CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-621

MEDICAL REVIEW

MEDICAL OFFICER NDA REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA # 21-621	TRADE NAME:	Zyrtec chewable tablets
APPLICANT:	Pfizer	USAN NAME:	Cetirizine
MEDICAL OFFICER:	Carol H. Bosken, MD		
TEAM LEADER:	Lydia Gilbert-McClain, MD	CATEGORY:	Anti-histamine
DUE DATE:	3/16/04	ROUTE:	Oral, chewable

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
5/15/03		N (000)	Original NDA submission
9/15/03	9/16/03	N (000) SU	Safety Update
9/19/03	9/23/03	N (000) BZ	Fed-Fasted Protocol A1431021
10/31/03	11/4/03	N (000) C	Response to filing letter
11/26/23	12/1/03	N(000) BM	Integrated Safety Update

RELATED APPLICATIONS

Document Date	Application Type	Comments
	NDA 19,835	Original NDA for cetirizine tablets
	NDA 20,346	NDA for cetirizine syrup
	NDA 21,150	NDA for the combination product with pseudoephedrine

REVIEW SUMMARY: This is an application to support approval of a 5-and 10-mg chewable tablet of cetirizine (Zyrtec). Zyrtec tablets in 5 and 10 mg strengths are approved for the treatment of seasonal allergic rhinitis, perennial allergic rhinitis, and chronic idiopathic urticaria and the current application is based on the demonstration of bioequivalence between the 10-mg chewable tablet and the commercially available 10-mg tablet. Two pivotal bioequivalence studies (49 healthy subjects 18-54 years old) demonstrated that the AUC and C_{max} of the chewable tablet/commercial tablet was within the 90% confidence interval providing conclusive evidence that the chewable tablet was bioequivalent to the commercial tablet. Four additional bioequivalence trials were supportive of this conclusion.. The safety profile of the chewable tablet was very similar to that of the commercial tablets with few exceptions. One patient with a prior history of liver disease developed elevated liver enzymes during the study, but no patient was withdrawn due to adverse events and no patient died during the studies. _In the pivotal trials 20.4% of the patients who received the chewable tablet complained of somnolence compared to 18.8% of the subjects who received the commercial tablet. The event was thought to be drug-related in 12.2 and 14.6% of the subjects treated with the chewable and commercial tablet respectively. When the results of the 6 studies are combined (n=124), somnolence was described in 21 cases (11 drug related). This is similar to what is reported in the approved label where somnolence is stated as occurring in 13.7% of the subjects in previous clinical trials.

The applicant has established bioequivalence of the 10 mg chewable tablet and it is acceptable to waive bioequivalence studies for the 5 mg chewable tablet given the similar dissolution profiles of the two strengths. From a clinical standpoint, this application can be approved.

OUTSTANDING ISSUES: No clinical Issues

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	X APPROVAL	____ APPROVABLE		NOT APPROVABLE
OTHER ACTION:	____	____		____

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CLINICAL REVIEW OF NDA # 21,621

EXECUTIVE SUMMARY

1. RECOMMENDATIONS

1.1. Recommendation on Approvability

Cetirizine chewable tablets in 5 and 10 mg strengths are recommended for approval on the basis of the demonstration of bioequivalence between the 10 mg commercial tablet and the 10 mg chewable tablet. In addition, the 5 and 10 mg chewable tablets were shown to have equivalent dissolution rates. Therefore, bioequivalence studies for the 5 mg tablet were waved.

1.2. Recommendation on Phase 4 Studies and/or Risk Management Steps

No Phase 4 studies are recommended.

2. SUMMARY OF CLINICAL FINDINGS

2.1. Brief Overview of Clinical Program

Cetirizine hydrochloride (Zyrtec) is currently approved for the treatment of seasonal allergic rhinitis (SAR) in patients over 2 years of age and the treatment of perennial allergic rhinitis (PAR) and chronic idiopathic urticaria (CIU) in patients 6 months and older. The dose is 5 or 10 mg OD in patients 6 years and older. The recommended dose in patients 2 to 5 years of age is 2.5 or 5 mg, and the dose in children less than 2 years of age in 2.5 mg OD with an increase to 5 mg if necessary. The approved formulations include 5 and 10 mg tablets that must be swallowed whole with water, a syrup that contains 1 mg/ml cetirizine, and an extended-relief tablet that includes pseudoephedrine. The development program for the chewable formulation includes 2 pivotal bioequivalence trials, 1 trial to determine the bioequivalence of the chewable formulation when taken in the fed and fasted state, and 4 additional supportive bioequivalence trials. Adverse events were recorded in all of the trials, and data have been submitted to demonstrate the dissolution characteristics of the chewable formulation.

2.2. Efficacy

Cetirizine has previously been demonstrated to be effective in the treatment of SAR, PAR, and CIU. No additional efficacy data are required for approval of the chewable formulation.

2.3. Safety

Adverse events after ingestion of the chewable formulation of cetirizine were reported for 124 healthy adults who were treated in the randomized bioequivalence trials. The spectrum

of adverse events was similar to that listed in the current label. The most common adverse event was somnolence and it occurred in 20.4% (12.2% drug-related) of the subjects who were treated with chewable cetirizine in the 2 pivotal studies. Almost 13% (6.6% drug-related) of the 124 subjects in the combined dataset who were treated with chewable cetirizine complained of somnolence. This compares with the 13.7% incidence of somnolence reported in the currently approved label.

Two Phase IV post-marketing studies on the commercial tablet performed by the sponsor showed that somnolence was the most common adverse event, however it occurred infrequently in these studies (5.1% of cetirizine-treated and 3.1% of placebo-treated patients).

2.4. Dosing

The dosing will be the same as is on the approved label. The syrup will continue to be recommended for patients under 2 years of age. In addition, the starting dose of cetirizine in patients 2-5 years of age is 2.5 mg, increasing to 5.0 mg OD if necessary. The syrup is recommended for the 2.5 mg dose.

2.5. Special Populations

The approved label includes a discussion of the decreased clearance that is seen in patients with hepatic and renal failure and in elderly patients. The dosage recommendations suggest decreasing the dose of cetirizine in the patients with hepatic and renal insufficiency, but not in elderly patients. Stratification of the results from two phase IV studies of the commercial Zyrtec tablets showed that patients treated with cetirizine and who were older than 44 years had a higher incidence of adverse events than patients in the same age group who were treated with placebo. An increase in the number of adverse events might be expected due to the changes in excretion with age.

The phase IV studies also showed that the incidence of treatment-emergent adverse events was lower in 225 African-Americans (13.7%) compared with 416 Caucasians (32.6%). This was true for both the cetirizine-treated and placebo-treated patients. Somnolence occurred more frequently in the African-Americans, but the differential was approximately the same in cetirizine (3.7% Caucasians and 7.1% African-Americans) and placebo-treated patients (1.7% Caucasian and 5.5% African-Americans). Since the increase in somnolence compared to placebo was no greater in the African-Americans than in the Caucasians it is unlikely that the effect is specific to cetirizine, and without additional data it would be inappropriate to suggest an elevated susceptibility to the effects of this antihistamine in general in African-Americans.

CLINICAL REVIEW

1. INTRODUCTION AND BACKGROUND

1.1. Established and Proposed Trade Name of Drug, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

This NDA is a 505(b)(2) application for a chewable tablet formulation of cetirizine hydrochloride. The 5 or 10 mg tablet is a grape-flavored bilayer tablet that can be chewed with or without water. The chewable tablet is recommended for patients 2 years and older for the treatment of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), and chronic idiopathic urticaria (CIU). The product will be marketed under the trade name Zyrtec® chewable tablet and there will be a single label that incorporates the bioequivalence data for the chewable formulation into the currently approved label.

Zyrtec® is currently approved for the treatment of SAR in patients over 2 years of age and the treatment of PAR and CIU in patients 6 months and older. The dose is 5 or 10 mg OD in patients 6 years and older. The recommended dose in patients 2 to 5 years of age is 2.5 or 5 mg, and the dose in children less than 2 years of age in 2.5 mg OD with an increase to 5 mg if necessary. The approved formulations include 5 and 10 mg tablets that must be swallowed whole with water, a syrup that contains 1 mg/ml cetirizine, and an extended relief tablet that contains cetirizine (5 mg) and pseudoephedrine (120 mg).

1.2. State of Armamentarium for Indications

Pharmaceuticals for the treatment of allergic manifestations have been available for years in the form of central nervous depressants such as hydroxyzine (Atarax, Vistaril) used to treat CIU, and promethazine (Phenergan) used to treat allergic rhinitis. Non-specific antihistamines such as diphenhydramine (Benadryl), Triplodine (Actifed), Cyproheptadine (Periactin), Brompheniramine (Dimetapp, Robitussin Allergy), and Chlorpheniramine (Sinutab, Extendryl) have been available since the early 1980s in many formulations, frequently in combination with pseudoephedrine. (See Table 2 for details). Benadryl, Actifed, Dimetapp, Robitussin, and Sinutab are available over the counter. Recently, anti-histamines and specific H_1-blockers that are less sedating than older antihistamines have been developed. (Table 1). Of these second generation anti-histamines, Claritin is the only one that is available OTC.

Table 1. Percent Somnolence/Drowsiness Found in Clinical Trials of Recently Approved Anti-histamine/H1-blockers

	Active Rx	Placebo
Fexofenadine (Allegra)	1.3	0.9
Desloratadine (Clarinex)	2.1	4.8
Cetirizine (Zyrtec)	13.7	6.3
Acrivastine (Semprex)	12	6
Aelastine (Medpointe)	11.5	5.4

Table 2. Summary of Drugs Approved for the Treatment of Allergic Diseases

Drug	Brand Name (Manufacturer)	Formulations	Other Components	Age* (years)	Indications*	Date of First Approval†	Date OTC†‡
ANTIHISTAMINE							
Fexofenadine	Allegra (Aventis)	Capsules, Tablets, Extended Release Tablet	--- Pseudoephedrine	≥ 6 ≥ 12	S, C	7/25/96	NA
Loratadine	Claritin (Schering)	Tablet, Syrup, Disintegrating Tablet Extended Release Tablet	--- --- Pseudoephedrine	≥2 ≥ 12	Hay fever Respiratory Allergies	11/22/02	11/19/03
Desloratadine	Clarinex (Schering)	Tablet Disintegrating Tablet	--- ---	≥ 12	S, P, C	12/21/01	NA
Cyproheptadine	Periactin (Merck)	Tablet	---	≥2	S, P, C	b 1/1/82	NA
Diphenhydramine	Benadryl (Pfizer)	Tablet, Capsule, Fastmelt Tablet, Caplet Gelcaps, Calpet Liqui-Gel Softgel	--- Pseudoephedrine Pseudoephedrine, Acetominophen ---	≥ 12 ≥ 6	Upper respiratory allergies	b 1/1/82	11/20/98
Triplodine	Actifed	Tablet	Pseudoephedrine	≥ 6	Upper respiratory allergies		b 1998
Azelastine	Astelin (Medpointe)	Nasal Spray	---	≥ 5	S	11/1/96	NA
Acrivastine	Semprex (Celltech)	Capsules	Pseudoephedrine	≥ 12	S	3/25/94	NA
Brompheniramine	Dimetapp (Wyeth)	Syrup, Tablet	Pseudoephedrine	≥2	Allergic Rhinitis	3/29/84	b 1998
	Robitussin Allergy (Wyeth)	Syrup	Dextromethorphan, Pseudoephedrine	≥ 6	Allergic Rhinitis	b 1982	b 1998
Chlorpheniramine	Extendryl (Fleming)	Capsule, Syrup Chewable tablet Extended release tablet	Phenylephrine, Methscopolamine	≥ 6	Allergic reaction, Urticaria	b 1982	NA
	Sinutab (Pfizer)	Tablet	Acetomjnophen, Pseudoephedrine	All	Upper respiratory allergies	b 1982	b 1998

Table 2 (Continued)

Topical Corticosteroid							
Mometasone	Nasonex (Schering)	Nasal Spray	---	≥2	S,P	10/1/97	NA
Beclomethasone	Beconase (GSK)	Nasal Spray	---	≥ 6	S, P	7/27/87	NA
Fluticasone	Flonase (GSK)	Nasal Spray	---	≥4	S,P	10/19/94	NA
Budesonide	Rhinocort (AstraZeneca)	Nasal Spray	---	≥ 6	S, P	10/1/99	NA
Triamcinolone	Nasacort (Aventis)	Nasal Spray	---	≥ 6	S, P	5/20/96	NA
Flunisolide	Nasarel (IVAX)	Nasal spray	---		S, P	3/8/95	NA
SYSTEMIC CORTICOSTEROID							
Dexamethasone	Decadron (Merck)	Tablet	---	All	Severe S or P	<1/1/82	NA
Hydrocortisone	Hydrocortisone (Merck)	Tablet	---	All	Severe S or P	<1/1/82	NA
OTHER							
Montelukast	Singulair (Merck)	Tablet, Chewable Tablet, Oral Granules	---	≥2	S	2/20/98	NA
Ipratropium	Atrovent (Boehringer)	Nasal Spray	---	≥ 6	P	10/20/95	NA
Hydroxyzine	Atarax (Pfizer)	Tablet, Syrup	---	All	C	<1/1/82	NA
	Vistaril (Pfizer)	Capsule, Oral suspension	---	All	C	<1/1/82	NA
Promethazine	Phenergan (Wyeth)	Tablet, Suppositories	---	≥2	S, P	<1/1/82	NA
Cromolyn	Nasalcrom (Pharmacia)	Nasal Spray	---	All	Hay fever, Nasal allergy	1/3/97	7/3/01

* For all generic formulations, use in patients younger than the recommended age is recommended only with a physician's advice.

** S = Seasonal Allergic Rhinitis, P = Perennial Allergic Rhinitis, C = Chronic Idiopathic Urticaria

b = before the date listed, NA = not available OTC

Glucocorticosteroids are also useful in the treatment of allergic diseases. Seasonal and perennial allergic rhinitis can be treated with systemic steroids such as Decadron and hydrocortisone if necessary. However, the most common current treatments are in the form of long acting synthetic corticosteroid nasal sprays. Mometasone (Nasonex), Beclomethasone (Beconase), Fluticasone (Flonase), Budesonide (Rhinocort), Triamcinolone (Nasacort), and Flunisolide (Nasarel) can all be used to treat seasonal and perennial allergic rhinitis in adults and children down to 6 years of age. Fluticasone is approved for use in children as young as four years and Mometasone is approved for use in two-year olds.

Several additional drug classes are currently approved for the treatment allergic rhinitis Montelukast, a leukotriene inhibitor is available in various oral formulations for the treatment of seasonal allergic rhinitis in children down to 2 years of age. Ipratropium, an anticholinergic agent is available as a nasal spray for the treatment of perennial allergic rhinitis in patients six years and older. Cromolyn, an agent that prevents the degranulation of mast cells is available as a nasal spray for the treatment of hay fever, and nasal allergy in patients two years and older. The cromolyn nasal spray is available OTC.

1.2. Important Milestones in Product Development

An End of Phase 2/Pre-NDA meeting was held with the Division on December 11, 2002. All of the questions and responses were related to chemistry and biopharm issues. The Biopharm reviewers identified dissolution as an important review issue and Pfizer agreed to submit complete datasets of both individual and mean values for the dissolution method.

2. CLINICALLY RELEVANT FINDINGS FROM OTHER REVIEWS

2.1. Chemistry, Manufacturing and Controls

The drug product is a bilayer tablet containing cetirizine and various flavors and sweeteners. The product contains betacyclodextrin (BCD) [redacted] and mannitol [redacted]. However, cetirizine [redacted] mannitol, so the [redacted] is restricted to the inactive layer of the tablet, while the cetirizine is restricted to the active layer. The sponsor has submitted dissolution studies that will be reviewed by the biopharm team. In addition, a clinical trial (A1431007) was conducted using two precursor chewable tablets that demonstrated bioequivalence between the tablet that contained BCD and one that did not. (Appendix 1.6)

2.2. Animal Pharmacology and Toxicology, Microbiology

The sponsor was not required to submit preclinical data with this application.

2.3. Statistics

Since this development program was a bioequivalence program and no clinical efficacy studies were conducted, a biostatistics review was not required for this application.

3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

3.1. Pharmacokinetics

The primary support for this application is the documentation of bioequivalence between the new chewable formulation of cetirizine and the commercially available tablet designed to be swallowed with water. The results are based on two pivotal studies (A1431019 and A1431018). Both were open, randomized 2-way crossover studies of single doses of 10 mg of cetirizine. In study A1431019 the commercial product was compared to chewable cetirizine taken with water, and in study A143018 the commercial product was compared to cetirizine taken without water. An additional study (A1431021), in which the chewable product was given after fasting and after eating a high fat breakfast, was submitted to demonstrate the effect of prior ingestion of food on the pharmacokinetic properties of the chewable tablet..

In both pivotal studies bioequivalence was established between cetirizine commercial tablet and the cetirizine chewable tablet due to the 90% confidence limits for the ratio $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max} falling within the 80%, 125% limits. For the chewable tablet taken with water the ratio and 90% confidence limits were 93.0 (89.3, 96.9), 93.2 (89.4, 97.1), and 101.2 (95.4, 107.5) for the $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max} respectively. For the chewable tablet taken without water the ratio and 90% confidence limits were 98.3 (95.4, 101.29), 98.2 (95.3, 101.2), and 97.3 (94.3, 100.4) for the $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max} respectively.

When the cetirizine chewable tablet was taken after a high fat meal the absorption was slower, but the overall exposure was similar to the exposure to cetirizine when the chewable formulation was taken on an empty stomach. Comparing absorption in the fed state to that in the fasted state the ratio and 90% confidence limits were 91.4 (88.0, 94.9), 91.4 (87.9, 94.9), and 63.1 (59.8, 66.6) for the $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max} respectively. After fasting the T_{max} occurred at 0.82 hours compared to 3.6 hours when taking the tablet after a high-fat meal.

Two supportive studies (A1431016 and A1431014) are early studies that use a design that is very similar to the pivotal studies and that had similar results. Two studies (A1431007 and UCBA00332) were not suitable for pharmacokinetic analysis because they either did not use the to-be-marketed chewable tablet (A1431007) or compared the to-be-marketed chewable tablet to a non-US approved standard (UCBA00332).

3.2 Pharmacodynamics

No pharmacodynamic data is provided with this application.

3.3 Other Biopharmaceutical Issues

It was noted during the filing review that betacyclodextrins (BCD) are used in the cetirizine chewable tablets _____, and that the BCD may affect the absorption of other drugs. On October 31, 2003 the sponsor sent a response to this concern. They present three primary arguments. 1) Study A1431007 tested two preliminary

formulations of the chewable tablet. One contained BCD and the other did not. The bioavailability of these two products was equivalent. 2) They state that it is unlikely that the BCD will affect the absorption of other drugs because binding to BCD is limited to molecules with a small size range, the acidity of the stomach promotes polarization of drugs and this in turn decreases binding to BCD; and 3) BCD will be present in the intestinal tract in very small amounts. These arguments are persuasive to the biopharmaceutical group at the FDA.

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1. Sources of Clinical Data

This submission consists entirely of single-dose bioequivalence trials conducted in adults. No measure of efficacy was obtained, however monitoring for adverse events and laboratory examinations were performed and these results were reviewed.

4.2. Overview of Clinical Trials

The submission consists of 2 pivotal trials, 4 supportive trials that compare the to-be-marketed chewable tablet to the product that is commercially available tablet (3 used the US commercial product as the standard and 1 used the European commercial product as the standard) and one study that compared two early monolayer formulations of the chewable tablet to the US commercial product. All of the studies were conducted in healthy volunteers and included an explicit exclusion for subjects with abnormal absorption (e.g. gastrectomy) and subjects with abnormal salivation (e.g. Sjogren's syndrome).

4.2.1. Study A1431019

This was a pivotal trial which tested the bioequivalence of the 10 mg to-be-marketed chewable tablet taken with water to the 10 mg commercial tablet. It was a randomized, open-label, two-way crossover, single dose study (7-day washout) conducted in 25 healthy fasted volunteers. Blood was drawn for PK studies pre-dose, 30 minutes, and 1, 2, 3, 4, 6, 8, 12, 24, 36, & 48 hours. Hematology, chemistry, and urinalysis studies were performed at baseline and 48 hours. Adverse events and vital signs were recorded at 1, 4, 12, 24, 36, & 48 hours. (hpbio\bio\a1421019.pdf, pages 13-23)

4.2.2. Study A1431018

This was a pivotal trial which tested the bioequivalence of the 10 mg to-be-marketed chewable tablet taken without water to the 10 mg commercial tablet. It was a randomized, open-label, two-way crossover, single dose study (7-day washout) conducted in 24 healthy fasted volunteers. Blood was drawn for PK studies pre-dose, 30 minutes, and 1, 2, 3, 4, 6, 8, 12, 24, 36, & 48 hours. Hematology, chemistry, and urinalysis studies were performed at baseline and 48 hours. Adverse events and vital signs were recorded at 1, 4, 12, 24, 36, & 48 hours. (hpbio\bio\a1421018.pdf, pages 15-24)

4.2.3 Study A1431021

This was a bioequivalence trial which tested the bioequivalence of the 10 mg to-be-marketed chewable tablet taken in the fasted state compared to the 10 mg chewable tablet taken after ingestion of a high-fat meal. It was a randomized, open-label, two-way crossover, single dose study (7-day washout) conducted in 24 healthy volunteers. Blood was drawn for PK studies pre-dose, 30 minutes, and 1, 2, 3, 4, 6, 8, 12, 24, 36, & 48 hours. Hematology, chemistry, and urinalysis studies were performed at baseline only. Adverse events and vital signs were recorded at 1, 4, 12, 24, 36, & 48 hours. (hpbio\bio\a1421021.pdf, pages 19-27)

4.2.4 Study A1431016

This was a pivotal trial which tested the bioequivalence of the 10 mg to-be-marketed chewable tablet taken without water, a monolayer chewable formulation taken without water and the 10 mg commercial tablet. It was a randomized, open-label, three-way crossover, single dose study (7-day washout) conducted in 18 healthy fasted volunteers. Blood was drawn for PK studies pre-dose, 30 minutes, and 1, 2, 3, 4, 6, 8, 12, 24, 36, & 48 hours. Hematology, chemistry, and urinalysis studies were performed at 48 hours. Adverse events and vital signs were recorded at 1, 4, 12, 24, 36, & 48 hours. (hpbio\bio\a1421016.pdf, pages 14-23)

4.2.5 Study A1431014

This study tested the bioequivalence of the 10 mg to-be-marketed chewable tablet taken without water to the 10 mg commercial tablet. It was a randomized, open-label, two-way crossover, single dose study (7-day washout) conducted in 14 healthy fasted volunteers. Blood was drawn for PK studies pre-dose, 30 minutes, and 1, 2, 3, 4, 6, 8, 12, 24, 36, & 48 hours. Hematology, chemistry, and urinalysis studies were performed at 48 hours. Adverse events and vital signs were recorded at 1, 4, 12, 24, 36, & 48 hours. (hpbio\bio\a1421014.pdf, pages 12-20)

4.2.6. Study A1431007

This study tested the bioequivalence of two mono-layer formulations of chewable cetirizine, one that contained BCD and one that did not and the commercial tablet. It was a randomized, open-label, three-way crossover, single dose study (7-day washout) conducted in 24 healthy fasted volunteers. Blood was drawn for PK studies pre-dose, 30 minutes, and 1, 2, 3, 4, 6, 8, 12, 24, 36, & 48 hours. Hematology, chemistry, and urinalysis studies were performed at 48 hours. Adverse events and vital signs were recorded at 1, 4, 12, 24, 36, & 48 hours. (hpbio\bio\a1421007.pdf, pages 13-22) Because the to-be-marketed chewable tablet was not included in this trial it was not reviewed in detail.

4.2.7. Study UCB A00332

This study tested the bioequivalence of the 10 mg to-be-marketed chewable tablet taken without water, the 10 mg to-be-marketed chewable tablet taken with 240 ml water and not

chewed, and the 10 mg tablet commercially available in Europe. It was a randomized, open-label, two-way crossover, single dose study (7-day washout) conducted in 20 healthy fasted volunteers. Blood was drawn for PK studies pre-dose, 30 minutes, and 1, 2, 3, 4, 6, 8, 12, 24, 36, & 48 hours. Hematology, chemistry, and urinalysis studies were performed at 48 hours. Adverse events and vital signs were recorded at 1, 4, 12, 24, 36, & 48 hours. (hpbio\bio\a1421018.pdf, pages 19-38)

4.3. Post-marketing Experience

Chewable cetirizine has not been marketed any place in the world. A summary of the post-marketing experience with commercially available Zyrtec was submitted by the sponsor with the 120-day safety update, and this was reviewed. In addition, the Division of Drug Risk Evaluation, CDER, FDA completed two recent reviews of the AERS database for Zyrtec adverse events. The report dated March 28, 2001 described the central nervous system effects of Zyrtec and the report dated May 27, 2003 described the experience with Zyrtec in the pediatric population. A summary of suicide, attempted suicide, and suicidal ideation was completed as part of the current review.

4.4. Literature Review

No literature review was submitted, however, a PubMed search of the recent literature was performed by the current reviewer.

5. CLINICAL REVIEW METHODS

5.1. Conduct of the Review

Seven bioequivalence studies were submitted with this application. Six, including the two pivotal trials were submitted in May, and an additional study to test the bioequivalence of the chewed tablet taken in the fasted as compared with the fed state was submitted in September. The original submission contained four supportive trials. Of these, one (A1431007) compared two prototype (monolayer) formulations of the chewable tablet to the commercial tablet. The objective of this study was to compare the bioavailability of a tablet containing BCD and one that did not. Because neither of these prototypes will be marketed, the study was not reviewed in detail. One of the supportive studies (UBCA00332) was conducted in Belgium and used a commercial product available only in Europe as the comparator formulation. Only adverse events recorded immediately after taking the chewable (to-be-marketed in the US) tablet were included in this review.

5.2. Materials Consulted and Documentation

This is an electronic submission. The original application arrived on May 15, 2003 and the archival copy is stored at \\CDSESSUB1\N21621n_000\2003-05-15. An amendment containing the fasted-fed bioequivalence study (A1431021) was submitted on September 19 and can be found at \\CDSESSUB1\N21621n_000\2003-09-19. The amendment contained an updated draft label that included references to the findings in study A143121. On

October 31, 2003 the sponsor sent a response to some of the Division's filing questions located at: \\CDSESSUB1\N21621n_000\2003-10-31 and \\CDSESSUB1\N21621n_000\2003-10-31A. Submission 2003-10-31A contains references that were not included in 2003-10-31. Also in response to a request from the Division, the sponsor submitted an integrated safety summary for all cetirizine products on November 26, 2003 (\\CDSESSUB1\N21621n_000\2003-11-26). The submission (\\CDSESSUB1\N21621n_000\2003-09-30) containing stability data was not reviewed by this reviewer. Both the Division's and the sponsor's meeting minutes from the December 11, 2002 EOP2 meeting were included in the original submission.

5.3. Data Quality and Integrity

The pivotal bioequivalence studies were performed at the Pfizer laboratories in Ann Arbor, Michigan. No audit was requested.

5.4. Ethical Standards

All of the studies were conducted according to ICH good clinical practices (summary\clinover.pdf, 2.5.1.4, pg 3)

The following items were included in this submission:

- Form FDA 356h (356h.pdf)
- Debarment certification (other\admin\debar.pdf)
- Statements that IRB approvals had been obtained

In none of the studies had any of the investigators been disbarred under Section 306 of the Federal Food, Drug, and Cosmetic Act.

All studies were conducted with formal IRB approval and written patient consent as described in 21 CFR Part 50.

(hpbio\bio\a1431019.pdf - pg 13, hpbio\bio\a1431018.pdf - pg 13, hpbio\bio\a1431016.pdf - pg 13, hpbio\bio\a1431014.pdf - pg 11, hpbio\bio\a1431007.pdf - pg 12, hpbio\bio\ubca00332.pdf - pg 15, and 21621_021.pdf - pg 17)

5.5. Financial Disclosure

- Found at "other\admin\financial. PDF"
- The investigators for studies A1431019 A1431018, A1431016, A1431014, and A1431007are employees of Pfizer and according to 21 CFR Part 54.4, certification regarding financial interest is not required.
- Study UBC A00332 was performed in Europe is not a covered study.

6. INTEGRATED REVIEW OF EFFICACY

This is a 505(b)(2) application with cetirizine 10-mg tablet as the reference product. The efficacy of cetirizine for allergic rhinitis and CU has been previously established in controlled clinical trials. No efficacy studies were conducted or required for this development program since approval of cetirizine chewable tablet will be based on demonstration of bioequivalence to the reference product. (3.1. Pharmacokinetics).

7. INTEGRATED REVIEW OF SAFETY

7.1. Brief Statement of Findings

Adverse events were recorded after ingestion of single 10-mg doses of chewable cetirizine by 124 healthy volunteers. The comparator group was 80 healthy adults who ingested 10 mg of the commercial Zyrtec tablet. There were no deaths, serious adverse events, or withdrawals from any of the studies due to adverse events. Of the 124 subjects who received the chewable formulation, 55.1% reported adverse events and 28.1% of the subjects were thought to have had drug-related AEs. For the commercial formulation the percentage with adverse events was 45.0% and 26.3% respectively. In the pivotal bioequivalence studies 49 subjects received the chewable formulation and 48 the commercial product. The incidence of the two most common AEs in subjects taking the commercial product and the new, chewable formulation was headache 14.6% and 24% and somnolence 18.9% and 20.4% respectively. The incidence of somnolence in adults who took 10 mg cetirizine is recorded in the approved label as 13.7%. In the supportive studies headache was more common in patients taking the commercial formulation. The incidence of dry mouth was 4.1% and 6.1% in the current studies of the commercial and chewable formulations respectively and compares to 5.0% recorded in the label.

Of the 124 patients, one had a clinically meaningful change in laboratory values over the course of the study. One 41 year-old female had an elevation of hepatic enzymes that was below the level predefined as "clinically significant" (maximum values: aspartate aminotransferase 59 U/L, alanine aminotransferase 120 U/L, alkaline phosphatase 149 U/L. Bilirubin was normal throughout). However, the enzymes were normal at baseline, increased during the study and returned to normal on follow-up. The sponsor stated that the subject had a history of abnormal liver function.

There were no abnormalities in cardiac rhythm or vital signs.

7.2. Methods and Content

The safety data were obtained from the submitted studies, from a safety update that covered studies performed by the sponsor and the sponsor's adverse event database through July 2003, from two reviews of the AERS data base that were performed by the Division of Drug Risk Evaluation I, CDER, FDA, and from a review of the recent literature performed by this reviewer.

7.3 Description of Patient Exposure

The combined studies describe 124 patients who received 247 x 10-mg doses of cetirizine (80 commercial tablets [A1431019, A1431018, A1431016, and A1431014] and 167 chewable tablets [All of the studies other than A143007]). Twenty of these subjects received one 10-mg tablet of a commercial product available in Europe (UCB A00332). Adverse events occurring after ingestion of the commercial formulation in the European study are not included in the tabulations. In the two pivotal trials a total of 48 subjects were given a single 10-mg dose of the commercial product and 49 received a single 10-mg chewable tablet (25 with water and 24 without water).

Of the total 124 patients, 56.8% were female. The majority of the patients were Caucasian. There were 9 African Americans and 4 of other ethnic background. The ages ranged from 18-54 years. In the two pivotal studies there were 49 subjects, 50% of whom were female. The ages ranged from 19-54 years and all expect 3 subjects were Caucasian.

7.4 Safety Findings from Clinical Studies

There were no deaths, serious adverse events, or a withdrawal of a patient from any of the studies due to an adverse event. There were no severe or clinically relevant events in the pivotal studies (A1431019 & A1431018). However in the food effect study (A1431021) one patient complained of sleeplessness for several nights. The investigator considered this to be a severe event that was not drug related.

Adverse events reported in the 2 pivotal studies are outlined in Table 3 below. There were approximately one third more adverse events in subjects who took the chewable formulation than in those treated with the commercial tablet. However, the differences did not reach statistical significance in this small number of subjects. In addition, the percentage of subjects with drug-related adverse events was the same in the two groups. Somnolence and headache were the most common adverse events in both treatment groups. There were 9 complaints of somnolence (18.8% of the patients) in the reference group and 10 (20.4%) in the patients treated with the chewable formulation. Seven (14.6% of subjects) and six (12.2% of subjects) were thought to have drug-related somnolence in the commercial tablet-treated and chewable tablet-treated subjects respectively. For headache the incidence was 14.6% (10.4% drug-related) for the subjects taking the commercial tablet and 24.5% (8.2%) for subjects taking the chewable tablets. Dry mouth was the only symptom that was seen more frequently in the subjects who took the chewable tablets but this differential was not seen when only the drug-related events was considered.

Table 3. Summary of Adverse Events in the Two Pivotal Bioequivalence Studies (A1431019 & A1431018)

	Commercial (n=48)				Chewable (n=49)			
	Total		Drug-Related		Total		Drug-Related	
	No	%*	No	%*	No	%*	No	%*
Asthenia	3	6.3	3	6.3	2	4.1	2	4.1
dry mouth	2	4.2	2	4.2	3	6.1	1	2.0
Headache	7	14.6	5	10.4	12	24.5	4	8.2
Somnolence	9	18.8	7	14.6	10	20.4	6	12.2
Other	20		8		23		7	
Total events	41		25		50		20	
Subjects with AE	23	47.9	16	33.3	31	63.3	17	34.7

* Percentage of subjects with the specific adverse event.

When the events from the six usable studies were combined (A1431019, A1431018, A1431021, A1431016, A1431014, UBC A00332) a similar picture was seen (Table 4). There was a higher incidence of total adverse events in the subjects taking the chewable formulation (55%) as compared to the subjects taking the commercial tablet (45%). However, the difference virtually disappeared when considering only the drug related events, 26.3% and 28.1% in the reference group and the subjects treated with the chewable formulation respectively. In this analysis 12.6% of the subjects who ingested the chewable tablet complained of somnolence.

Table 4. Summary of Adverse Event From all the Reported Studies (A1431019, A1431018, A1431021, A1431016, , A1431014, UBC A00332)

	Commercial (n=80)		Chewable (n=124)	
	Total	Drug Related	Total	Drug-Related
Number of Subjects with any Event	36	21	92	47
% Subjects with an Event	45.0	26.3	55.1	28.1
Total number of 10-mg doses	80	80	167	167
Number of Events	57	30	144	49
Number of Events/10-mg dose	0.7	0.4	0.9	0.3
Number somnolence events	9	7	21	11
Number somnolence events/10-mg dose	0.11	0.088	0.126	0.066

Reviewer: There were slightly more adverse events in the patients treated with the chewable formulation, however, this did not reach statistical significance. In addition, these studies were not blinded and there is no way to account for differences in patient and investigator perceptions due to knowledge of the formulation.

Of the subjects receiving chewable cetirizine, 101 had blood drawn for hematology and routine chemistries. The only clinically important abnormality was seen in a 41 year-old female who had abnormal hepatic enzymes at the end of the study. (GOT 36 to 59 U/L, GPT 60 to 120 U/L, and alkaline phosphatase 84 to 149 U/L. Total bilirubin normal (0.5 to 0.4 mg/dl). The values were normal at baseline, and returned to normal on follow-up four days after the end of the study. It is stated that the subject had a past medical history of abnormal hepatic function. Five subjects had a normal percentage of eosinophils in their peripheral blood at baseline and mildly elevated percentages at the end of the study. Two subjects had an elevated percentage at baseline that normalized during the study. The sponsor did not attribute the changes in the eosinophil counts to the drug.

7.5. Literature Review of Safety

Recent additions to the medical literature have shown a wide safety margin for cetirizine. In a clinical trial conducted in Europe and Canada (1) 817 patients between 1 and 2 years of age were randomized to receive treatment of atopic dermatitis with cetirizine or placebo for 18 months. The mean and median number of symptoms were similar in the two treatment groups (15.0 ± 9.9 in cetirizine-treated children and 15.1 ± 9.7 in placebo-treated children). The most common side effects were related to upper respiratory or gastrointestinal tract infections. Somnolence was reported in 9 cetirizine-treated patients and 8 placebo-treated patients ($p=1.0$). However Insomnia (35 vs 21, $p=0.071$) and Fatigue (13 vs 5, $p = 0.093$) were seen more frequently in the cetirizine-treated patients. Growth was unaffected and the QT interval did not change. In a more recent report (2) the behavioral and psychomotor development of 600 of the above patients was studied in detail. There were no differences in the measures of development or psychomotor function at visit 7 – 11 which corresponds to the end of the treatment period and 6 months of follow-up. No baseline measurements were obtained.

Another trial was conducted exclusively in Canada (3) and focused on younger children. The subjects were 6 to 11 months old, with a history of treatment with an H_1 blocker for allergic rhinitis, urticaria, atopic dermatitis, or other disorder. They were randomized to receive twice daily therapy with cetirizine (0.25 mg/kg) or placebo for a total of 7 days. The 85 patients were evenly distributed between treatments and genders. Adverse events were more common in the placebo-treated group than the cetirizine-treated patients. The overall event rate was 73.8% in the cetirizine-treated patient and 88.4% in the placebo group. The incidence of treatment-related adverse events was 45.2% and 62.8% respectively. Of note, the incidence of nervousness (28.6 vs 44.2%), insomnia (23.8% vs 44.2%), and somnolence (21.4% vs 30.2%) was less in the cetirizine-treated patients than in the placebo group.

Reviewer: The investigations summarized above were all double-blind, placebo-controlled trials. However, they were all industry supported. It is very unfortunate that the sub-study that looked at psychomotor function did not include baseline measurements because the placebo group had more subjects at visit 7 & 8 with scores of >10 (considered significantly

predictive of later difficulty in learning) on the behavioral test. Over time, the placebo-treated patients had a greater improvement in their scores than the cetirizine-treated children, so that at the end of follow-up the placebo-treated patients had fewer children with a score >10. Without the raw data it is impossible to do a formal analysis of these changes, but it leaves open the possibility that the placebo-treated patients had more behavioral problems at baseline. If this were the case, then the comparison of unadjusted values at the end of treatment is meaningless. The only other recent studies of adverse events from cetirizine describe skin reactions, both allergic and non-allergic.

7.6. Post-marketing Surveillance

The Division of Drug Risk Evaluation I, CDER, FDA has performed three post-marketing reviews of cetirizine. A report dated March 28, 2001 summarized the nervous system and psychiatric events submitted to MedWatch as of March 12, 2001. In that report it was noted that 39% of the AEs in AERS for cetirizine included one or more nervous system or psychiatric symptom. Cetirizine was thought to be causal in many of the cases of hallucinations and abnormal dreams because of the temporal relationship (including abatement with discontinuation and recurrence with reinstitution of therapy) and the absence of any other etiologic factor. Seizures were also reported frequently, but the etiologic role of cetirizine was not as clear. Of note, half of the reports of hallucination, abnormal dreams, and seizures occurred in pediatric patients.

At the request of the Division of Pediatric Drug Development, the DDRE reviewed the adverse events reported to MedWatch for pediatric patients between 3/13/02 and 4/13/2003. As in the prior review, psychiatric, emotional, and behavioral problems were commonly seen and were thought to be causally related to cetirizine. The etiologic role of cetirizine in the development of seizures was again thought to be suggestive, but not definitive.

In the course of the current review, the DDRE reviewed reports of suicide, suicidal ideation and self-inflicted trauma (Report January 13, 2003). They concluded that suicide and suicidal ideation, though reported infrequently, were probably causally related to the ingestion of cetirizine. Of the 34 cases reviewed, eight patients developed suicidal ideation after taking cetirizine and had no known confounding factors (prior psychiatric history or other drugs). In 4 cases the symptoms disappeared after discontinuing the medication and in one they reappeared on rechallenge.

7.7. Safety Update

A safety update was submitted on September 15, 2003 (N[000]Su). The sponsor reports no serious adverse events, deaths or study discontinuations due to adverse event in the one on-going clinical trial that was being conducted during the reporting period. The chewable formulation is not marketed and therefore there have been no post-marketing reports of adverse events.

The safety update submitted on November 26, 2003 covers all safety information obtained between July 28, 2002 and July 27, 2003. The update includes a summary of the Adverse event observed during the conduct of two Phase IV randomized trials conducted by the sponsor, a list of adverse events reported in trials conducted by other manufacturers, and a list of adverse events reported by consumers and medical professionals to the sponsor.

The two phase 4 trials (A1431012, A1431015) were designed to compare the efficacy and safety of cetirizine to placebo and desloratadine and were identical in design. Patients with SAR were primed with antigen and then challenged in a controlled environmental chamber before and after taking the assigned medication. The studies were conducted over a two day period. A total of 680 subjects were studies (486 cetirizine, 194 placebo). Sixty five percent of the subjects were female and 37.5% were African-American. The sex and ethnic distribution was the same in the active and placebo-treated groups. No deaths or serious adverse events were reported. However, three cetirizine-treated patients withdrew due to adverse events, two of whom were thought to have drug-related events (gastroenteritis and lightheadedness). One placebo patient withdrew due to a non drug-related event. As in other studies, somnolence was the most common adverse event, occurring in 5.1% of cetirizine treated patients and 3.1% of those treated with placebo, The only other event that occurred in more than 1% of the subjects was rhinitis that was reported in 1.2% of the patients taking cetirizine and none of the placebo patients. The data from these two studies were stratified on the basis of age and race and those results are described below (8.1 Special Populations).

The safety update also includes lists of serious adverse events obtained from several sources. In the text the sponsor states that a detailed review of this data revealed no new safety concerns. However, there are no other details provided in the update itself. One list is labeled "Serious adverse events in other company clinical trials". Of the 18 events listed, 8 were described as hepatitis or hepatic cytolysis. The patients ranged in age from 29 to 53 and the event occurred between 18 and 43 days after the start of double blind therapy. The patients were all treated in France and the investigator thought that the adverse events were not related to the drug.

Eighty eight deaths were listed by the sponsor in patients taking cetirizine during the year covered by the update. Of these, 70 were listed as NOS (Not Otherwise Specified) and most of the others were clearly unrelated to the drug such as cancer, heart attack, and murder. There was one suicide in a 22 year-old. Of the 356 serious adverse events in clinical use, 22 (6.2%) were seizures, 21 (5.9%) were of emotional problems, lethargy, or hallucinations (2 cases). Thirteen cases of hepatitis (3.4% of AEs) were reported from the US, Europe, and Japan.

7.8. Drug Withdrawal, Abuse, and Overdose Experience

The current label states that there is no information to suggest drug dependence or abuse. There is also no indication of abuse or dependence submitted with the safety update or any found in the AERS database review.

The current label includes a description of two patients who took excessive amounts of cetirizine: an adult who consumed 150 mg and an 18 month-old who consumed 180 mg. In both cases somnolence ensued and the baby exhibited restlessness and irritability during the course of observation. A review of the AERS database shows at least 5 other cases of substantial overdoses of cetirizine (ISR number 3154315, 3371998, 4019177, 4019590,(4030381) The patients ranged from 31 months to "adult" and they ingested 50-300 mg of cetirizine. Symptoms were restricted to somnolence and transient sensation of a thick tongue and difficulty speaking. There were no permanent sequelae reported.

7.9. Adequacy of Safety Testing

No safety testing of the chewable tablet has been performed in children for this development program. However, the drug substance cetirizine has been studied in children down to age 6 months. As this development program is based on bioequivalence, no further testing is required in children.

7.10. Labeling Safety Issues and Post-marketing Commitments

In the most recent amendment to the NDA, the sponsor has added "seizures" and "aggressive reaction" to the list of adverse events seen in the post-marketing period. On the basis of the DDRE reviews we will add suicidal ideation and hallucinations to this list of adverse events. In addition, a change in dosage for patients over 77 years old will be suggested based on the pharmakodynamic data that is already in the approved label (See Appendix – Labeling Suggestions for Applicant)

8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

The proposed dose for the chewable table is exactly the same as the currently approved doses for the tablet and syrup, 5 and 10 mg. The bioequivalence studies demonstrated bioequivalence of the commercial tablet with the chewable tablet whether the chewable tablet was taken with or without water. Additionally, study A143021 demonstrated bioequivalence between the chewable formulation taken in the fasted state and after a high fat meal. Therefore, the tablets can be taken without regard to meals.

9. USE IN SPECIAL POPULATIONS

9.1. Evaluation of Applicant's Gender, Age, Race, or Ethnicity Efficacy and Safety Analyses and Adequacy of Investigation

Of the 124 subjects included in this review, only 13 were not Caucasian. Therefore, no information is provided relative to racial differences in bioequivalence or safety. Similarly, the oldest patient was 54 years old so that no new information is provided relative to use in the geriatric population. Fifty seven percent of the patients were female, however, the safety and bioequivalence data are not presented in gender-specific sub-sets, so no information relative to gender differences in safety or bioequivalence is provided.

The post-marketing safety update includes race, gender, and age-stratified data from 680 patients treated (486 cetirizine and 194 placebo) in phase IV studies. Of the patients treated with cetirizine 65.5% were female and 37.4% were African-American. There were 392 (80.7%) between the ages of 16 and 44 years, 91 (18.7%) between 45 and 64 years and 3 were older than 64. Severe adverse events were reported by 7.1% of the subjects 16-44 years and 6.6% of subjects 45-65 years. Similar proportions were seen in the placebo-treated patients. All of the study withdrawals occurred in patients less than 44 years old. There were 73 (18.6%) drug-related events in the 392 patients age 16-44 years treated with cetirizine and 17 (18.5%) in the 94 cetirizine-treated patients who were older than 44 years (Table 5.).

Table 5. Adverse Events Stratified by Age in Studies A1431012 and A1431015

	Cetirizine		Placebo	
	16-44 yr old (n=392)	>44 yr old (n=94)	16-44 yr old (n=161)	>44 yr old (n=33)
Total AE (n (n/subject))	144 (0.38)	31 (0.33)	66 (0.41)	9 (0.27)
Drug Related AE (n (n/subject))	73 (0.19)	17 (0.18)	27 (0.17)	2 (0.06)

There were 27 (16.8%) events reported to be drug-related in the 161 patients age 16 -44 years treated with placebo and 2 (6.1%) events reported as drug-related in the 33 placebo-treated patients who were older than 44 years. There were two noteworthy changes in vital signs, both in cetirizine-treated younger (< 44 years) patients (1 systolic blood pressure of 90 and 1 heart rate of 48).

Of the 486 cetirizine-treated patients 37.4% were African-American as were 37.6% of the placebo-treated patients. The age distribution and withdrawal rates were similar in the two ethnic groups. Adverse events were less common in African-American patients than in Caucasian patients in both the cetirizine and placebo-treated groups. For the Caucasian patients 32.6% of the cetirizine-treated patients described an adverse event whereas 33.1% of the placebo-treated patients had an event. The percentages for the African-American patients was 13.7% and 16.4% respectively. However, despite the lower rate of events in the African-American subjects they complained of somnolence more than twice as often as the Caucasians.

Table 6. Adverse Events by Race in Studies A1431012 and A1431015

All Causality Treatment-Emergent Adverse Events By Race
Events Reported by ≥ 1% Cetirizine Subjects of Any Race
and More Frequently than Placebo Subjects

	Cetirizine				Placebo			
	White		Black		White		Black	
	n	%	N	%	n	%	n	%
Total Subjects	298	100	182	100	118	100	73	100
Subjects with Adverse Events	97	32.6	25	13.7	39	33.1	12	16.4
Respiratory Tract Infection	13	4.4	0	0.0	5	4.2	1	1.4
Somnolence	11	3.7	13	7.1	2	1.7	4	5.5
Asthenia	9	3.0	1	0.5	1	0.8	0	0.0
Cough Increased	5	1.7	0	0.0	1	0.8	0	0.0
Rhinitis	5	1.7	1	0.5	1	0.8	0	0.0
Dizziness	4	1.3	1	0.5	0	0.0	0	0.0
Accidental Injury	3	1.0	0	0.0	0	0.0	0	0.0
Back Pain	3	1.0	0	0.0	0	0.0	0	0.0
Nausea	3	1.0	0	0.0	0	0.0	0	0.0
Muscular Hypertonia	3	1.0	0	0.0	0	0.0	0	0.0

Source: Table 2.2.5 and Table 2.2.6

Since most of the somnolence was thought to be drug-related, the differential rate in the two ethnic groups was also seen in the number of drug-related events.

Thirty-five percent of the patients were female. In the cetirizine-treated patients all three of the withdrawals were female whereas the 1 withdrawal in the placebo-treated patients was male. There were a few more complaints in women than men. In the cetirizine-treated female patients 28.2% of them described an AE as compared with 21.0% of the males, In the placebo-treated patients 28.5% of the females and 22.5% of the males described an event. As in the other studies, somnolence was the most frequent AE: 3.6% and 2.8% (males) and 6.0% and 3.3% (females) treated with cetirizine and placebo respectively.

9.2. Pediatric Program

All of the subjects treated in the submitted studies were between 18 and 54 years of age. Therefore, there is no new information provided relative to pediatric patients. Cetirizine has been studied and is approved in children 6 months of age and older. Therefore, given that this is a bioequivalence program and that the dissolution of the 5 mg chewable tablet is comparable to the dissolutions of the 10 mg tablet, no additional pediatric studies are required. It is appropriate to conduct the bioequivalence studies in adults.

9.3. Comments on Data Available or Needed in Other Populations

As described in the label, hepatic insufficiency and old age (mean 77 years) prolong the half-life of cetirizine by 50%. Moderate impairment of renal function (creatinine clearance 11-31 mL/min) had a 3-fold increase in half-life. Less that 10% of the administered dose was removed during a single hemodialysis session. A recommendation for decreasing the dose of cetirizine in patients with renal and hepatic impairment is included in the current label. Cetirizine is not teratogenic, however, there are no studies in pregnant women and its use in this population is advised "only if clearly indicated". Similarly, it is not recommended for lactating women.

10. CONCLUSIONS AND RECOMMENDATIONS

10.1. Conclusions Regarding Safety and Efficacy

In the pivotal trials submitted with this application, the chewable formulation of cetirizine has been shown to be bioequivalent to the commercial tablet. Absorption is not affected by the presence of water or food in the stomach. Efficacy was not formally tested in these studies and for the purposes of approval the bioequivalence program is adequate.

The spectrum of adverse events associated with the ingestion of the chewable formulations is similar to that seen with the commercial product. In all of the studies submitted as well as the post-marketing surveillance, somnolence is the most common adverse event in all ages, genders, and races. In the trials reported in this application, 12.6% of the doses were associated with somnolence compared to 11.2% of the doses of the commercial tablet. This compares to an incidence of 13.7% as stated in the current label. In the sponsor's phase IV trials somnolence was also the most common adverse event though it only occurred in 5.1%

of the subjects. Somnolence and drowsiness were also the most commonly noted symptoms from overdosing. No reports of gender or ethnic differentials in the safety could be found in the recent literature by this reviewer.

10.2. Recommendations on Approvability

The chewable formulation of cetirizine is recommended for approval on the basis of bioequivalence with the commercial tablet and the demonstration of a low incidence of adverse events. These adverse events are qualitatively and quantitatively similar to those seen with the commercial product.

10.3. Labeling

The sponsor has submitted an edited label that is identical to the currently approved label with the addition of descriptions of the formulation and use of the chewable tablet. They note that it is bioequivalent to the commercial tablet taken with and without water and that it may be taken without regard to food consumption. The post-marketing section has also been amended by the sponsor to include "aggressive reactions" and "seizures" as adverse events seen in the post-marketing period.

Specific comments will be sent to the sponsor (Appendix 2 "Labeling Comments to the Applicant") suggesting a change in the wording in the DOSAGE AND ADMINISTRATION Section, Age 2-5 sub-section , the addition of a separate section for Post-Marketing experience with a list of adverse events, and a warning to decrease the dose in patients over 77 years old.

APPENDIX

1. DETAILED STUDY REVIEWS

1.1 Study # A1431019.

Phase 1, Open-Label Randomized, 2-way Crossover Pivotal Bioequivalence Study Comparing the Cetirizine Chewable Tablet Taken With Water to the Commercial Zyrtec(Cetirizine)Tablet Taken With Water in Healthy Subjects.

1.1.1. Protocol

1.1.1.1. Administrative

Study Dates: June 26, 2002 to July 19, 2002

Study Center: Pfizer Global Research & Development in Ann Arbor, Michigan.

Principal Investigator: Dr. Candace R. Bramson .

1.1.1.2. Objective/Rationale

To assess the bioequivalence of the cetirizine chewable tablet when chewed and taken with water to the cetirizine commercial tablet when swallowed whole and taken with water.

To evaluate the safety and tolerability of the cetirizine chewable tablet in healthy volunteers.

1.1.1.3. Overall Design

This is a randomized, open-label, two-way crossover, single dose study with a 7-day washout between the two treatment periods. Each subject was randomized to receive either 10 mg Cetirizine Commercial Tablet or 10 mg Cetirizine Chewable tablet. Each treatment was followed by the ingestion of 240 cc water. Patients were treated after an 8-hour fast and were not permitted to lie down or eat for 4 hours after the dose. On the second study visit (day 8) the alternate formulation was ingested.

Blood was drawn for PK studies pre-dose, 30 minutes, and 1, 2, 3, 4, 6, 8, 12, 24, 36, & 48 hours. Hematology, chemistry, and urinalysis studies were performed at 48 hours. Adverse Events and vital signs were recorded at 1, 4, 12, 24, 36, & 48 hours. Patients stayed in the clinic for 9 hours after the dose.

1.1.1.4. Study Population

The study population was made up of 25 healthy men and women 18-55 years old. The BMI had to be between 18 and 30 kg/m^2.

Exclusion criteria included other diseases (other than seasonal allergy), gastrectomy, history of drug or alcohol abuse or tobacco smoking, and pregnancy. Prescription and over the

counter drugs were prohibited for 7 days prior to the study except the following: acetaminophen < 2 gms/day, hormone replacement therapy, hormonal methods of contraception.

1.1.2. Results

1.1.2.1. Subject Disposition

Twenty five subjects were screened and enrolled. One subject did not have blood drawn prior to dosing and so was not included in the efficacy outcome. Table 7. outlines the demographics of the study population. The table is copied from the sponsor's submission.

Table 7. Demographic Characteristics of Study Population (A1431019)

	All Subjects		
	Male	Female	Total
Number of Subjects	12	13	25
Age (years), mean ± SD (range)	36.0 ± 13.2 (19 - 54)	38.2 ± 8.6 (23 - 48)	37.1 ± 10.8 (19 - 54)
Weight (kg), mean ± SD (range)	84.6 ± 10.1 (69.5 - 97.6)	66.0 ± 6.6 (55.5 - 80.2)	74.9 ± 12.6 (55.5 - 97.6)
Body Mass Index (kg/m^2), mean ± SD (range)	24.8 ± 2.7 (22.0 - 29.0)	23.7 ± 3.3 (20.0 - 30.0)	24.2 ± 3.0 (20.0 - 30.0)
Height (cm), mean ± SD (range)	184.7 ± 7.0 (175.1 - 202.0)	167.1 ± 5.6 (157.0 - 175.0)	175.6 ± 10.9 (157.0 - 202.0)

Source: Table 2.1 and Section 11, Item 1.
Ethnic Group: White – 12 male, 12 female; Black - 1 female.

1.1.2.3 Pharmcokinetics

Bioequivalence was established between the cetirizine commercial tablet and the cetirizine chewable tablet formulation due to the 90% confidence limits for the ratio of their AUC_{0-inf}, AUC_{0-t} and C_{max} falling within the 80%, 125% limits.

The mean concentration-time profiles were similar across the two treatments. Peak plasma concentrations were achieved approximately 1 hour after dosing. Plasma concentrations, with both formulations, declined thereafter with an elimination half-life of approximately 9 hours. The PK results are depicted below in Tables 8 and 9 and figure 1 as copied from the sponsor's submission.

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ON ORIGINAL