Figure 2.** Box plot of the individual Cmax values following single dose of cetirizine (oral solution; 10 mg/mL) 0.25 mg/kg to children 6 months to 2 years of age, 5 mg cetirizine (oral solution, 10 mg/mL) to children 2-5 years of age, 5 mg cetirizine (capsule) to children 6 - 12 year, and 10 mg cetirizine (tablet) to adult.

**6 months- 2 yrs**  
 Min: 205.00  
 1st Qu.: 78.500  
 Mean: 390.20  
 Median: 344.0  
 3rd Qu.:531.00  
 Max: 603.00  
 N: 15.00000  
 Std Dev.:134.93  
 SE Mean:34.840  
 LCL Mean:315.474  
 UCL Mean:464.925

**2-5 yrs**  
 Cmax Min: 196.30  
 1st Qu.:481.32  
 Mean: 633.05  
 Median: 703.45  
 3rd Qu.:756.17  
 Max: 962.00  
 Total N: 16.00000  
 Std Dev.: 206.85334  
 SE Mean: 51.71334  
 LCL Mean: 522.83188  
 UCL Mean: 743.28062

**6-12 yrs**  
 Min: 172.0  
 1st Qu.: 228.25  
 Mean: 275.03  
 Median: 279.250  
 3rd Qu.: 326.8  
 Max: 354.50  
 Total N: 14.000  
 Std Dev.:57.8  
 SE Mean: 15.46206  
 LCL Mean: 241.63195  
 UCL Mean: 308.43947

**Adults**  
 Min: 226.0  
 1st Qu.:265.50  
 Mean: 330.80  
 Median: 313.00  
 3rd Qu.:364.00  
 Max: 595.00  
 Total N: 35.00  
 Std Dev.:81.79  
 SE Mean:13.8261  
 LCL Mean: 302.70  
 UCL Mean:358.89



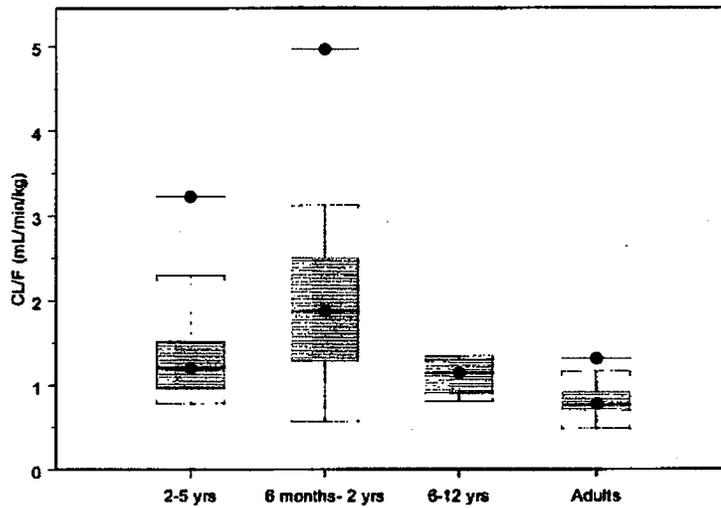
**Figure 3.** Box plot of the individual AUCt values following single dose of cetirizine (oral solution; 10 mg/mL) 0.25 mg/kg to children 6 months to 2 years of age, 5 mg cetirizine (oral solution, 10 mg/mL) to children 2-5 years of age, 5 mg cetirizine (capsule) to children 6-12 year, and 10 mg cetirizine (tablet) to adult.

**6 months- 2 yrs**  
 Min: 736.80  
 1st Qu.:1483.90  
 Mean: 2504.9  
 Median: 2102.30  
 3rd Qu.:2760.15  
 Max: 7103.50  
 Total N:15.00  
 Std Dev.:1672.73  
 SE Mean:431.89  
 LCL Mean:1578.6  
 UCL Mean:3431.31

**2-5 yrs**  
 Min: 2156.0  
 1st Qu.:3744.0  
 Mean: 4362.56  
 Median: 4386.50  
 3rd Qu.:5336.75  
 Max: 6108.0  
 Total N: 16.0  
 Std dev.:1190.115 SE  
 Mean:297.52  
 LCL Mean: 3728.39  
 UCL Mean:4996.7

**6-12 yrs**  
 Min: 1737.00  
 1st Qu.:1992.00  
 Mean: 2201.28  
 Median:2135.50  
 3rd Qu.:2401.000  
 Max: 2683.00  
 Total N:14.0  
 Std Dev.:279.96  
 SE Mean: 74.82  
 LCL Mean: 2039.6  
 UCL Mean: 2362.93

**Adults**  
 Min: 1738.00  
 1st Qu.:2471.50  
 Mean: 2925.80  
 Median: 2839.00  
 3rd Qu.:3256.50  
 Max: 4957.00  
 Total N:35.00  
 Std Dev.:687.66 SE  
 Mean:116.23  
 LCL Mean: 2689.57  
 UCL Mean: 3162.02



**Figure 4.** Box plot of the individual CL/F values following single dose of cetirizine (oral solution; 10 mg/mL) 0.25 mg/kg to children 6 months to 2 years of age, 5 mg cetirizine (oral solution, 10 mg/mL) to children 2-5 years of age, 5 mg cetirizine (capsule) to children 6-12 year, and 10 mg cetirizine (tablet) to adult.

**2-5 years**  
 Min:0.785  
 1st Qu.:0.991  
 Mean:1.3730  
 Median:1.20  
 3rd Qu.:1.503  
 Max:3.2222  
 Total N:16.000  
 Std Dev.:0.6268  
 SE Mean:0.156  
 LCL Mean:1.0390  
 UCL Mean:1.7070

**6 months-2 yrs**  
 Min:0.5700  
 1st Qu.:1.36  
 Mean: 2.0613  
 Median:1.87  
 3rd Qu.:2.465  
 Max:4.9600  
 Total N:15.000  
 Std Dev.:1.1126  
 SE Mean:0.28  
 LCL Mean:1.445  
 UCL Mean:2.6717

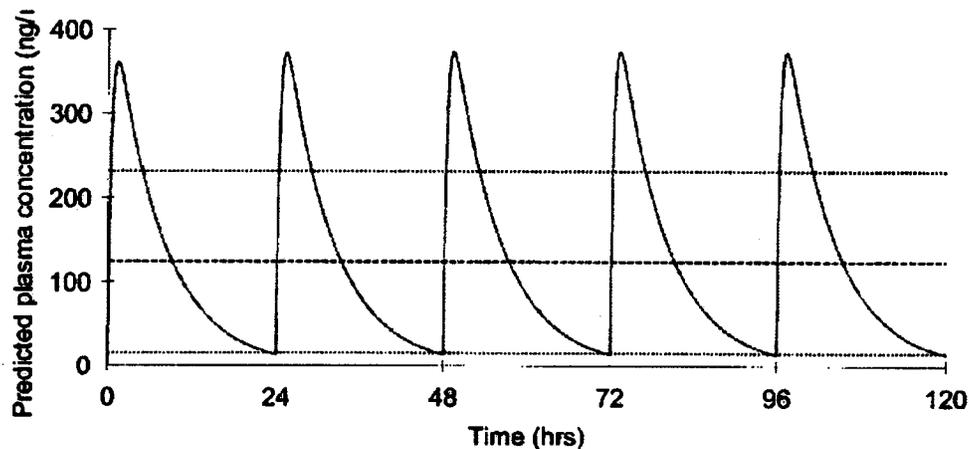
**6-12 yrs**  
 Min: 0.804  
 1st Qu.:0.9168  
 Mean: .101969  
 Median:1.14163  
 3rd Qu.:1.28523  
 Max:- 1.34221  
 Total N:14.000  
 Std Dev.:0.193026  
 SE Mean:0.0513  
 LCL Mean:0.9905  
 UCL Mean:1.2134

**Adults**  
 Min: 0.4786  
 1st Qu.:0.692  
 Mean:0.80426  
 Median:0.77  
 3<sup>rd</sup>Qu.:0.895  
 Max:1.31109  
 Total N:35  
 Std :0.16843976  
 SE Mean:0.028  
 LCL Mean:0.74640  
 UCL Mean:0.86212  
 UCL Mean: 3.8450

**Table 2. Mean (SD) PK parameters in different subject populations receiving cetirizine**

	PK parameters						
	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	AUC <sub>t</sub> (ng*hr/mL)	AUC <sub>inf</sub> (ng*hr/mL)	V/F (L/kg)	CL/F (mL/min/kg)
<sup>a</sup> Children 6m-2y (0.25mg/kg)	390.2 ±135	1.8 ±1.3	3.06 ±1.4	2505 ±1673	2699 ±1796	0.44 ±0.19	2.05 ±1.15
<sup>b</sup> Children 6m-2y (0.25mg/kg)	390.2 ±135	2 ±1.3	3.1 ±1.8	2523 ±1676	2704 ±1839	0.44 ±19	2.13 ±1.15
Children 2-5 y (5 mg sol)	660 ±231	1.44 ±1.39	4.91 ±0.98	4130 ±1251	4772 ±1318	0.63 ±0.38	1.38 ±0.8
Children 6-12y (5 mg capsule)	275 ±58	1.1 ±0.4	5.6 ±1.1	2201 ±286		0.58	1.01 ±0.2
Adults (10 mg tablet)	315 ±85	1.0 ±0.6	8.2 ±1.15	2915 ±729		0.58	0.70 ±0.16
<sup>c,c</sup> Children 6m-2y (2.5mg bid)	444.7	1.25	3.1	6048	-	-	2.13
<sup>d,c</sup> Children 6m-2y (2.5mg QD)	373.6	1.33	3.1	3024.8	-	-	2.13

<sup>a</sup>Data calculated by this reviewer using non-compartmental methods; <sup>b</sup>Data reported by the sponsor based on compartmental methods (ICBM with first order absorption); <sup>c,d</sup>Data generated from computer simulations assuming multiple dose of cetirizine at steady state. <sup>c</sup>PK values at steady state



**Figure 5. Predicted plasma concentration-time profiles following multiple dose administration of 2.5 mg cetirizine QD to children 6 months to 2 years of age.**

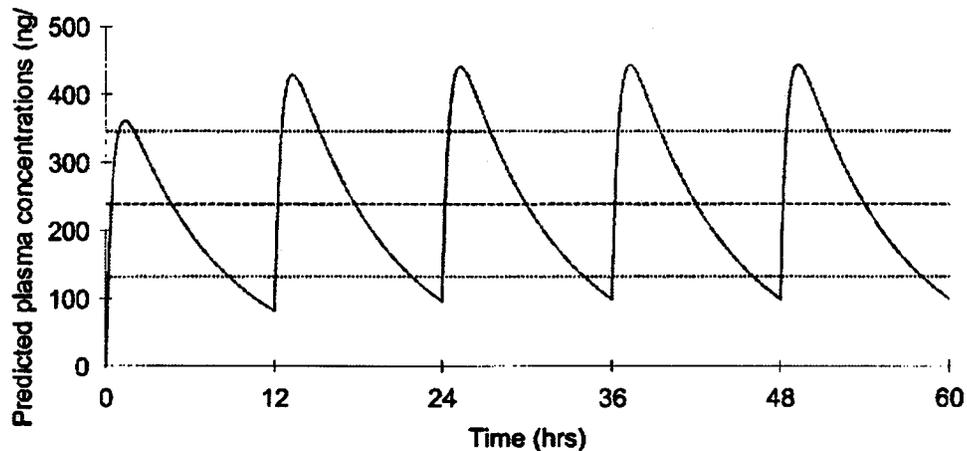


Figure 6. Predicted plasma concentration-time profile following multiple dose administration of 2.5 mg cetirizine BID given to children 6 months to 2 years old.

#### Urinary Excretion

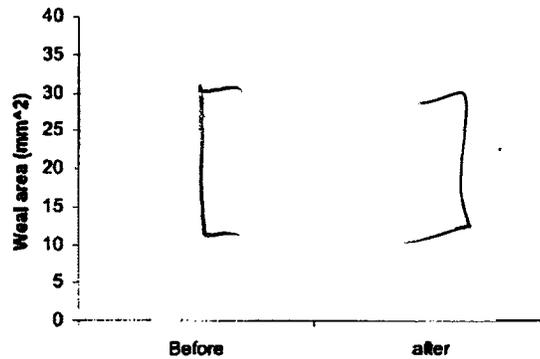
There were only six cases out of 15 in which urinary collection was considered complete. In these 6 infants,  $62.7\% \pm 13.1$  of the administered dose was recovered and the renal clearance was  $1.64 \pm 1.31$  mL/min/kg.

#### Pharmacodynamic Evaluation

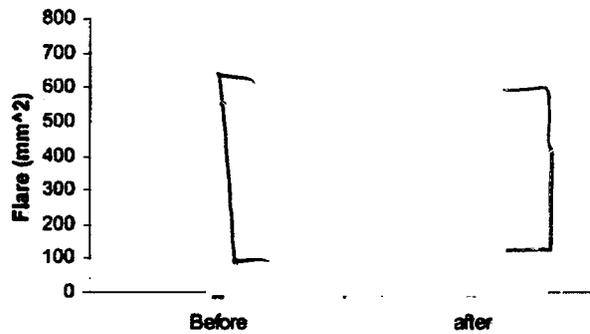
The individual wheal and flare areas for the 10 children submitted to the histamine-induced wheal and flare pharmacodynamic evaluation are shown in Figures 7 and 8, respectively.

There was a delay of several months between the pharmacokinetic and pharmacodynamic studies in the 8 first infants in whom the pharmacodynamic study could be performed. Infant #001 could not be included in the pharmacodynamic study. In the 2 last infants, the pharmacodynamic study was performed just after the pharmacokinetic study. At the moment of the pharmacodynamic testing, the infants were aged  $15.2 \pm 6.2$  months (range: 7-25).

According to the sponsor, all infants had a clinically relevant inhibition of their wheal and flare. There was still a  $90 \pm 12\%$  inhibition of the wheal and  $87 \pm 17\%$  inhibition of the flare 12 h after the last cetirizine intake. Despite of these findings, the clinical relevance of histamine wheal skin testing is unknown, and therefore, it should not be used as a supportive information for the approval of this drug.



**Figure 7.** Individual data for the inhibition of the histamine-induced wheal areas recorded 12 hr after the last dose in a multiple dose regimen of cetirizine 0.25mg/kg bid for 4 to 9 days to children 6 months to 2 years of age.



**Figure 8.** Individual data for the inhibition of the histamine-induced flare areas recorded 12 hr after the last dose in a multiple dose regimen of cetirizine 0.25mg/kg bid for 4 to 9 days to children 6 months to 2 years of age.

## DISCUSSION

The data presented in this submission showed that the systemic exposure (in terms of  $C_{max}$  and AUC) in children 6 months to 2 years of age receiving a single dose of cetirizine solution 0.25 mg/kg was similar to that previously reported for older children (6-12 years of age) and adults receiving a single dose of cetirizine 10 mg (see Table 2).

Faster CL/F and shorter  $t_{1/2}$  were observed in these 6 months to 2 year old children than that in older age groups; however, as expressed above, systemic exposure was similar, likely due to the higher dose/kg administered to the children (0.25mg/kg vs. 0.14 mg/kg in adults). It should be noted that this comparison is based on a once a day regimen and the possibility exists that this drug is administered BID as per proposed label. Computer simulations performed by this reviewer showed that the steady state AUC in children 6 months to 2 years of age receiving cetirizine 2.5 mg BID is two-fold higher

than that observed in adults receiving a 10 mg dose of cetirizine (Table 2).

In addition to blood sampling, the sponsor also collected urine samples for PK analysis. In the 6 infants whose urinary collection was considered complete,  $62.70 \pm 13.15$  % of the administered dose was recovered. However, these findings should be interpreted with caution since the sponsor noted that for some subjects the calculated percentage of administered dose was abnormally high in 3 out of the other 9 infants, most likely due to an error of transcription of the urinary volume.

An additional pharmacodynamic study was performed later after the PK study in the 10 Czech infants, following repeated cetirizine intake. This study was conducted because of the sponsor's concern about the higher CL/F and lower  $t_{1/2}$  values found in the younger children compared to adults. The sponsor concluded that despite a  $t_{1/2}$  of  $3.2 \pm 2.2$  h in the 10 infants tested, there was still a  $90 \pm 12$  % inhibition of the wheal and a  $87 \pm 17$  % inhibition of the flare 12 h after the last cetirizine intake (Figures 7 and 8). However, the clinical relevance of the histamine wheal skin testing is unknown, and therefore, cannot be used as a supportive information for the approval of this drug.

#### CONCLUSIONS

- The mean AUC<sub>t</sub> and C<sub>max</sub> in children 6 months to 2 years of age receiving a single dose of cetirizine solution 0.25 mg/kg were 15% lower and 24% higher, respectively, compared to those in adults receiving a single dose of cetirizine 10 mg.
- Children 6 months to 2 years of age had apparent oral clearance (normalized for body weight) and half-life values, which were 3-fold faster and 2.5 shorter, respectively than those observed in adults.
- Computer simulation performed considering a multiple dose regimen of 2.5 mg BID to children 6 months to < 2 years of age resulted in AUC and C<sub>max</sub> values which are two-fold higher than those observed in adults.
- A  $90 \pm 12$ % inhibition of the wheal and  $87 \pm 17$ % inhibition of the flare was observed 12 h after last dose of a multiple dosing regimen of cetirizine 0.25 mg/kg to children 6 months to 2 years of age. However, the clinical relevance of the histamine wheal and flare skin testing is unknown, and therefore, these findings should be interpreted with caution.

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**Office of Clinical Pharmacology and Biopharmaceutics**  
**New Drug Application Filing and Review Form**

General Information About the Submission			
	Information		Information
NDA Number	19-835	Brand Name	Zyrtec Pediatric Exclusivity Sp.
OCPB Division (I, II, III)	II	Generic Name	Cetirizine HCL
Medical Division	DPADP	Drug Class	Antihistamine
OCPB Reviewer	Sandra Suarez-Sharp	Indication(s)	Treatment <input type="checkbox"/> Perennial Allergic Rhinitis <input checked="" type="checkbox"/>
OCPB Team Leader	Emmanuel Fadran	Dosage Form	Oral Solution
PM Reviewer		Dosing Regimen	pediatric patients 6 months to < 2 years of age: 2.5 mg QD or 2.5 mg BID depending on symptoms severity
Date of Submission	December 21, 2001	Route of Administration	oral
Estimated Due Date of OCPB Review	Sep 20, 2002	Sponsor	Pfizer
PDUFA Due Date	Oct 21, 2002	Priority Classification	Standard
Division Due Date	October 7, 2002		

**3 Clin. Pharm. and Biopharm. Information**

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies				
HPK Summary	X			
Labeling				
Reference Bioanalytical and Analytical Methods				
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	X	1		
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	x	1		
Phase 3:				
PK/PD:				

Phase 1 and/or 2, proof of concept:			
Phase 3 clinical trial:			
<b>Population Analyses -</b>			
Data rich:			
Data sparse:			
<b>II. Biopharmaceutics</b>			
Absolute bioavailability:			
Relative bioavailability -			
solution as reference:			
alternate formulation as reference:			
Bioequivalence studies -			
traditional design; single / multi dose:			
replicate design; single / multi dose:			
Food-drug interaction studies:			
Dissolution:			
(IVIVC):			
Bio-waiver request based on BCS			
BCS class			
<b>III. Other CPB Studies</b>			
Genotype/phenotype studies:			
Chronopharmacokinetics			
Pediatric development plan			
Literature References			
<b>Total Number of Studies</b>	<b>1</b>	<b>2</b>	
<b>Fileability and QBR comments</b>			
	<b>"X" if yes</b>	<b>Comments</b>	
Application fileable ?	<b>X</b>	Reasons if the application is not fileable (or an attachment if applicable). For example, is clinical formulation the same as the to-be-marketed one?	
Comments sent to firm ?	<b>NO</b>	Comments have been sent to firm (or attachment included). FDA letter date if applicable. 1. Submit data (i.e. calibration curve statistics, quality control statistics) for the analytical methods used in study UCB-123: Pharmacokinetic study of a single oral administration of cetirizine (0.25mg/kg) in infants aged from 6 to 24 months. 2. Provide individual concentration-time profiles, individual Cmax, individual AUC, and individual CL/F for children 2-5 years of age receiving a single 5 mg dose of cetirizine, for children 6-12 years of age receiving a single 5 mg dose of cetirizine, and for adults receiving a single 10 mg dose of cetirizine. 3. Submit information about the relative oral bioavailability of the solution formulation of cetirizine (10mg/mL) use in study UCB-123 (Pharmacokinetic study of a single oral administration of cetirizine (0.25 mg/kg) in infants aged from 6 to 24 months).	
QBR questions (key issues to be considered)		<ol style="list-style-type: none"> <li>1. Was the to-be marketed formulation used in the clinical/Pharmacokinetic studies?</li> <li>2. Does the pharmacokinetic data support the dose regimen proposed in children 6 months to &lt; 2 years of age?</li> <li>3. Is cetirizine effective in reducing the induced histamine wheal and flare reaction in children 6 months to &lt; 2 years receiving a multiple dose of cetirizine 0.25 mg/kg BID.</li> <li>4. Was the suitability of the analytical method supported by the submitted information?</li> </ol>	
Other comments or information not included above		This reviewer will review the population PK study with the guidance of He Sun (PM reviewer).	
Primary reviewer Signature and Date			
Secondary reviewer Signature and Date			

CC: NDA 19-835, HFD-870 (Electronic Entry), HFD-570 (Ostroff), HFD-870 (Fadiran, Hunt, Malinowski), CDR B. Murphy)

**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**

/s/

-----  
Sandra Suarez  
10/16/02 12:56:24 PM  
BIOPHARMACEUTICS

Emmanuel Fadiran  
10/16/02 01:44:16 PM  
BIOPHARMACEUTICS  
I concur

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**NDA 19-835/S-015**

**NDA 20-346/S-008**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

**TIME SENSITIVE PATENT INFORMATION**  
**PURSUANT TO 21 C.F.R. § 314.53**  
for  
**NDA No.'s 19-835 and 20-346 -- ZYRTEC® Pediatric**

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	ZYRTEC
Active Ingredient(s):	cetirizine dihydrochloride
Strength(s):	5.00 mg and 10.00 mg (tablets); and 1.00 mg/ml (syrup)
Dosage Form:	tablets and syrup

**A. Information for Each Individual Patent**

U.S. Patent Number: 4,525,358

Expiration Date: June 25, 2007

Type of Patent:

1. Drug Substance (Active Ingredient)  Y  N
2. Drug Product (Composition/Formulation)  Y  N
3. Method of Use  Y  N

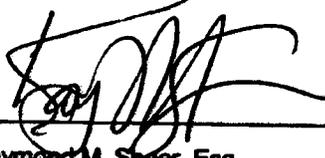
The above-identified patent claims method(s) of use; accordingly, the specific method(s) of use for which approval is being sought that are covered by said patent are the following: perennial allergic rhinitis.

Name of Patent Owner: UCB Pharmaceuticals, Inc., Dover, Delaware.

**B. Declaration Statement for Patents Having Composition/Formulation or Method of Use Claims**

The undersigned declares that the above-stated United States Patent Number 4,525,358 covers the composition, formulation and/or method of use of the drug product cetirizine. This product is the subject of this application for which approval is being sought.

Signed: \_\_\_\_\_

  
Raymond M. Speer, Esq.

Date: \_\_\_\_\_

January 30, 2002

Title: \_\_\_\_\_

Senior Patent Counsel

Telephone Number: \_\_\_\_\_

212-733-4606

EXCLUSIVITY SUMMARY for NDA # 19-835 SUPPL # 015  
Trade Name Zyrtec Tablets Generic Name cetirizine HCl  
EXCLUSIVITY SUMMARY for NDA # 20-346 SUPPL # 008  
Trade Name Zyrtec Syrup Generic Name cetirizine HCl  
Applicant Name Pfizer HFD- 570  
Approval Date October 21, 2002

**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 questions about the submission.

a) Is it an original NDA? YES/\_\_\_/ NO /\_X\_/

b) Is it an effectiveness supplement? YES /\_X\_/ NO /\_\_\_/

If yes, what type (SE1, SE2, etc.)? SE5

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 /\_X\_/

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.

N/A

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 /\_X\_/

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

---

---

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /\_X\_/ NO /\_\_\_/

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /\_\_\_/ NO /\_X\_/

If yes, NDA \_\_\_\_\_ Drug Name \_\_\_\_\_

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

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

YES /\_\_\_/ NO /\_X\_/

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 / X / NO / \_\_\_ /

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

NDA # <u>19-835</u>	<u>Zyrtec Tablets</u>
NDA # <u>20-346</u>	<u>Zyrtec Syrup</u>
NDA # <u>21-150</u>	<u>Zyrtec-D</u>

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 / \_\_\_ /

If "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 9. 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 "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /\_X\_/      NO /\_\_\_/

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (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 /X/      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 9:**

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- (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 /X/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /\_\_\_/      NO /X/

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 /\_X\_/

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:

Investigation #1, Study # 1010

Investigation #2, Study # 3222

Investigation #3, Study # \_\_\_\_\_

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 /\_X\_/

Investigation #2                      YES /\_\_\_/                      NO /\_X\_/

Investigation #3                      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:

NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_

- (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 /\_X\_/

Investigation #2                      YES /\_\_\_/                      NO /\_X\_/

Investigation #3                      YES /\_\_\_/                      NO /\_\_\_/

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

NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_

- (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"):

Investigation # 1, Study # 1010

Investigation # 2, Study # 3222

Investigation #\_\_, Study # \_\_\_\_\_

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 form 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 /_X_/	!	NO /___/ Explain: _____
	!	_____
	!	_____
	!	
Investigation #2	!	
	!	
IND # _ — _ YES /_X_/	!	NO /___/ Explain: _____
	!	_____
	!	_____
	!	

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in 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 /\_X\_/

If yes, explain: \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

Craig Ostroff, Pharm.D.  
Signature of Preparer  
Title: Regulatory Management Officer

\_\_\_\_\_  
Date

Badrul Chowdhury, M.D., Ph.D.  
Signature of Division Director

\_\_\_\_\_  
Date

cc:

Archival NDA 19-835  
Archival NDA 20-346  
HFD-570/Division File  
HFD-570/C. Ostroff  
HFD-093/Mary Ann Holovac  
HFD-104/PEDS/T.Crescenzi

Form OGD-011347

Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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this page is the manifestation of the electronic signature.**

/s/

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Badrul Chowdhury  
10/21/02 06:08:26 PM

# PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

## PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA: 9/3/1999. Application Written Request was made to: NDA 19-835 & 20-346  
 Timeframe Noted in Written Request for Submission of Studies 12/31/2001.

NDA# 19-835 Supplement # 015 Choose one: SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8 SLR

NDA# 20-346 Supplement # 008 Choose one: SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8 SLR

Sponsor Pfizer

Generic Name cetirizine HCl Trade Name Zyrtec

Strength : Tablet: 5 & 10 mg; Syrup: 1 mg/ml Dosage Form/Route: 19-835: Tablet / 20-346: Syrup

Date of Submission of Reports of Studies 12/21/2001.

Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies) 03/21/2002.

Was a formal Written Request made for the pediatric studies submitted?	Y <u>X</u>	N <u>  </u>
Were the studies submitted after the Written Request?	Y <u>X</u>	N <u>  </u>
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y <u>X</u>	N <u>  </u>
Was the timeframe noted in the Written Request for submission of studies met?	Y <u>X</u>	N <u>  </u>
If there was a written agreement, were the studies conducted according to the written agreement?  OR If there was no written agreement, were the studies conducted in accord with good scientific principles?	Y <u>X</u>  N <u>  </u>  <u>3/13/2002</u>	N <u>  </u>
Did the studies fairly respond to the Written Request?	Y <u>X</u>	N <u>  </u>

SIGNED Richard Nicklas, MD, Medical Officer R. Nicklas MD 2/27/2002 DATE 02-27-2002

**FORWARD TO THE PEDIATRIC EXCLUSIVITY BOARD, HFD-960.**

## PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity

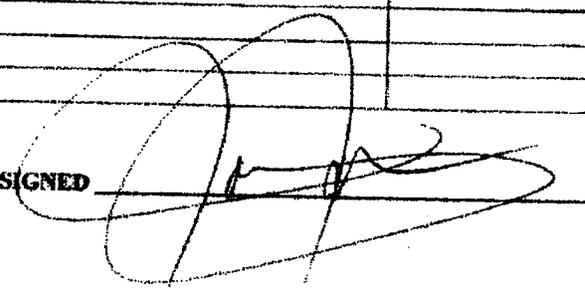
**Granted**

**Denied**

Existing Patent or Exclusivity Protection:

NDA/Product #	Eligible Patents/Exclusivity	Current Expiration Date
<u>19-835, 20-346</u>	<u>4535351</u>	<u>22 Jan - 2007</u>

SIGNED



DATE

3/13/02

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this page is the manifestation of the electronic signature.**

/s/

Grace Carmouze

3/15/02 03:55:44 PM

## PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 19-835 Supplement Type (e.g. SE5): SE5 Supplement Number: 015

Stamp Date: 12-21-2001 Action Date: 10-21-2002

HFD -570 Trade and generic names/dosage form: Zyrtec (cetirizine) Tablets

Applicant: Pfizer Therapeutic Class: \_\_\_\_\_

### Indication(s) previously approved:

**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 2 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 2 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, postnasal 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 2 years of age and older. It significantly reduces the occurrence, severity, and duration of hives and significantly reduces pruritus.

**Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.**

Number of indications for this application(s): 2

**Indication #1: 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 6 months to 23 months. Symptoms treated effectively include sneezing, rhinorrhea, postnasal discharge, nasal pruritus, ocular pruritus, and tearing.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

### Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. 0 yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. 5 yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. 6 yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 2 Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

**Indication #2: Chronic Urticaria:** ZYRTEC is indicated for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 months to 23 months. It significantly reduces the occurrence, severity, and duration of hives and significantly reduces pruritus

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

Min _____	kg _____	mo. <u>0</u>	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. <u>5</u>	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. 6 yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 2 Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

Regulatory Management Officer

cc: NDA 19-835 & NDA 20-346  
HFD-950/Terrie Crescenzi  
HFD-960/Grace Carmouze  
(revised 9-24-02)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960;301-594-7337**

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this page is the manifestation of the electronic signature.**

/s/

-----  
Craig Ostroff  
10/20/02 04:04:57 PM

**PEDIATRIC PAGE**

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 20-346 Supplement Type (e.g. SE5): SE5 Supplement Number: 008

Stamp Date: 12-21-2001 Action Date: 10-21-2002

HFD 570 Trade and generic names/dosage form: Zyrtec (cetirizine) Syrup

Applicant: Pfizer Therapeutic Class: \_\_\_\_\_

**Indication(s) previously approved:**

**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 2 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 2 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, postnasal 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 2 years of age and older. It significantly reduces the occurrence, severity, and duration of hives and significantly reduces pruritus.

**Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.**

Number of indications for this application(s): 2

**Indication #1: 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 6 months to 23 months. Symptoms treated effectively include sneezing, rhinorrhea, postnasal discharge, nasal pruritus, ocular pruritus, and tearing.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. 0 yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. 5 yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/d/yyyy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. 6 yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 2 Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

**Indication #2: Chronic Urticaria:** ZYRTEC is indicated for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 months to 23 months. It significantly reduces the occurrence, severity, and duration of hives and significantly reduces pruritus

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. 0 yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. 5 yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. 6 yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 2 Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

Regulatory Management Officer

cc: NDA 19-835 & NDA 20-346  
HFD-950/Terrie Crescenzi  
HFD-960/Grace Carmouze  
(revised 9-24-02)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960;301-594-7337**

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/s/

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Craig Ostroff  
10/20/02 04:06:45 PM

16. Debarment Certification

APPEARS THIS WAY  
ON ORIGINAL

Also included in this submission is proposed labeling that we believe is warranted based on the data contained in this supplement.

In accordance with the requirements of the Generic Drug Enforcement Act of 1992, and in connection with this supplement, Pfizer certifies that it did not and will not use in any capacity the service of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act.

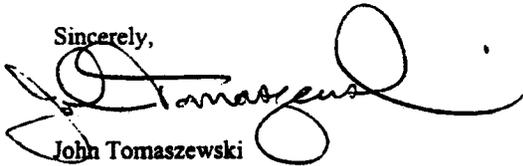
Although this supplement is exempt from a User Fee requirement, a User Fee Cover Sheet is included.

Financial Disclosure information for Pfizer Study # A 143-1010 is contained in Item 19.

As requested we have provided a copy of this cover letter to the Office of Generic Drugs (HFD-600).

Thank you for your consideration of this matter and please let me know as soon as possible if you have any questions or concerns.

Sincerely,

A handwritten signature in black ink, appearing to read "John Tomaszewski", written over a printed name. The signature is fluid and cursive, with a large loop at the end.

John Tomaszewski

cc: Office of Generic Drugs

\* Cover Letter Only

# USER FEE COVER SHEET

## See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1 APPLICANT'S NAME AND ADDRESS

Pfizer Inc  
235 East 42nd Street  
New York, NY 10017

4 BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 19-835/20-346

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES  NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

\_\_\_\_\_  
(APPLICATION NO. CONTAINING THE DATA).

2 TELEPHONE NUMBER (Include Area Code)

( 212 ) 733-6295

3 PRODUCT NAME

Zyrtec (cetirizine HCl)

6. USER FEE I.D. NUMBER

7 IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8 HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES  NO

(See item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
CBER, HFM-99  
1401 Rockville Pike  
Rockville, MD 20852-1448

Food and Drug Administration  
CDER, HFD-94  
and  
12420 Parklawn Drive, Room 3046  
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

TITLE

DATE

Director, Worldwide Regulatory Strategy

12/21/01

**Zyrtec® (cetirizine HCl) Tablets  
NDA 19-835  
Zyrtec® (cetirizine HCl) Syrup  
NDA 20-346**

**FINANCIAL DISCLOSURE COVER NOTE**

**Section 19.1**

There is one covered study for this supplemental NDA. The covered study was not funded via variable compensation and none of the investigators in any study hold any form of propriety interest in Zyrtec®.

Information regarding Pfizer efforts to eliminate bias in this study are described in NDA Section 19.2. Pfizer has examined its financial data regarding significant payments of other sorts made to all investigators in this study and equity information as provided by the investigators, as defined in 21 CFR 54.2. Disclosure: Financial Interests and Arrangements of Clinical Investigators (NDA Section 19.3).

With a total of 79 investigators listed in this multi-centered study, none of the listed investigators had financial information to disclose. Therefore there are no FDA 3455 forms in this section.

It is important to note that the investigator list for the studies determined by 1572s is not necessarily the same as that for financial disclosure. The FDA criteria for the two lists are not equivalent. Personnel involved with the study but not necessarily with the data are listed on FDA form 1572. There is a complete investigator population list for the covered study attached to this cover note

Pfizer Inc. is submitting financial disclosure information on the following covered study:

**Protocol A1431010 entitled "A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study of the Safety of Zyrtec (Cetirizine Hydrochloride) Syrup in Pediatric Subjects 6 Months to 11 Months of Age."**

Each of the individuals listed was sent the Financial Disclosure Form directly or via the principal investigator for their site. In addition, if necessary we contacted the site by telephone and/or sent 2 separate follow-up letters to those individuals who did not return the Financial Disclosure Form. All investigator contacted were reminded to disclose financial information for Warner-Lambert Company and its affiliates including Parke-Davis and Agouron, as they are now wholly owned by Pfizer.

**CERTIFICATION**

Per Form 3454, certification is provided for 79 investigators indicating

- Certified investigators (A total of 79 investigators are certified as having no Financial Arrangements as defined in 21 CFR 54.2)

**Please note that all investigators are assessed for Significant Payments of Other Sorts, Variable Compensation, & Propriety Interest.**

**DISCLOSURE**

In the covered study, no investigator had financial arrangements as defined in 21 CFR 54.2 therefore as there is nothing to report, form 3455 has not been included.

**APPEARS THIS WAY  
ON ORIGINAL**

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service Food and Drug Administration	Form Approved: OMB No. 0910-0396 Expiration Date: 3/31/02 NDA Number : 19-835 and 20-
<b>CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS          OF CLINICAL INVESTIGATORS</b>	<b>FORM FDA 3454 (3/99)</b>
<i>TO BE COMPLETED BY THE APPLICANT</i>	

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Applicable check box is marked

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Investigators (See attached.)

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

Investigators (See attached)

NAME <b>JOHN J. REGAN</b>	TITLE <b>SENIOR DIRECTOR - MEDICAL FINANCE</b>
FIRM/ORGANIZATION <b>PFIZER INC</b>	
SIGNATURE <i>John J. Regan</i>	DATE <b>OCTOBER 29, 2001</b>

<b>Paperwork Reduction Act Statement</b> An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:	Department of Health and Human Services Food and Drug Administration 5600 Fishers Lane, Room 14C-03 Rockville, MD 20857
--	--

Regulatory Affairs  
Pfizer Inc  
235 East 42nd Street 150/7/5  
New York, NY 10017  
Tel 212 733 6295 Fax 212 857 3558  
Email tomasj@pfizer.com



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## Pfizer Pharmaceuticals Group

**John Tomaszewski**  
Director  
Worldwide Regulatory Strategy

December 21, 2001

Robert J. Meyer, MD, Director  
Division of Pulmonary and Allergy Drug Products (HFD-570)  
Document Control Room 10B-03  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20852 -9787

RE: Zyrtec (cetirizine HCl) Tablets NDA 19-835  
\*Zyrtec (Cetirizine HCl) Syrup NDA 20-346

**SUBMISSION OF PEDIATRIC STUDY REPORTS –  
PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**

Dear Dr. Meyer:

Please refer to approved NDA's 19-385 (Zyrtec Tablets) and 20-346 (Zyrtec Syrup) and FDA's WRITTEN REQUEST dated September 3, 1999 and FDA's WRITTEN REQUEST #2 dated November 17, 2000.

As required under Written Request # 2, this submission contains a full study report of a Pfizer study # A143-1010 entitled, "A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study of the Safety of Zyrtec (cetirizine hydrochloride) Syrup in Pediatric Subjects 6 Months to 11 Months of Age". The electronic archive copy is contained in a CD ROM 4.71MB in size with 31 files and 18 folders. The CD ROM has been scanned with McAfee VirusScan Version 4.0.3 and is virus free. This study specifically requested by Written Request # 2, was filed to IND 24,084 and IND 40,377 (cover letter only) on February 9, 2001.

Additionally, also included in this submission are full reports of pharmacokinetic and multiple dose clinical studies in the population of interest. These studies while not required to obtain exclusivity as part of Written Request #2 are being submitted as requested by the agency.

Specifically these additional studies include a pharmacokinetic study in children  $\geq 6$  months to  $< 24$  months of age and both controlled and uncontrolled multiple-dose clinical studies in children  $\geq 12$  months of age. These studies were conducted overseas by our licensing partner, UCB Pharma, S.A. and were discussed with the agency at the August 14, 2000 Pfizer/FDA meeting. These study protocols were not filed to any U.S. IND.

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.



NDA 19-835/S-015

NDA 20-346/S-008

**PRIOR APPROVAL SUPPLEMENT**

Pfizer Pharmaceuticals  
Pfizer, Inc.  
235 East 42<sup>nd</sup> Street  
New York, NY 10017

Attention: John Tomaszewski, M.S.  
Director, Regulatory Affairs

Dear Mr. Tomaszewski:

We have received your supplemental drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA Number	Supplement Number	Drug Name
19-835	S-015	Zyrtec (cetirizine hydrochloride) Tablets
20-346	S-008	Zyrtec (cetirizine hydrochloride) Syrup

Date of Supplements: December 21, 2001

Date of Receipt: December 21, 2001

These supplements provide pediatric data in patients aged six months to less than two years of age.

Unless we notify you within 60 days of our receipt date that the applications are not sufficiently complete to permit a substantive review, these applications will be filed under section 505(b) of the Act on February 19, 2002, in accordance with 21 CFR 314.101(a). If the applications are filed, the primary user fee goal date will be October 21, 2002.

Please cite the application numbers listed above at the top of the first page of any communications concerning these applications. All communications concerning these supplemental applications should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Pulmonary and Allergy Drug Products, HFD-570  
Attention: Division Document Room  
5600 Fishers Lane  
Rockville, Maryland 20857

NDA 19-835/S-015  
NDA 20-346/S-008  
Page 2

If you have any questions, call Craig Ostroff, Pharm.D., Regulatory Management Officer, at (301) 827-1050.

Sincerely,

*{See appended electronic signature page}*

Sandy Barnes  
Supervisory CSO  
Division of Pulmonary and Allergy Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Craig Ostroff  
2/20/02 08:57:12 PM  
Craig Ostroff for Sandy Barnes

## MEMORANDUM OF TELECONFERENCE

DATE: March 14, 2002

APPLICATION NUMBER:

NDA 19-835/S-015, Zyrtec (cetirizine hydrochloride) Tablets, 5 and 10 mg.  
NDA 20-346/S-008, Zyrtec (cetirizine hydrochloride) Syrup, 1 mg/ml.

BETWEEN:

Name: John Tomaszewski, MS, Director, Regulatory Affairs  
Representing: Pfizer

AND

Name: Craig Ostroff, Pharm.D., Regulatory Management Officer  
Representing: Division of Pulmonary and Allergy Drug Products, HFD-570

SUBJECT: Notice of grant of pediatric exclusivity

BACKGROUND:

On 12-21-02 the applicant submitted a request for a pediatric exclusivity determination. There is a 90-day time period for this action to occur. The Pediatric Exclusivity Board met on 3-13-02 and reviewed the submission to determine if the submitted data did in fact meet the pediatric written request. The request was granted.

DISCUSSION:

I informed the applicant that their request dated 12-21-02 for pediatric exclusivity was granted. It will be listed on the FDA's website as having that status within a few days. The exact dates for the exclusivity period will be listed in the Orange Book at its next update (done monthly with the electronic version). I mentioned that no letter would be issued and this telephone call, in addition to it's listing in the Orange Book, was documentation of the exclusivity.

APPEARS THIS WAY  
ON ORIGINAL

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/s/

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Craig Ostroff  
3/15/02 05:21:27 PM  
CSO



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
HFD-570

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** 6 August 2002

<b>To:</b> Denise Andrews Director Regulatory Affairs (Allergy)	<b>From:</b> Craig Ostroff, Pharm.D. Regulatory Management Officer Division of Pulmonary and Allergy Drug Products
<b>Company:</b> Pfizer Inc.	<b>Through:</b>
<b>Fax number:</b> 212-857-3558	<b>Fax number:</b> 301-827-1271
<b>Phone number:</b> 212-573-3865	<b>Phone number:</b> 301-827-5585
<b>Subject:</b> NDA 19-835/S-015; NDA 20-346/S-008: Clinical Pharmacology Information Request	

**Total no. of pages including cover:** 3

**Comments:** See Attached comments.

**Document to be mailed:**  YES  NO

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

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NDA 19-835/S-015

NDA 20-346/S-008

Page 2

We are currently reviewing the clinical pharmacology portion of your submission, and have the following request for information. We would appreciate a prompt response for we are actively reviewing this application.

1. Provide individual concentration-time profiles, individual C<sub>max</sub>, individual AUC, and individual CL/F for:
  - a. children 2-5 years of age receiving a single 5 mg dose of cetirizine
  - b. children 6-12 years of age receiving a single 5 mg dose of cetirizine
  - c. adults receiving a single 10 mg dose of cetirizine.
2. Submit information about the relative oral bioavailability of the solution formulation of cetirizine (10 mg/mL) used in study UBC-123 (Pharmacokinetic study of a single oral administration of cetirizine (0.25 mg/kg) in infants aged from 6 to 24 months).

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ON ORIGINAL**

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/s/

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Craig Ostroff  
8/6/02 05:24:23 PM  
CSO



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
HFD-570

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: 7 August 2002**

<b>To:</b> Denise Andrews Director Regulatory Affairs (Allergy)	<b>From:</b> Craig Ostroff, Pharm.D. Regulatory Management Officer Division of Pulmonary and Allergy Drug Products
<b>Company:</b> Pfizer Inc.	<b>Through:</b>
<b>Fax number:</b> 212-857-3558	<b>Fax number:</b> 301-827-1271
<b>Phone number:</b> 212-573-3865	<b>Phone number:</b> 301-827-5585
<b>Subject:</b> NDA 19-835/S-015; NDA 20-346/S-008: Clinical Pharmacology Information Request #2	

**Total no. of pages including cover: 3**

**Comments: See Attached comments.**

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**Document to be mailed:**       YES       NO

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disclosure, dissemination, copying, or other action based on the content of  
this communication is not authorized. If you have received this document  
in error, please notify us immediately by telephone at (301) 827-1050.  
Thank you.**

NDA 19-835/S-015

NDA 20-346/S-008

Page 2

We are currently reviewing the clinical pharmacology portion of your submission, and have the following request for information. We would appreciate a prompt response for we are actively reviewing this application.

1. Was the formulation used in S-018 and S-008 the same formulation as is approved for children aged 2-5 years?

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/s/

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Craig Ostroff  
8/7/02 10:26:12 AM  
CSO



Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II  
DPADP/HFD-570

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**FACSIMILE TRANSMITTAL SHEET**

---

**DATE: 3 October 2002**

<b>To:</b> Mr. John Kennedy Director Regulatory Affairs (Allergy)	<b>From:</b> Craig Ostroff, Pharm.D. Regulatory Management Officer Division of Pulmonary and Allergy Drug Products
<b>Company:</b> Pfizer Inc.	<b>Through:</b> Marianne Mann, M.D. Deputy Division Director
<b>Fax number:</b> 212-857-3558	<b>Fax number:</b> 301-827-1271
<b>Phone number:</b> 212-733-7131	<b>Phone number:</b> 301-827-5585
<b>Subject:</b> N 19-835/S-015 & 20-346/S-008 – Zyrtec: Proposed Labeling	

**Total no. of pages including cover: 186**

**Comments:** The attached represents our proposal for this label. Revisions were made to your label, as submitted on 3-18-2002.

---

**Document to be mailed:**       YES       NO

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15 pages of draft labeling have  
been removed from this portion  
of the document.

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/s/

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Craig Ostroff  
10/2/02 05:14:21 PM  
CSO

Marianne Mann  
10/2/02 05:18:20 PM  
MEDICAL OFFICER



Food and Drug Administration  
 Center for Drug Evaluation and  
 Research  
 Office of Drug Evaluation II  
 DPADP/HFD-570

**FACSIMILE TRANSMITTAL SHEET**

**DATE: 16 October 2002**

<b>To:</b> Ms. Denise Andrews Director Regulatory Affairs (Allergy)	<b>From:</b> Craig Ostroff, Pharm.D. Regulatory Management Officer Division of Pulmonary and Allergy Drug Products
<b>Company:</b> Pfizer Inc.	<b>Through:</b> Badrul Chowdhury, M.D., Ph.D. Acting Division Director
<b>Fax number:</b> 212-857-3558	<b>Fax number:</b> 301-827-1271
<b>Phone number:</b> 212-733-7131	<b>Phone number:</b> 301-827-5585
<b>Subject:</b> N 19-835/S-015 & 20-346/S-008 – Zyrtec: Recommended Labeling	

**Total no. of pages including cover: 17**

**Comments:** The attached changes were made to your proposed label, as sent on October 11, 2002. I will also email you an identical copy of the attached label. The only revisions to your proposed label can be found in the following sections:

- **PRECAUTIONS/Pediatric Use** – Paragraphs 1 and 2
- **ADVERSE REACTIONS** – Paragraph 9
- **HOW SUPPLIED/Storage** – Both storage statements for the tablet and syrup formulations

**Document to be mailed:**  YES  NO

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16 pages of draft labeling have been removed from this portion of the document.

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/s/

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Craig Ostroff  
10/16/02 06:43:05 PM  
CSO

Badrul Chowdhury  
10/16/02 06:47:42 PM  
MEDICAL OFFICER

**Ostroff, Craig**

---

**From:** Lenkel, Laurie  
**Sent:** Wednesday, October 16, 2002 9:29 PM  
**To:** Ostroff, Craig  
**Subject:** RE: Zyrtec Ped sNDA - Label from Pfizer

Craig,

I have reviewed the changes. I have no further comments to add.

Laurie

-----Original Message-----

**From:** Ostroff, Craig  
**Sent:** Friday, October 11, 2002 2:19 PM  
**To:** Nicklas, Richard A; Chowdhury, Badrul A; Fadiran, Emmanuel O; Suarez, Sandra; Lenkel, Laurie; Guo, Ted; Poochikian, Guiragos K; Kammerman, Lisa A; Bertha, Craig M; Huff, Robin A; Shah, Jui; Mann, Marianne C  
**Subject:** Zyrtec Ped sNDA - Label from Pfizer

Dear Team:

Here's the counter proposal of the label for Zyrtec. Make sure your view changes is on and that you track changes by author.

The section that they changed was the portion of the Adverse Reactions section that talks about the somnolence, irritability etc. They re-wrote it. Recall that we had said it was OK for them to include the frequency of occurrence of a particular reaction, say irritability, vs. placebo (e.g. 9% vs. 5%).

Since we don't have any labeling meetings left and Monday is a federal holiday, Please email me back your comments after your sub team (reviewer and TL) has discussed it. Remember that the NDA is due next Friday (10-18), so please DFS your reviews as soon as you are able to, if you haven't done so already.

Thank you all for your cooperation,  
Craig

<< File: PfizerDraftPI\_10\_11\_02.doc >>



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
HFD-570

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** 16 October 2002

<b>To:</b> Denise Andrews Director Regulatory Affairs (Allergy)	<b>From:</b> Craig Ostroff, Pharm.D. Regulatory Management Officer Division of Pulmonary and Allergy Drug Products
<b>Company:</b> Pfizer Inc.	<b>Through:</b> Guirag Poochikian, Ph.D. Chemistry Team Leader
<b>Fax number:</b> 212-857-3558	<b>Fax number:</b> 301-827-1271
<b>Phone number:</b> 212-573-3865	<b>Phone number:</b> 301-827-5585
<b>Subject:</b> NDA 19-835/S-015; NDA 20-346/S-008: Labeling: Recommended Revision to Storage Statements	

**Total no. of pages including cover:** 3

**Comments:** See Attached comments.

---

**Document to be mailed:**       YES       NO

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We have the following revision to the below section of the labeling for these products. The section below is an excerpt from your proposed labeling sent 10-11-02. We would appreciate receiving a prompt response concerning this change.

---

#### HOW SUPPLIED

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

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

Bottles of 100: NDC 0069-5500-66

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

Bottles of 100: NDC 0069-5510-66

**STORAGE:** ~~Store at room temperature 59° to 86°F (15° to 30°C)~~ Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].

ZYRTEC® syrup is colorless to slightly yellow with a banana-grape flavor. Each teaspoonful (5 mL) contains 5 mg cetirizine hydrochloride. ZYRTEC® syrup is supplied as follows:

120 mL amber glass bottles

NDC 0069-5530-47

1 pint amber glass bottles

NDC 0069-5530-93

**STORAGE:** ~~Store at 41° to 86°F (5° to 30°C).~~ **INSERT PFIZER'S CHOICE HERE**

[FDA COMMENT: For a drug product demonstrated to be stable both at refrigeration and at room temperature you may choose between the following statement options:

a) **Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]; Store refrigerated, 2°-8°C (36°-46°F)**

b) **Store at 2°-25°C (36°-77°C)**

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/s/

-----  
Craig Ostroff  
10/16/02 01:55:57 PM  
CSO

Guiragos Poochikian  
10/16/02 01:58:17 PM  
CHEMIST

**Ostroff, Craig**

---

**From:** Chowdhury, Badrul A  
**Sent:** Friday, October 18, 2002 11:28 AM  
**To:** Ostroff, Craig  
**Cc:** Nicklas, Richard A  
**Subject:** RE: labeling for Zyrtec

Craig,

The word should be "irritability/fussiness," because that is what was captured in the AE table. The company is correct that "restlessness during sleep" was not captured and therefore the word "restlessness" should come out. I have asked Dick to give you a copy of the study report where the words are stated. You can refer to the page when you talk to the company. Talk to me before you call Pfizer. This should be pretty simple.

--Badrul

-----Original Message-----

**From:** Ostroff, Craig  
**Sent:** Friday, October 18, 2002 9:45 AM  
**To:** Chowdhury, Badrul A  
**Cc:** Nicklas, Richard A  
**Subject:** RE: labeling for Zyrtec  
**Importance:** High

BC,  
Please comment/concur and then I'll work with Pfizer on it.  
Thanks,  
CO  
PS>Thanks Dick, for your quick turnaround on this one!

-----Original Message-----

**From:** Nicklas, Richard A  
**Sent:** Friday, October 18, 2002 8:27 AM  
**To:** Ostroff, Craig  
**Cc:** Chowdhury, Badrul A  
**Subject:** labeling for Zyrtec

would recommend changing "restlessness" to "fussiness" in the labeling. They probably mean the same thing and the data faxed by the sponsor would support a greater incidence of this side effect in the cetirizine group.

Dick

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/s/

-----  
Craig Ostroff

10/20/02 04:21:27 PM

CSO

E-mail comment on label being committed to file

## Ostroff, Craig

---

From: Bertha, Craig M  
Sent: Monday, October 21, 2002 9:41 AM  
To: Ostroff, Craig  
Cc: Poochikian, Guiragos K  
Subject: RE: Zyrtec: Pfizer's counter label: NOTE CMC STORAGE STMT ISSUE!

Craig,

The latest proposal sent Friday the 18th will be acceptable for the tablet and syrup HOW SUPPLIED section.

Craig

-----Original Message-----

From: Ostroff, Craig  
Sent: Friday, October 18, 2002 6:12 PM  
To: Chowdhury, Badrul A; Fadiran, Emmanuel O; Nicklas, Richard A; Suarez, Sandra; Mann, Marianne C; Huff, Robin A; Shah, Jui; Guo, Ted; Kammerman, Lisa A; Bertha, Craig M; Poochikian, Guiragos K; Lenkel, Laurie  
Subject: Zyrtec: Pfizer's counter label: NOTE CMC STORAGE STMT ISSUE!

Team:

Pfizer has accepted all of the changes proposed/negotiated. The one sticking point is the Storage statement. This has been the source of a number of phone calls today (Fri.). The entire label is attached and the storage statement is found on the last page.

UPDATE:

OSTROFF/CRAIG: Pfizer remains insistent on including language concerning "excursions" in the room temperature portion of the statement. (I was able to convince them to accept the refrigerated portion of the statement for the syrup product) They cite the fact that we had them include it in the Zyrtec-D action back in 8-01. I explained the position on the statements' specific wording and "held the line" on keeping that specific wording, as we had discussed on Thursday. We really need your input on this issue. I let them know that this was the standard language and our current thinking and reminded them (when they brought up the guidance) that it was DRAFT and clearly labeled as not for implementation. This is the only hold-up for approval of the package. Badrul has been briefed in on this issue and is interested in hearing your guidance on this issue.

THANKS!

Craig

-----Original Message-----

From: Andrews, Denise F. [mailto:denise.f.andrews@Pfizer.com]  
Sent: Friday, October 18, 2002 5:38 PM  
To: 'Ostroff, Craig'  
Subject: RE: Proposed label

Craig,

The attached changes were made to your propose label sent on Oct. 16, 2002.

I will follow up with a hard copy on Monday October 25, 2002

Adverse Reactions - Change irritability/restlessness to irritability/fussiness

How Supplied Section -

Tablets -STORAGE: Store at 20°-25°C (68°-77°F) excursions permitted to

15-30C (59-86F) [see USP Controlled Room Temperature].

Syrup - a) Store at 20°-25°C (68°-77°F) excursions permitted to 15-30C (59-86F) [see USP Controlled Room Temperature]; or Store refrigerated, 2°-8°C (36°-46°F).

-----Original Message-----

From: Ostroff, Craig [mailto:OstroffC@cdcr.fda.gov]  
Sent: Thursday, October 17, 2002 9:58 AM  
To: 'denise.f.andrews@pfizer.com'  
Subject: FW: Proposed label

> -----Original Message-----

> From: Ostroff, Craig  
> Sent: Wednesday, October 16, 2002 7:08 PM  
> To: John Kennedy (E-mail)  
> Subject: Proposed label  
>  
> John, This is our current proposed label.  
> The attached changes were made to your proposed label, as sent on October 11, 2002. I will also email you an identical copy of the attached label.  
> The only revisions to your proposed label can be found in the following sections:  
> \* PRECAUTIONS/Pediatric Use - Paragraphs 1 and 2  
> \* ADVERSE REACTIONS - Paragraph 9  
> \* HOW SUPPLIED - Both storage statements for the tablet and syrup formulations

> Please respond as soon as you can,  
> Regards, Craig  
>  
> PS>I will send a copy to Denise Tomorrow (thurs)  
>  
> <<FDADraftPI\_10\_16\_02.doc>>  
>  
>

"MMS <secure.pfizer.com>" made the following annotations on 10/17/02 09:58:10

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[INFO] -- Access Manager:  
This message was sent in secure form from cder.fda.gov

=====  
==  
"MMS <secure.pfizer.com>" made the following annotations on 10/18/02 17:38:45

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[INFO] -- Content Manager:  
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/s/

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Craig Ostroff  
10/21/02 02:46:20 PM  
CSO  
Committing E-mail label comment to file

**NDA 19-835/S-015 ; NDA 20-346/S-008**  
**NDA REGULATORY FILING REVIEW**  
**(Including Filing Meeting Minutes)**

NDA 19-835/S-015 Zyrtec (cetirizine HCl) Tablets  
NDA 20-346/S-008 Zyrtec (cetirizine HCl) Syrup

Applicant: Pfizer

Date of Application: 12-21-2002  
Date of Receipt: 12-21-2002  
Date of Filing Meeting: 02-13-2002  
Filing Date: 02-19-2002

Proposed Changes: Modify indication to include: "Treatment of \_\_\_\_\_ Perennial Allergic Rhinitis and Chronic idiopathic urticaria in patients 6 months to < 2 years of age."

Type of Application: Full NDA \_\_\_--\_\_\_ Supplement SE5  
(b)(1) X (b)(2) \_\_\_\_\_  
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S X P \_\_\_\_\_  
Resubmission after a withdrawal or refuse to file \_\_\_N/A\_\_\_  
Chemical Classification: (1,2,3 etc.) N/A  
Other (orphan, OTC, etc.) N/A

If the application is affected by the application integrity policy (AIP), explain. N/A

User Fee Status: Paid N/A Waived (e.g., small business, public health) pediatric  
sNDA submitted prior to Jan 4, 2002. Exempt (orphan, government) \_\_\_\_\_  
Form 3397 (User Fee Cover Sheet) submitted: YES X NO \_\_\_\_\_  
User Fee ID# N/A  
Clinical data? YES X NO \_\_\_\_\_ Referenced to NDA# \_\_\_\_\_  
Date clock started after UN N/A

User Fee Goal date: October 21, 2002

Action Goal Date (optional) October 7, 2002

- Does the submission contain an accurate comprehensive index?  YES  NO
- Form 356h included with authorized signature?  
If foreign applicant, the U.S. Agent must countersign.  YES  NO
- Submission complete as required under 21 CFR 314.50?  
If no, explain: Includes Items as they relate to an SE8  YES  NO

- If electronic NDA, does it follow the Guidance?  YES NO NA  
If an electronic NDA: all certifications must be in paper and require a signature.
- If Common Technical Document, does it follow the guidance? YES NO  NA
- Patent information included with authorized signature?  YES NO
- Exclusivity requested? YES; If yes, \_\_\_\_\_ years  NO  
Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.
- Correctly worded Debarment Certification included with authorized signature?  YES NO  
If foreign applicant, the U.S. Agent must countersign.

Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that \_\_\_\_\_ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix \_\_\_\_." Applicant may not use wording such as, "To the best of my knowledge, ...."

- Financial Disclosure included with authorized signature?  YES NO  
(Forms 3454 and/or 3455)  
If foreign applicant, the U.S. Agent must countersign.
- Has the applicant complied with the Pediatric Rule for all ages and indications?  YES NO  
If no, for what ages and/or indications was a waiver and/or deferral requested:
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES  NO (N/A)

**Refer to 21 CFR 314.101(d) for Filing Requirements**

PDUFA and Action Goal dates correct in COMIS?  YES NO  
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

List referenced IND numbers: IND 24084 (tablets); IND.40377 (syrup)

End-of-Phase 2 Meeting? Date \_\_\_ N/A NO  
If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? Date(s) \_\_\_ N/A NO  
If yes, distribute minutes before filing meeting.

**Project Management**

- Copy of the labeling (PI) sent to DDMAC?  YES  NO
- Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support? YES  NO  N/A
- MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support? YES  NO  NA
- OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? YES  NO  NA
- Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_  NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?  N/A  
YES \_\_\_\_\_ NO \_\_\_\_\_

**Chemistry**

- Did sponsor request categorical exclusion for environmental assessment?  YES  NO  
If no, did sponsor submit a complete environmental assessment?  YES  NO  
If EA submitted, consulted to Nancy Sager (HFD-357)? YES  NO
- Establishment Evaluation Request (EER) package submitted? YES  NO ; N/A
- Parenteral Applications Consulted to Sterile Products (HFD-805)? YES  NO  N/A

**If 505(b)(2), complete the following:**

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

Name of listed drug(s) and NDA/ANDA #:

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)?

Yes \_\_\_\_\_ No \_\_\_\_\_

(Normally, FDA will refuse-to-file such applications.)

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?

Yes \_\_\_\_\_ No \_\_\_\_\_

If yes, the application must be refused for filing under 314.54(b)(1)

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?

Yes \_\_\_\_\_ No \_\_\_\_\_

If yes, the application must be refused for filing under 314.54(b)(2)

Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

\_\_\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

\_\_\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

\_\_\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

\_\_\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

*If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].*

\_\_\_\_\_ 21 CFR 314.50(i)(1)(ii): No relevant patents.

\_\_\_\_\_ 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

\_\_\_\_\_ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference? YES \_\_\_\_\_ NO \_\_\_\_\_
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity? YES \_\_\_\_\_ NO \_\_\_\_\_
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug? YES \_\_\_\_\_ NO \_\_\_\_\_

Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application? YES \_\_\_\_\_ NO \_\_\_\_\_

**ATTACHMENT**

**MEMO OF FILING MEETING**

DATE: February 13, 2002

**BACKGROUND**

The original NDA for Zyrtec Tablets was approved on December 8, 1995, and Zyrtec Syrup was approved on September 27, 1996. These pediatric exclusivity supplements propose to \_\_\_\_\_ to the age of 6 months. Currently they are approved down to age 2. The applicant has also requested a pediatric exclusivity determination.

**ATTENDEES:**

Badrul Chowdhury, Richard Nicklas, Young-Moon Choi, Marianne Mann, Craig Ostroff, Jui Shah.

**ASSIGNED REVIEWERS:**

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Richard Nicklas, MD
Secondary Medical:	Badrul Chowdhury; MD, PhD
Statistical:	Ted Guo, PhD
Pharmacology:	Jui Shah, PhD
Statistical Pharmacology:	N/A
Chemist:	Craig Bertha, PhD
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Sandra Suarez-Sharp, PhD
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	N/A
Project Manager:	Craig Ostroff, PharmD
Other Consults: DDMAC	Laurie Lenkel, JD

Per reviewers, all parts in English, or English translation? YES  NO

CLINICAL -- File  Refuse to file

• Clinical site inspection needed: YES  NO

MICROBIOLOGY CLINICAL -- File  N/A  Refuse to file

STATISTICAL -- File  Refuse to file

BIOPHARMACEUTICS -- File  Refuse to file

• Biopharm. inspection Needed: YES  NO

NDA 19-835/S-015 Zyrtec (cetirizine HCl) Tablets  
NDA 20-346/S-008 Zyrtec (cetirizine HCl) Syrup  
NDA Regulatory Filing Review  
Page 6

PHARMACOLOGY – File  Refuse to file \_\_\_\_\_

CHEMISTRY –

- Establishment(s) ready for inspection? YES  NO \_\_\_\_\_ File  Refuse to file \_\_\_\_\_

REGULATORY CONCLUSIONS/DEFICIENCIES:

The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

\_\_\_\_\_ The application is unsuitable for filing. Explain why:

---

Craig Ostroff, Pharm.D.  
Regulatory Management Officer, HFD-570

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/s/

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Craig Ostroff  
10/18/02 10:36:12 AM  
CSO

Sandra Barnes  
10/21/02 05:14:39 PM  
CSO

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 19-835 NDA 20-346	Efficacy Supplement Type SE-5	Supplement Number S-015 S-008
Drug: Zyrtec (cetirizine HCl) Tablets; Zyrtec (cetirizine HCl) Syrup		Applicant: Pfizer
RPM: Craig Ostroff, PharmD	10-21-02	HFD-570 <span style="float: right;">Phone # 301-827-5585</span>
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	
<b>❖ Application Classifications:</b>		
• Review priority	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
• Chem class (NDAs only)	N/A	
• Other (e.g., orphan, OTC)	N/A	
<b>❖ User Fee Goal Dates</b>	October 21, 2002	
<b>❖ Special programs (indicate all that apply)</b>	<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review	
<b>❖ User Fee Information</b>		
• User Fee	<input type="checkbox"/> Paid	
• User Fee waiver	<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other	
• User Fee exception	<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input checked="" type="checkbox"/> Other; Pediatric sNDA prior to 1-4-02	
<b>❖ Application Integrity Policy (AIP)</b>		
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
• This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
• Exception for review (Center Director's memo)	N/A	
• OC clearance for approval	N/A	
<b>❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.</b>	<input checked="" type="checkbox"/> Verified	
<b>❖ Patent</b>		
• Information: Verify that patent information was submitted	<input checked="" type="checkbox"/> Verified	
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii) N/A	
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	<input type="checkbox"/> Verified N/A	

❖ Exclusivity Summary (approvals only)	X
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	PM: 10-21-02
<b>❖ Actions</b>	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
<b>❖ Public communications</b>	
• Press Office notified of action (approval only)	( X ) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
<b>❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))</b>	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)	PM: 10-21-02; DDMAC: 10-16-02
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
<b>❖ Labels (immediate container &amp; carton labels)</b>	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	N/A
• Reviews	N/A
<b>❖ Post-marketing commitments</b>	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
<b>❖ Minutes of Meetings</b>	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
<b>❖ Advisory Committee Meeting</b>	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	X
❖ Clinical review(s) (indicate date for each review)	MOR#1: 2-20-02; MOR#2:10-21-02
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	Included in MOR #2
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) (indicate date for each review)	10-17-02
❖ Biopharmaceutical review(s) (indicate date for each review)	10-16-02
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
❖ CMC review(s) (indicate date for each review)	02-05-02
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	02-05-02
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
• Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	(X) Completed ( ) Requested ( ) Not yet requested
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	10-16-02
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A