

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-621**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

APPEARS THIS WAY  
ON ORIGINAL

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

---

<b>NDA:</b>	21-621
<b>Proprietary Drug Name:</b>	ZYRTEC CHEWABLE TABLET
<b>Generic Name:</b>	Cetirizine HCl
<b>Indication:</b>	Treatment of SAR, PAR, and CIU
<b>Dosage Form:</b>	Bilayer Tablet: immediate Release Tablet
<b>Strength:</b>	5- and 10-mg
<b>Route of Administration:</b>	Oral
<b>Dosage and administration:</b>	<p><b>Adults and Children 12 Years and Older:</b> The recommended initial dose of ZYRTEC is 5 or 10 mg per day, depending on symptom severity.</p> <p><b>Children 6 to 11 Years:</b> The recommended initial dose of ZYRTEC is 5 or 10 mg once daily depending on symptom severity.</p> <p><b>Children 2 to 5 Years:</b> The recommended initial dose of ZYRTEC syrup 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) syrup or one 5 mg chewable tablet once daily, or as ½ teaspoon (2.5 mg) given every 12 hours.</p>
<b>Applicant:</b>	Pfizer, Inc.
<b>Clinical Division:</b>	DPADP (HFD-570)
<b>Submission Dates:</b>	May 15, 2003; September 19, 2003; October 31, 2003
<b>Reviewer:</b>	Sandra Suarez-Sharp, Ph.D.
<b>Team Leader:</b>	Emmanuel O. Fadiran, Ph. D.

---

APPEARS THIS WAY  
ON ORIGINAL

## I. TABLE OF CONTENTS

<b>ITEM</b>	<b>PAGE NUMBER</b>
1. Table of Contents	2
2. Executive Summary	3
2.1. Recommendation	3
2.2. Summary of Clinical Pharmacology and Biopharmaceuticals Findings	3
3. Question-Based Review	6
3.1 General Attributes	6
3.2 General Clinical Pharmacology	9
3.3 Extrinsic Factors	13
3.4 Intrinsic Factors	13
3.5 General Biopharmaceutics	13
3.6 Analytical Section	20
4. Labeling Recommendations	20
5. Appendices	
5.1 Proposed package insert	21
5.2 Individual Study Reviews	31
5.2.1 Assessment of BE without water	31
5.2.2 Assessment of BE in the presence of water	36
5.2.3 Food effect study	41
5.3 OCPB Filing/Review Form	46

APPEARS THIS WAY  
ON ORIGINAL

## 2. EXECUTIVE SUMMARY

Pfizer Inc. seeks approval for a chewable tablet formulation of cetirizine hydrochloride (HCl) for the treatment of seasonal and perennial allergic rhinitis (SAR and PAR) and chronic idiopathic urticaria (CIU) on the basis of bioequivalence with the Zyrtec commercial tablet. Cetirizine HCl, the active component of Zyrtec tablets and syrup, is an orally active and selective H<sub>1</sub>-receptor antagonist. Zyrtec tablets and syrup have been approved by the FDA for the symptomatic treatment of PAR and CIU in adults and children aged 6 months and older and for SAR in adults and children 2 years of age and older. The recommended initial dose of Zyrtec is 5 mg or 10 mg once daily for those 6 years and older, and 2.5 mg once daily for those 6 months to 5 years. The sponsor assessed the clinical pharmacology of Zyrtec chewable tablets in 7 studies, but only 3 were considered to be relevant to the NDA. The results of these studies showed that the Zyrtec chewable tablet taken with or without water is bioequivalent to the already approved Zyrtec immediate release table. The in vivo BE requirement for the 5 mg strength of Zyrtec chewable tablet was waived based on proportionally similar composition and on dissolution profiles comparison ( $f_2$  test > 50). A high-fat, high-caloric meal decreased C<sub>max</sub> by 38% and increased T<sub>max</sub> by approximately 3 hours. This change in C<sub>max</sub> and T<sub>max</sub> may not be clinically relevant; therefore the Zyrtec chewable tablets can be taken without regard to meals. There are no major clinical pharmacology and safety issues.

### 2.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/ Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed NDA 21-621 submitted on May 15, 2003. We found this NDA acceptable from a CPB standpoint provided that the sponsor agrees with the Agency's labeling recommendations. The labeling comments should be conveyed to the sponsor (see page 20).

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 21-621 : Division File

HFD-870: Malinowski, Hunt

HFD-570: Fadiran, Bosken, Chowdhury, Jackson, Suarez-Sharp

### 2.2. Summary of clinical Pharmacology and Biopharmaceutics Findings

The sponsor, Pfizer Inc. is seeking approval of Zyrtec chewable tablets for the treatment of SAR, PAR and CIU on the bases of BE studies. Cetirizine hydrochloride is approved for use as Zyrtec immediate release tablets (5 mg and 10 mg), as Zyrtec oral syrup and in a combination product with pseudoephedrine hydrochloride, Zyrtec-D, under Pfizer NDAs 19-835, 20-346 and 21-150, respectively. Cetirizine HCl, the active component of Zyrtec tablets and syrup, is an orally active and selective H<sub>1</sub>-receptor antagonist. Zyrtec tablets and syrup have been approved by the FDA for the symptomatic treatment of PAR and CIU in adults and children aged 6 months and older and for SAR in adults and children 2 years of age and older. The recommended initial

dose of Zyrtec is 5 mg or 10 mg once daily for those 6 years and older, and 2.5 mg once daily for those 6 months to 5 years.

In support of this application the sponsor submitted the results of seven safety and pharmacokinetic studies conducted in healthy male and female volunteers. Four of these studies were not reviewed because they were conducted with experimental formulations of the product. The intention of the PK studies were to determine the in vivo BE of Zyrtec Chewable Tablet compared to an already approved reference product (Zyrtec Immediate Release Tablets), and to assess the effect of food on the BA of cetirizine HCl delivered from the chewable tablet. Dissolution data was also provided to support the dissolution method and specification proposed for this product.

### BE Assessment

Two single dose, two-way crossover studies were conducted to show that Zyrtec chewable tablets taken with or without water are bioequivalent to Zyrtec immediate release tablets. The 90% CI for cetirizine HCl were within BE specifications (see Tables 1 and 2).

**Table 1.** Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of cetirizine following single administration of the treatments (chewable tablets taken without water).

Comparison	PK parameter	Point estimates	90% confidence intervals
		Sponsor's findings	Sponsor's findings
Chewable WITHOUT water/ Commercial with water	Cmax	97.3	94.3-100.4
	AUCt	98.2	95.3-101.2
	AUCinf	98.3	95.4-101.3

**Table 2.** Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of cetirizine following single administration of the treatments (chewable tablets taken with water)

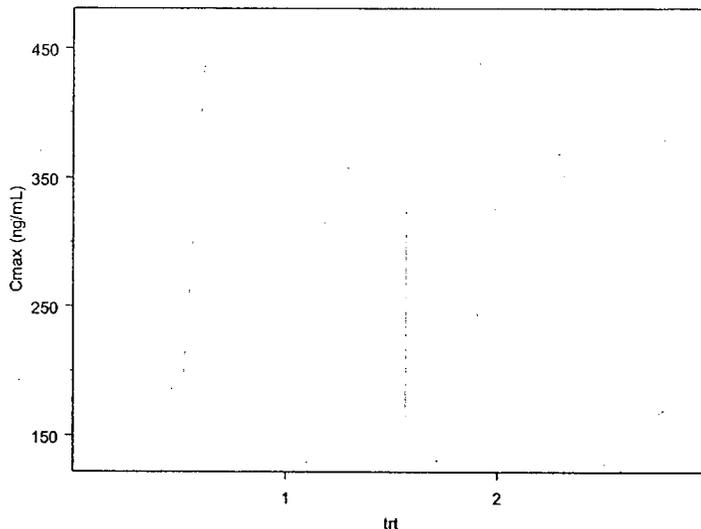
Comparison	PK parameter	Point estimates	90% confidence intervals
		Sponsor's findings	Sponsor's findings
Chewable WITH water/ Commercial with water	Cmax	101.2	95.4-107.5
	AUCt	93.2	89.4-97.1
	AUCinf	93	89.3-96.9

### Effect of Food

The effect of food on the BA of cetirizine HCl was assessed in a single, 2-way crossover study comparing the Zyrtec chewable tablet with and without food. This study showed that a high-fat and high-caloric meal had no effect on the AUCinf of cetirizine, but decreased the Cmax by 37.8%. The Tmax was delayed by approximately 3 hours (see Table 3 and Figure 1). The approximately 40% decrease in the Cmax and increase in Tmax of 3 hours of Zyrtec chewable tablet when given with a high fat meal compared to fasting conditions may not be clinically relevant. Therefore, Zyrtec chewable tablet can be taken without regard to meals. It should be noted that a high-fat and high-caloric meal also decreased the cetirizine Cmax (by 25%) and delayed Tmax by 1.5 hrs for the Zyrtec immediate release tablets.

**Table 3.** Mean ( $\pm$ SD) pharmacokinetic parameters of cetirizine following single administration of the treatments

Treatment	Mean (SD) PK Parameters				
	Cmax (ng/mL)	Tmax (hr)	AUCt ( $\mu$ g*hr/mL)	AUCinf ( $\mu$ g*hr/mL)	T1/2 (hr)
Chewable tablet under fasting	333 (50)	0.82 (0.44)	2.65 (0.4)	2.75 (0.4)	8.6 (3.3)
Chewable tablet under fed	208 (28)	3.6 (0.6)	2.38 (0.4)	2.48 (0.4)	8.3 (1.7)



**Figure 1.** Individual cetirizine Cmax values following single administration of the treatments: TRT 1:10 mg Zyrtec chewable tablet under fast conditions; TRT 2: 10 mg Zyrtec chewable tablet under fed conditions.

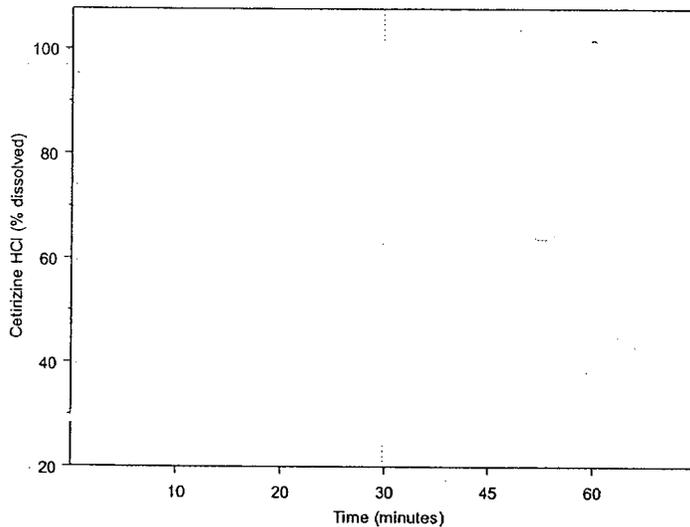
**Dissolution Method and Specifications**

Pfizer has proposed a dissolution method that was developed based on the Zyrtec immediate release tablet dissolution method, described as follows:

Strength	5- and 10 mg
Apparatus	USP apparatus 2 (paddle)
Medium	Water
Volume	900 mL
Speed of Rotation	_____
Sampling Time	30 min
Brief description of analytical method	_____ HPLC with _____ at _____
Proposed dissolution specifications	Q= _____ in 30 min

The proposed dissolution acceptance criterion for the cetirizine HCl chewable tablets is identical to that for the Zyrtec immediate release tablet, *i.e.*, a Q of \_\_\_\_\_ in 30 minutes. The acceptance criteria is supported by dissolution profiles performed on the batches used in the pivotal BE studies (see Figure 2)

**APPEARS THIS WAY  
ON ORIGINAL**



**Figure 2.** Individual dissolution profiles of cetirizine HCl chewable tablets 10 mg (lot 11629-G1, used in pivotal BE studies) in water (n=12).

The sponsor also included a comparison of the dissolution profiles of the 10 mg cetirizine hydrochloride chewable tablets used in the BE study and a batch of the 5 mg cetirizine hydrochloride chewable tablets. The dissolution profiles for the 10 mg chewable tablets from batch 11629 used for the BE studies were compared to those for the 5 mg tablet batch 11631 using the similarity factor,  $f_2$ . The  $f_2$  value calculated by this reviewer was — using dissolution points at 10, 20 and 30 min. The sponsor reported an  $f_2$  value of —, however this value was calculated considering only 2 dissolution points (at 20 and 30 min). Therefore, the in vivo BE requirement for the 5 mg strength of Zyrtec chewable tablet was waived based on proportionally similar composition and on dissolution profiles comparisons ( $f_2$  test > 50)..

Additionally, Pfizer compared the dissolution profiles of the primary stability batches (manufactured at UCB, Belgium) to those of tablets made at commercial scale at the proposed commercial manufacturing site —. The dissolution profiles of the 5 mg and 10 mg primary stability and commercial site/scale batches were similar; the similarity factors,  $f_2$ , were — respectively.

### 3. QUESTION BASED REVIEW

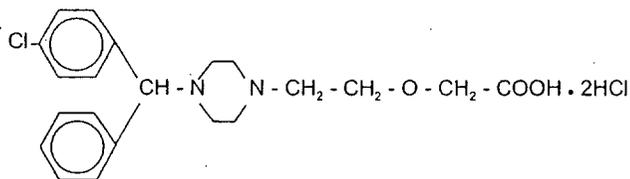
#### 3.1 General Attributes

**3.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?**

##### Drug Substance

**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. Cetirizine hydrochloride has pKa values of pK.

**Drug Product**

ZYRTEC chewable tablets are formulated as purple round tablets for oral administration and are available in 5 and 10 mg strengths. Inactive ingredients of the chewable tablets are: acesulfame potassium; artificial grape flavor; betadex; blue dye; colloidal silicon dioxide; lactose monohydrate; magnesium stearate; mannitol; microcrystalline cellulose; natural flavor; red dye. The product will be packaged in aluminum foil/foil blisters

The commercial formulation of cetirizine hydrochloride chewable tablets, 5 mg and 10 mg, are composed of two common blends, one for each layer of both strengths of the bilayer tablets. Table 3.1.1.1 provides the commercial composition of each tablet strength.

**Table 3.1.1.1.** Commercial formulation for Cetirizine HCl chewable tablets 5- and 10-mg

Ingredient	5 mg Tablet	10 mg Tablet
	FG-22707	FG-22712
	Amt/tablet (mg)	Amt/tablet (mg)
<b>Active Layer</b>		
Cetirizine Hydrochloride, Pharm	5.00	10.00
Betadex, NF		
Acesulfame Potassium, Ph.Eur.		
Colloidal Silicon Dioxide, NF		
Microcrystalline Cellulose, NF		
Artificial Grape Flavor, Food		
Sweet Flav Pwdr Nat (K)		
Lactose Monohydrate, NF		
Carmin Dye, 21 CFR 70-82		
FD&C Blue, FDA Certified		
Magnesium Stearate, NF		
Total:		
<b>Inactive Blend</b>		
Mannitol, USP		
Acesulfame Potassium, Ph.Eur.		
Artificial Grape Flavor, Food		
Sweet Flav Pwdr Nat (K)		
Carmin Dye, 21 CFR 70-82		
FD&C Blue, FDA Certified		
Magnesium Stearate, NF		
Total:	125.000	250.00

The to-be marketed formulation (commercial) was used in the pivotal PK studies. The tablet size for all the batches used in the PK studies was \_\_\_\_\_ which represents more than \_\_\_\_\_ of the commercial batch size \_\_\_\_\_.

### **3.1.2 What are the proposed therapeutic indications and dosage recommendations for Zyrtec chewable tablets?**

#### **Mechanism of Action**

Cetirizine, a human metabolite of hydroxyzine, is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H<sub>1</sub> receptors. *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.

#### **Proposed Indication**

**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.

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

ZYRTEC is available as 5 mg and 10 mg tablets, 5 mg and 10 mg chewable tablets, and 1 mg/ml syrup. ZYRTEC chewable tablets can be taken with or without water.

**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 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) syrup or one 5 mg chewable tablet 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. Syrup is recommended for children under the age of 2 years.

**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.

### 3.2 General Clinical Pharmacology

#### 3.2.1 Is the Zyrtec chewable tablet bioequivalent to the Zyrtec immediate release tablet (reference)?

Two studies were conducted to assess the BE of these two products. Study A1431018 was an open-label, two-way crossover, single dose study to assess the BE of the cetirizine chewable tablet when taken without water to the commercial Zyrtec tablet when taken with water. Healthy volunteers (24) were randomized to one of two treatment sequences as shown in the following table:

Treatment Sequence	Treatment Periods		
	Period 1	Washout*	Period 2
AB	10 mg Cetirizine HCl Commercial Zyrtec® Tablet With Water		10 mg Cetirizine HCl Chewable Tablet Without Water
BA	10 mg Cetirizine HCl Chewable Tablet Without Water		10 mg Cetirizine HCl Commercial Zyrtec® Tablet With Water

\* 7-day wash out period

The mean plasma concentration-time profiles for cetirizine following administration of the treatments are shown in Figure 3.2.1.1. The mean pharmacokinetic parameters for cetirizine following administration of the treatments are summarized in Table 3.2.1.1. The point estimates and the 90% CIs for the log-transformed C<sub>max</sub> and AUC(I) for cetirizine are presented in Table 3.2.1.2

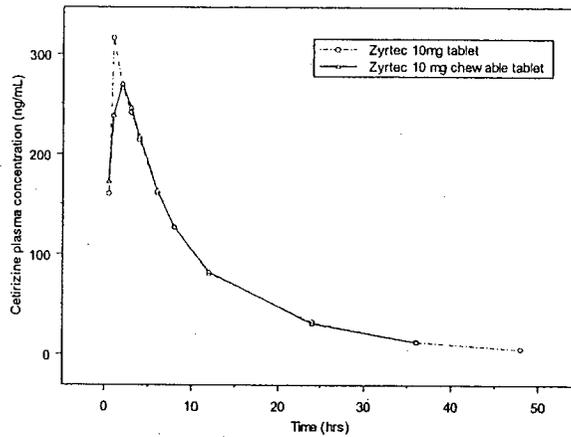


Figure 3.2.1.1. Mean cetirizine plasma concentration-time profiles following single administration TRT A:10 mg Zyrtec commercial tablet TRT B: 10 mg Zyrtec chewable tablet taken without water.

Table 3.2.1.1. Mean ( $\pm$ SD) pharmacokinetic parameters of cetirizine following single administration of the treatments

Treatment	Mean (SD) PK Parameters				
	Cmax (ng/mL)	Tmax (hr)	AUCt (ng*hr/mL)	AUCinf (ng*hr/mL)	T1/2 (hr)
Commercial tablet with water	330 (78)	1.3 (0.7)	3020 (466)	3130 (475)	9.3 (1.8)
Chewable tablet without water	321 (77)	1.6 (0.9)	2960 (346)	3060 (344)	8.9 (1.6)

Table 3.2.1.2. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of cetirizine following single administration of the treatments

Comparison	PK parameter	Point estimates	90% confidence intervals
		Sponsor's findings	Sponsor's findings
Chewable without water/ Commercial with water	Cmax	97.3	94.3-100.4
	AUCt	98.2	95.3-101.2
	AUCinf	98.3	95.4-101.3

## CONCLUSION

- The 10 mg Zyrtec chewable tablet taken without water was BE to the 10 mg Zyrtec commercial tablet taken with water. The 90% CI for the ratio of the log-transformed Cmax, AUCt and AUCinf were within the 80-125 goal post for BE.

Study A1431019 was an open-label, two-way crossover, single dose study to assess the bioequivalence of the cetirizine chewable tablet when taken WITH water to the commercial Zyrtec tablet when taken with water. Healthy volunteers (24) were randomized to one of two treatment sequences as shown in the following table:

Treatment Sequence	Treatment Periods		
	Period 1	Washout*	Period 2
AB	10 mg Cetirizine HCl Commercial Tablet With Water		10 mg Cetirizine HCl Chewable Tablet With Water
BA	10 mg Cetirizine HCl Chewable Tablet With Water		10 mg Cetirizine HCl Commercial Tablet With Water

\* 7-day wash out period

The mean plasma concentration-time profiles for cetirizine following administration of the treatments are shown in Figure 3.2.1.2. The mean pharmacokinetic parameters for cetirizine following administration of the treatments are summarized in Table 3.2.1.3. The point estimates and the 90% CIs for the log-transformed Cmax and AUC(I) for cetirizine are presented in Table 3.2.1.4.

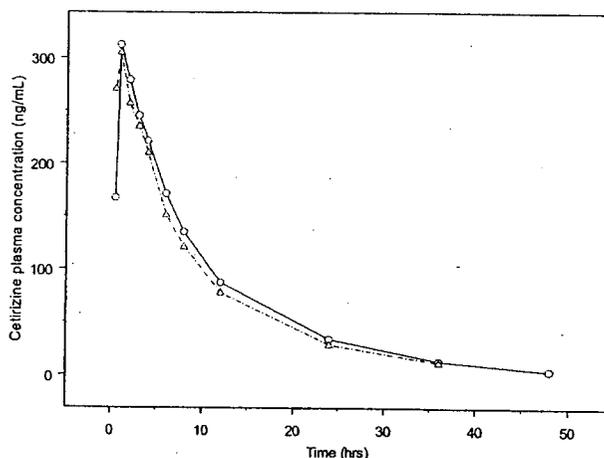


Figure 3.2.1.2. Mean cetirizine plasma concentration-time profiles following single administration of TRT A: 10 mg Zyrtec commercial tablet (circles); TRT B: 10 mg Zyrtec chewable tablet taken WITH water (triangles).

Table 3.2.1.3. Mean ( $\pm$ SD) pharmacokinetic parameters of cetirizine following single administration of the treatments

Treatment	Mean (SD) PK Parameters				
	Cmax (ng/mL)	Tmax (hr)	AUCt (ng*hr/mL)	AUCinf (ng*hr/mL)	T1/2 (hr)
Commercial tablet with water	329 (80)	1.3 (0.6)	3180 (743)	3300 (756)	9.1 (1.7)
Chewable tablet WITH water	330 (67)	1.0 (0.8)	2940 (529)	3040 (534)	9.0 (1.4)

Table 3.2.1.4. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of cetirizine following single administration of the treatments

Comparison	PK parameter	Point estimates	90% confidence intervals
		Sponsor's findings	Sponsor's findings
Chewable WITH water/ Commercial with water	Cmax	101.2	95.4-107.5
	AUCt	93.2	89.4-97.1
	AUCinf	93	89.3-96.9

## CONCLUSION

- The 10 mg Zyrtec chewable tablet taken WITH was BE to the 10 mg Zyrtec commercial tablet taken with water. The 90% CI for the ratio of the log-transformed C<sub>max</sub>, AUC<sub>t</sub> and AUC<sub>inf</sub> were within the 80-125 goal post for BE.

### 3.2.2 What are the basic PK parameters of cetirizine HCl?

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 (10mg tablets once daily for 10 days), a mean peak plasma concentration (C<sub>max</sub>) of 311ng/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 25-1000ng/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.

## 3.3 Extrinsic Factors

### 3.3.1 Does cetirizine affect the PK of other drugs and viceversa?

DDI studies for cetirizine have been previously reported in NDAs 19-835 and 20-346. 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.

### 3.4 Intrinsic Factors

#### 3.4.1 Do age, gender, race, disease status, etc. affect the PK of the drug? What dosage regimen adjustments are recommended for each of these subgroups?

The effect of intrinsic factor on the PK of cetirizine have been previously reported in NDAs 19-835 and 20-346.

**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 decrease 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.

### 3.5 General Biopharmaceutics

#### 3.5.1 Was the to-be-marketed formulation used in the Pharmacokinetic studies?

Yes. In order to develop a palatable cetirizine hydrochloride chewable tablet formulation, the \_\_\_\_\_ of the drug substance had to be \_\_\_\_\_

Formulations both with and without Betadex, NF (betacyclodextrin), \_\_\_\_\_ were evaluated. Additionally, because cetirizine hydrochloride \_\_\_\_\_ mannitol and other \_\_\_\_\_ bilayer tablets using carefully selected excipients were used to \_\_\_\_\_ while minimizing \_\_\_\_\_ cetirizine hydrochloride. By restricting the mannitol and drug substance to separate layers, the contact between the two is minimized, while the mannitol still contributes significantly to the overall \_\_\_\_\_ of the product. The commercial formulation \_\_\_\_\_ contains betadex, lactose, mannitol and flavorants/enhancers to produce a product that is \_\_\_\_\_ children (see Table 3.1.1.1).

Betacyclodextrin (Betadex, NF) (BCD) is included in the formulation of Zyrtec chewable tablets \_\_\_\_\_ in a molar ratio of \_\_\_\_\_. Each zyrtec chewable tablet (10 mg strength) contains \_\_\_\_\_ mg of BCD. In aqueous solution, betadex's molecular geometry allows it to confine part of the cetirizine molecule in its cavity, thereby imparting \_\_\_\_\_ properties. In solution (e.g. saliva), cetirizine and betadex form a weak \_\_\_\_\_ complex that fully dissociates upon dilution in the gastric fluid and does not affect performance (such as BA). However, complexation between betadex and cetirizine does not occur in dry blends containing \_\_\_\_\_ of cetirizine and up to \_\_\_\_\_ of betadex.

Published articles have shown the potential for BCD to interact with certain poor water soluble drugs, such as some vitamins. It is also known that not all drugs interact with BCD and the degree of interaction depends on several factors, such as the size of the molecule, its physicochemical characteristics, and the amount of BCD in the formulation. Such an interaction may result in a potential change in the bioavailability of the coadministered drug. \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_. However, this is not the case for cetirizine in the chewable tablet, since the purpose of BCD \_\_\_\_\_

Up to date, the Agency does not have sufficient information on the maximum amount of BCD allowed in a formulation, so that no formulation-formulation interactions are present. \_\_\_\_\_ was turned down because of potential concerns related to interaction. The sponsor has not considered the issue about interaction of Zyrtec chewable tablet with other formulations. For this reason, the following comment was sent to the sponsor at NDA filing:

- Information from published literature has shown that the coadministration of formulations containing betacyclodextrins (BCD) with some oral formulations may change the oral BA of the coadministered drug (drug in formulation not containing BCD). Please provide information related to this issue with Zyrtec chewable tablets.

On October 31, 2003 the sponsor sent the following response to the above request: *Due to the small quantity of BCD ingested with a single cetirizine hydrochloride chewable tablet, an impact on other medications taken in close proximity is unlikely. Therefore, the use of cetirizine hydrochloride chewable tablet, containing BCD, is not expected to create interaction liabilities for co-administered drugs.* This reviewer agrees with this statement.

**3.5.2. What is the effect of food on the BA of cetirizine released from the Zyrtec chewable tablet formulation?**

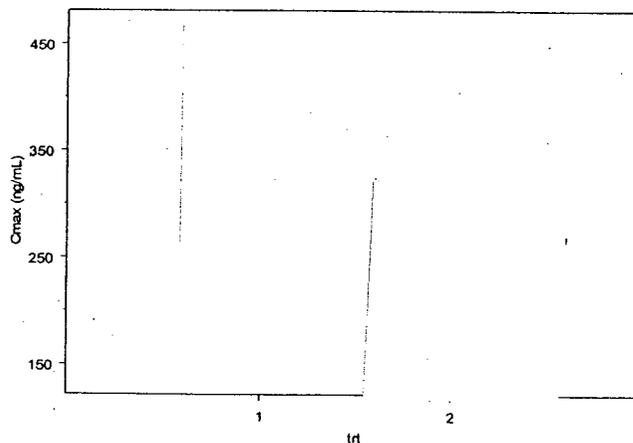
Study A1431021 was an open-label, single-dose, 2-way crossover study conducted to estimate the effect of a high-fat meal on the bioavailability of cetirizine chewable tablet following a single dose administration with water under fed and fasted conditions. Healthy volunteers (24) were randomized to receive the following 2 treatments separated by 1 week:

Treatment	Dose	Dosing Regimen	Duration of Treatment	Route
Cetirizine Chewable Tablet	10 mg	1 × 10-mg tablet/fasted state	Single Dose	Oral
Cetirizine Chewable Tablet	10 mg	1 × 10-mg tablet/fed state	Single Dose	Oral

The mean pharmacokinetic parameters for cetirizine following administration of the treatments are summarized in Table 3.5.2.1. Individual cetirizine C<sub>max</sub>, AUC<sub>t</sub> and AUC<sub>(inf)</sub> values following the administration of the treatments are shown in Figures 3.5.2.1 and 3.5.2.2, respectively. Figure 3.5.2.3 shows the individual T<sub>max</sub> values as a function of treatment. The point estimates and the 90% CIs for the log-transformed C<sub>max</sub> and AUC(I) for cetirizine are presented in Table 3.5.2.2.

**Table 3.5.2.1.** Mean (±SD) pharmacokinetic parameters of cetirizine following single administration of the treatments

Treatment	Mean (SD) PK Parameters				
	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	AUC <sub>t</sub> (µg*hr/mL)	AUC <sub>inf</sub> (µg*hr/mL)	T <sub>1/2</sub> (hr)
Chewable tablet under fasting	333 (50)	0.82 (0.44)	2.65 (0.4)	2.75 (0.4)	8.6 (3.3)
Chewable tablet under fed	208 (28)	3.6 (0.6)	2.38 (0.4)	2.48 (0.4)	8.3 (1.7)



**Figure 3.5.2.1.** Individual cetirizine C<sub>max</sub> values following single administration of the treatments: TRT 1:10 mg Zyrtec chewable tablet under fast conditions; TRT 2: 10 mg Zyrtec chewable tablet under fed conditions.

**BEST POSSIBLE COPY**

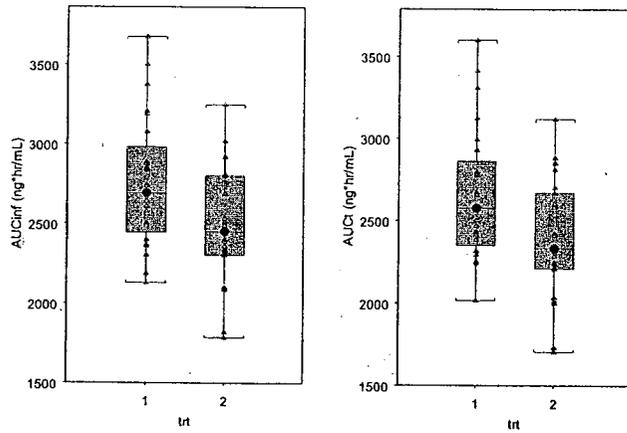


Figure 3.5.2.2. Individual cetirizine AUCinf and AUCt values following single administration of the treatments. TRT 1: 10 mg Zyrtec chewable tablet under fast conditions; TRT 2: 10 mg Zyrtec chewable tablet under fed conditions.

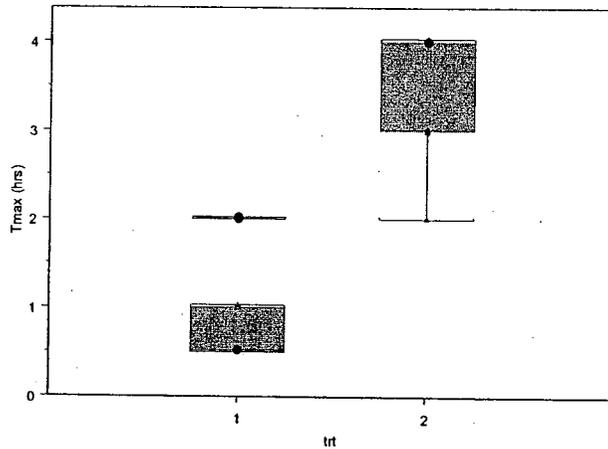


Figure 3.5.2.3. Individual cetirizine Tmax values following single administration of the treatments. TRT 1: 10 mg Zyrtec chewable tablet under fast conditions; TRT 2: 10 mg Zyrtec chewable tablet under fed conditions.

Table 3.5.2.2. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of cetirizine following single administration of the treatments

Comparison	PK parameter	Point estimates		90% confidence intervals	
		Sponsor's findings		Sponsor's findings	
Chewable under fed/ chewable under fasting	Cmax	63.1		59.8-66.6	
	AUCt	91.4		88-94.9	
	AUCinf	91.4		87.9-94.9	

### SUMMARY OF FINDINGS

- The mean AUCinf following Zyrtec chewable tablet under fed conditions was 10% lower than that under fasting conditions.
- The mean Cmax following Zyrtec chewable tablet under fed conditions was 37.8% lower than that under fasting conditions.

- The mean Tmax following Zyrtec chewable tablet under fed conditions increased 2.8 hrs compared to that under fasting conditions.
- It should be noted that food had no effect on the extent of cetirizine exposure (AUC) but Tmax was delayed by 1.7 hours and Cmax was decreased by 23% in the presence of food for Zyrtec immediate release tablets.

### CONCLUSION

- The approximately 40% decrease in the Cmax and increase in Tmax of 3 hours of Zyrtec chewable tablet when given with a high fat meal compared to fasting conditions may not be clinically relevant. Therefore, Zyrtec chewable table can be taken without regard of meals.

### 3.5.3 Are the method and dissolution specifications supported by the data provided by the sponsor?

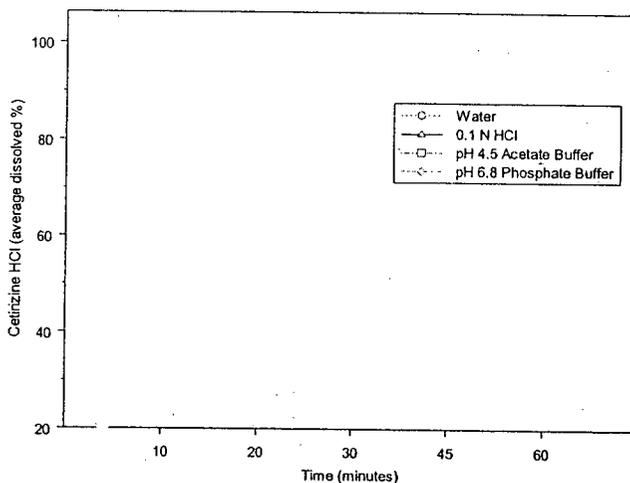
For the cetirizine HCl chewable tablets, Pfizer has proposed a dissolution method that was developed based on the Zyrtec immediate release tablet dissolution method, described as follows:

Dosage Form	Tablet
Strength	5 mg, 10 mg
Apparatus	USP Apparatus 2
Medium	Water
Volume	900 mL
Speed of Rotation	
Sampling Time	
Brief Description of Dissolution Analytical Method	high performance liquid chromatography with
Proposed Dissolution Specification	Q =

### Selection of Medium

Dissolution profiles were obtained for one 10 mg lot of the cetirizine hydrochloride chewable tablets (lot 11629, n=12) in four different media spanning a pH range of approximately

The dissolution profiles of the tablets were comparable in water, (Figure 3.5.3.1). Water was selected as the medium since acetate (pH 4.5) and phosphate (pH 6.8) buffers and 0.1N HCl were no more discriminating than water in measuring the dissolution profiles of cetirizine hydrochloride chewable tablets. Furthermore, the proposed method is consistent with the approved method for Zyrtec® IR tablets.



**Figure 3.5.3.1.** Average dissolution profiles of cetirizine HCl chewable tablets 10 mg (lot 11629-G1, used in pivotal BE studies) in different media (n=12).

### Selection of Apparatus

The dissolution profile for one lot of cetirizine HCl 10 mg chewable tablets (lot 11629) was determined in water utilizing both USP Apparatus 1 and USP Apparatus 2 at 100 RPM. The data show (not shown in here) no discernable difference between the dissolution profiles obtained with Apparatus 1 and Apparatus 2. Therefore, Apparatus 2 was chosen to be consistent with the methodology currently utilized for the testing of Zyrtec® IR tablets.

### Selection of Agitation (Paddle Speed)

The dissolution profiles of cetirizine hydrochloride chewable tablets in water were determined using Apparatus 2 with paddles rotating at 100 RPM and 200 RPM. The profiles demonstrate that a milder agitation of 100 RPM would be more discriminatory and is appropriate for dissolution testing of the chewable tablets.

### Specification

The proposed dissolution acceptance criterion for the cetirizine HCl chewable tablets is identical to that for the Zyrtec immediate release tablet, *i.e.*, a Q of 80% in 30 minutes. The acceptance criteria is supported by dissolution profiles performed in the batches used in the pivotal BE studies (see Figure 3. 5.3.2)

**APPEARS THIS WAY  
ON ORIGINAL**

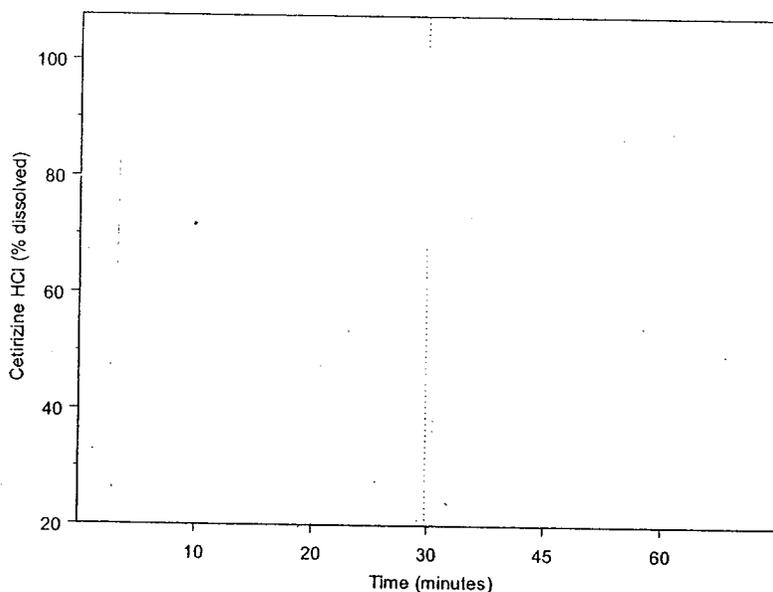


Figure 3.5.3.2. Individual dissolution profiles of cetirizine HCl chewable tablets 10 mg (lot 11629-G1, used in pivotal BE studies) in water (n=12).

### 3.5.4 What data support a waiver of in vivo BE data for the 5 mg strength and change in manufacturing site?

The sponsor is seeking approval of two strengths of Zyrtec chewable tablets: 5- ad 10 mg. In vivo BE studies showed that the 10 mg chewable tablet taken with or without water was bioequivalent to Zyrtec immediate release tablet.

The sponsor included a comparison of the dissolution profiles of the 10 mg cetirizine hydrochloride chewable tablets used in the BE study and a batch of the 5 mg cetirizine hydrochloride chewable tablets. The dissolution profiles for the 10 mg chewable tablets from batch 11629 used for the BE studies were compared to those for the 5 mg tablet batch 11631 using the similarity factor,  $f_2$ . The  $f_2$  value calculated by this reviewer was \_\_\_\_\_ using dissolution points at 10, 20 and 30 min. The sponsor reported an  $f_2$  value of \_\_\_\_\_ however this value was calculated considering only 2 dissolution points (\_\_\_\_\_ 30 min). Therefore, the in vivo BE requirement for the Zyrtec chewable tablet 5 mg strength was waived based on proportionally similar composition of the 5 mg tablet to that for the 10 mg tablet (see Table 3.1.1.1) and on dissolution profiles comparison ( $f_2 > 50$ ).

Additionally, Pfizer compared the dissolution profiles of the primary stability batches (manufactured at UCB, Belgium) to those of tablets made at commercial scale at the proposed commercial manufacturing site (\_\_\_\_\_). The dissolution profiles of the 5 mg and 10 mg primary stability and commercial site/scale batches were similar; the similarity factors,  $f_2$ , were \_\_\_\_\_ respectively.

### 3.6 Analytical Methodology

#### 3.6.1 Was the suitability of the analytical method supported by the submitted information?

Plasma concentrations of cetirizine HCl in the pharmacokinetic studies included in this review were determined using a HPLC with a lower limit of quantification (LLQ) of \_\_\_\_\_. The accuracy and inter-day precision were acceptable for all the studies (\_\_\_\_\_ Bias or %CV) for in-study validation information. Information regarding % of recovery was also provided. Table below summarizes the findings for the validation method used in the pivotal BE study.

**Table 3.6.1.1.** Assay performance (Pre-study validation) for Cetirizine

	Cetirizine
Linearity	Satisfactory: Standard curve range from _____
Accuracy	Satisfactory: %: _____
Inter-day Precision	Satisfactory: %CV: _____
Specificity	Satisfactory: sample chromatograms submitted

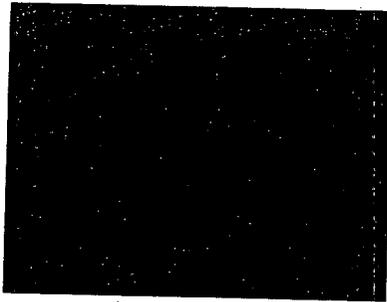
#### 4. LABELING COMMENTS

The following underlined changes (in red) are recommended for the Clinical Pharmacology Section of the label:

**Absorption:** Cetirizine was rapidly absorbed with a time to maximum concentration (Tmax) of approximately 1 hour following oral administration of tablets, chewable tablets or syrup in adults. Comparable bioavailability was found between the tablet and syrup dosage forms. Comparable bioavailability was also found between the Zyrtec tablet and the Zyrtec chewable tablet taken with or without water. When healthy volunteers were administered multiple doses of cetirizine (10 mg tablets once daily for 10 days), a mean peak plasma concentration (Cmax) 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 Tmax was delayed by 1.7 and \_\_\_\_\_ hours and Cmax was decreased by 23% and \_\_\_\_\_ in the presence of food; \_\_\_\_\_

APPEARS THIS WAY  
ON ORIGINAL

WITHHOLD 10 PAGE(S)



## 5.2 INDIVIDUAL STUDY REVIEWS

"Phase 1, Open, Randomized, 2-way Crossover Pivotal Bioequivalence Study Comparing the Cetirizine Chewable Tablet Taken Without Water to the Commercial Zyrtec® (Cetirizine) Tablet Taken With Water in Healthy Subjects "

**Protocol:** A1431018  
**Study Dates:** 03 June 2002 to 21 June 2002  
**Phase:** I  
**Investigator(s):** Candace R. Bramson, M.D.

### Objectives

- To assess the bioequivalence of the cetirizine chewable tablet when taken without water to the commercial Zyrtec tablet when taken with water.
- To evaluate the safety and tolerability of the cetirizine chewable tablet in healthy subjects.

### Study Population

The demographic characteristics of the subjects enrolled in the study are described below:

	Male	All Subjects Female	Total
Number of Subjects	12	12	24
Age, years, mean $\pm$ SD (range)	34.9 $\pm$ 8.5 (23-53)	40.3 $\pm$ 8.4 (29-53)	37.6 $\pm$ 8.7 (23-53)
Weight, mean kg $\pm$ SD (range)	83.4 $\pm$ 8.9 (74.2-100.2)	64.3 $\pm$ 7.5 (51.3-80.7)	73.8 $\pm$ 12.6 (51.3-100.2)
Body Mass Index, kg/m <sup>2</sup> $\pm$ SD (range)	25.4 $\pm$ 2.2 (22.0-30.0)	23.7 $\pm$ 2.3 (21.0-28.0)	24.6 $\pm$ 2.4 (21.0-30.0)
Height, mean cm $\pm$ SD (range)	181.0 $\pm$ 7.7 (170.0-196.0)	164.6 $\pm$ 6.5 (156.0-177.0)	172.8 $\pm$ 10.9 (156.0-196.0)

### STUDY DESIGN, TREATMENT AND ADMINISTRATION

This was a randomized, open-label, two-way crossover, single dose study. All subjects received the 10 mg cetirizine hydrochloride (HCl) chewable tablet without water and the 10 mg cetirizine HCl commercial Zyrtec tablet with water according to a randomization schedule. At least a 7-day washout period was required between doses. Subjects were randomized to one of two treatment sequences as shown in the following table:

APPEARS THIS WAY  
ON ORIGINAL

**BEST POSSIBLE COPY**

Treatment Sequence	Treatment Periods		
	Period 1	Washout*	Period 2
AB	10 mg Cetirizine HCl Commercial Zyrtec® Tablet With Water		10 mg Cetirizine HCl Chewable Tablet Without Water
BA	10 mg Cetirizine HCl Chewable Tablet Without Water		10 mg Cetirizine HCl Commercial Zyrtec® Tablet With Water

APPEARS THIS WAY  
ON ORIGINAL

BEST POSSIBLE COPY

## FORMULATION

The following batch numbers of the drug treatments were used in this study:

	10 mg Cetirizine HCl	
	Commercial Tablet With Water	Chewable Tablet Without Water
Formulation	Tablet	Chewable Tablet (UCB Bilayer Formulation)
Dose Unit	10 mg	10 mg
Duration	Single Dose	Single Dose
Lot Number	0599K01A-G1	11629-G1
FID Number	Pfizer - USA	UCB PHARMA; 10910-DEB

## PHARMACOKINETIC MEASUREMENTS

Blood samples for cetirizine determination were collected at the following times: 0 (just prior to dosing), 0.5, 1, 2, 3, 4 (prior to meal), 6, 8, 12, 24, 36, and 48 hours after drug administration.

### Analytical Method

Plasma samples were assayed for cetirizine HCl using a HPLC/UV (lower limit of quantification, LLQ= \_\_\_\_\_).

## SAFETY MEASUREMENTS

Safety was evaluated in this study by monitoring of adverse events, laboratory safety data, physical examinations, and vital sign evaluations.

## DATA ANALYSIS

### Pharmacokinetic Data Analysis

Pharmacokinetic parameters were determined using the non-compartmental pharmacokinetic analysis.

### Statistical Analysis

For the comparison of treatment mean differences, natural log-transformed AUC and C<sub>max</sub> and untransformed (or raw) T<sub>max</sub> and half-life were analyzed using a mixed effects model containing fixed effects for sequence, period, and treatment and random effects for subject (within sequence). Compound symmetry was assumed and Restricted Maximum Likelihood Estimates (REML) were utilized. Estimates of the adjusted treatment mean differences (LSMeans), as well as their associated standard errors, were calculated, followed by the construction of the 90% confidence intervals around the differences. For AUC<sub>0-inf</sub>, AUC<sub>0-t</sub>, and C<sub>max</sub>, the anti-log (exponent) of the differences and confidence limits were taken to estimate the ratios between treatments and the confidence intervals of the ratios. The 10 mg cetirizine chewable tablet taken without water (test formulation) was compared to the 10 mg commercial Zyrtec® tablet taken with water (reference formulation) for AUC<sub>0-inf</sub>, AUC<sub>0-t</sub>, C<sub>max</sub> and T<sub>max</sub>.

**BEST POSSIBLE COPY**

## RESULTS

### Analytical Method

**The limit of quantitation for cetirizine:** \_\_\_\_\_

**Stability and % of Recovery:** The mean recovery of cetirizine was 66.2% and the mean recovery for the standard was 46.5%

**Freeze/Thaw of Plasma:** Not reported

**Bench Top Stability:** Not reported

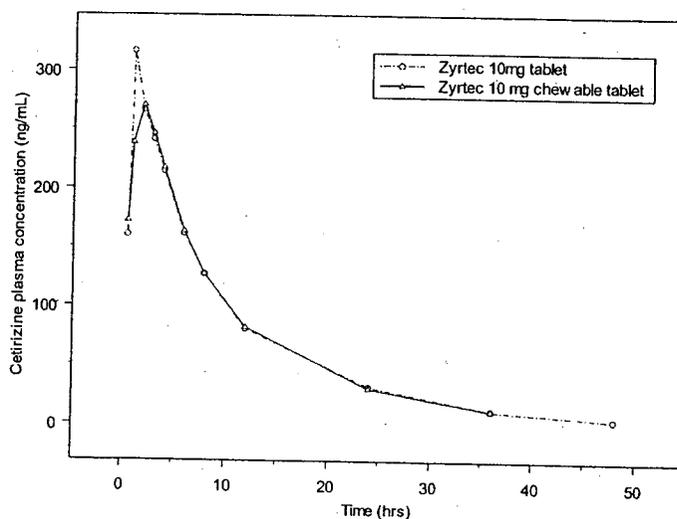
### In-Study Validation

**Table 1.** Assay performance (Pre-study validation) for Cetirizine

Cetirizine	
Linearity	Satisfactory: Standard curve range from _____
Accuracy	Satisfactory: %: _____
Inter-day Precision	Satisfactory: %CV: _____
Specificity	Satisfactory: sample chromatograms submitted

### Pharmacokinetic Results

The mean plasma concentration-time profiles for cetirizine following administration of the treatments are shown in Figure 1. The mean pharmacokinetic parameters for cetirizine following administration of the treatments are summarized in Table 2. Individual cetirizine C<sub>max</sub>, AUC<sub>t</sub> and AUC(inf) values following the administration of the treatments are shown in Figures 2 and 3, respectively.



**Figure 1.** Mean cetirizine plasma concentration-time profiles following single administration TRT A: 10 mg Zyrtec commercial tablet TRT B: 10 mg Zyrtec chewable tablet taken without water.

**Table 2.** Mean ( $\pm$ SD) pharmacokinetic parameters of cetirizine following single administration of the treatments

Treatment	Mean (SD) PK Parameters				
	Cmax (ng/mL)	Tmax (hr)	AUCt (ng*hr/mL)	AUCinf (ng*hr/mL)	T1/2 (hr)
Commercial tablet with water	330 (78)	1.3 (0.7)	3020 (466)	3130 (475)	9.3 (1.8)
Chewable tablet without water	321 (77)	1.6 (0.9)	2960 (346)	3060 (344)	8.9 (1.6)

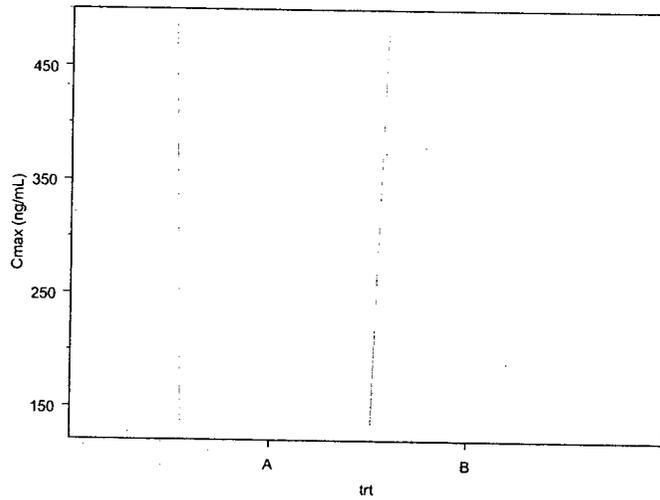


Figure 2. Individual cetirizine Cmax values following single administration of the treatments: TRT A: 10 mg Zyrtec commercial tablet TRT B: 10 mg Zyrtec chewable tablet taken without water.

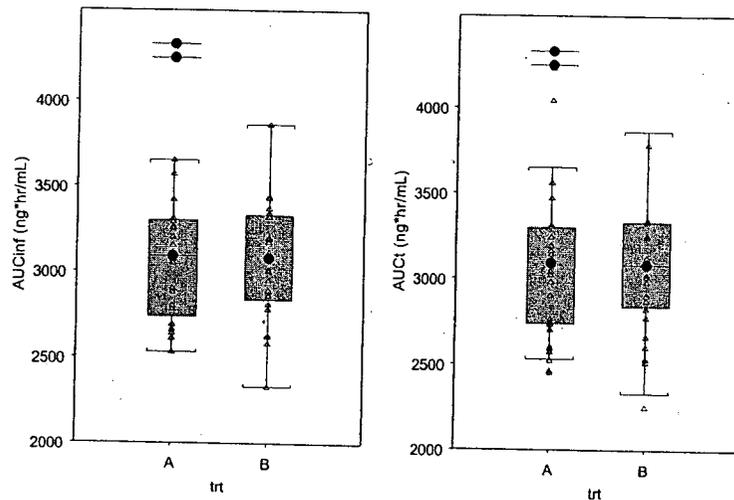


Figure 3. Individual cetirizine AUCinf and AUCt values following single administration of the treatments. TRT A: 10 mg Zyrtec commercial tablet TRT B: 10 mg Zyrtec chewable tablet taken without water.

The point estimates and the 90% CIs for the log-transformed Cmax and AUC(I) for cetirizine are presented in Table 3.

Table 3. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of

**BEST POSSIBLE COPY**

cetirizine following single administration of the treatments

Comparison	PK parameter	Point estimates	90% confidence intervals
		Sponsor's findings	Sponsor's findings
Chewable without water/ Commercial with water	Cmax	97.3	94.3-100.4
	AUCt	98.2	95.3-101.2
	AUCinf	98.3	95.4-101.3

#### CONCLUSION

- The 10 mg Zyrtec chewable tablet taken without was BE to the 10 mg Zyrtec commercial tablet taken with water. The 90% CI for the ratio of the log-transformed Cmax, AUCt and AUCinf were within the 80-125 goal post for BE.

APPEARS THIS WAY  
ON ORIGINAL

**"Phase 1, Open, 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 "**

**Protocol:** A1431019  
**Study Dates:** 26-June-2002 to 19-July-2002  
**Phase:** I  
**Investigator(s):** Candace R. Bramson, M.D.

**Objectives**

- To assess the bioequivalence of the cetirizine chewable tablet when taken WITH water to the commercial Zyrtec tablet when taken with water.
- To evaluate the safety and tolerability of the cetirizine chewable tablet in healthy subjects.

**Study Population**

This study included a total of 25 male and female healthy volunteers between 19 and 54 years of age. The demographic characteristics of the subjects enrolled in the study are described below:

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

**STUDY DESIGN, TREATMENT AND ADMINISTRATION**

This was a randomized, open-label, two-way crossover, single dose study. All subjects received the 10 mg cetirizine hydrochloride (HCl) chewable tablet WITH water and the 10 mg cetirizine HCl commercial Zyrtec tablet with water according to a randomization schedule. At least a 7-day washout period was required between doses. Subjects were randomized to one of two treatment sequences as shown in the following table:

**APPEARS THIS WAY  
ON ORIGINAL**

**BEST POSSIBLE COPY**

Treatment Sequence	Treatment Periods		
	Period 1	Washout	Period 2
AB	10 mg Cetirizine HCl Commercial Tablet With Water		10 mg Cetirizine HCl Chewable Tablet With Water
BA	10 mg Cetirizine HCl Chewable Tablet With Water		10 mg Cetirizine HCl Commercial Tablet With Water

## FORMULATION

The following batch numbers of the drug treatments were used in this study:

10 mg Cetirizine HCl		
	Commercial Tablet	Chewable Tablet
Formulation	Tablet	Chewable Tablet (UCB Bilayer Formulation)
Dose Unit	10 mg	10 mg
Lot Number	0040K02A-G1	11629-G1
FID Number	Pfizer - USA	UCB PHARMA; 10910-DEB

## PHARMACOKINETIC MEASUREMENTS

Blood samples for cetirizine determination were collected at the following times: 0 (just prior to dosing), 0.5, 1, 2, 3, 4 (prior to meal), 6, 8, 12, 24, 36, and 48 hours after drug administration.

### Analytical Method

Plasma samples were assayed for cetirizine HCl using a HPLC/UV (lower limit of quantification, LLQ= \_\_\_\_\_).

## SAFETY MEASUREMENTS

Safety was evaluated in this study by monitoring of adverse events, laboratory safety data, physical examinations, and vital sign evaluations.

## DATA ANALYSIS

### Pharmacokinetic Data Analysis

Pharmacokinetic parameters were determined using the non-compartmental pharmacokinetic analysis.

### Statistical Analysis

For the comparison of treatment mean differences, natural log-transformed AUC and C<sub>max</sub> and untransformed (or raw) T<sub>max</sub> and half-life were analyzed using a mixed effects model containing fixed effects for sequence, period, and treatment and random effects for subject (within sequence). Compound symmetry was assumed and Restricted Maximum Likelihood Estimates (REML) were utilized. Estimates of the adjusted treatment mean differences (LSMeans), as well as their associated standard errors, were calculated, followed by the

BEST POSSIBLE COPY

construction of the 90% confidence intervals around the differences. For AUC0-inf, AUC0-t, and Cmax, the anti-log (exponent) of the differences and confidence limits were taken to estimate the ratios between treatments and the confidence intervals of the ratios. The 10 mg cetirizine chewable tablet taken WITH water (test formulation) was compared to the 10 mg commercial Zyrtec® tablet taken with water (reference formulation) for AUC0-inf, AUC0-t, Cmax and Tmax.

## RESULTS

### Analytical Method

The limit of quantitation for cetirizine: \_\_\_\_\_

Stability and % of Recovery: The mean recovery of cetirizine was 66.2% and the mean recovery for the standard was 46.5%

Freeze/Thaw of Plasma: Not reported

Bench Top Stability: Not reported

### In-Study Validation

Table 1. Assay performance (Pre-study validation) for Cetirizine

	Cetirizine
Linearity	Satisfactory: Standard curve range from _____
Accuracy	Satisfactory: % _____
Inter-day Precision	Satisfactory: %CV: _____
Specificity	Satisfactory: sample chromatograms submitted

### Pharmacokinetic Results

Twenty-five subjects were screened and randomized in this 2-way crossover study. One subject (1001-0015) was discontinued from the study after receiving the 10 mg cetirizine chewable tablet due to failure to collect the subject's blood sample for cetirizine pharmacokinetics assay prior to dosing. This subject was excluded from pharmacokinetic analysis but was included in safety and assessments.

The mean plasma concentration-time profiles for cetirizine following administration of the treatments are shown in Figure 1. The mean pharmacokinetic parameters for cetirizine following administration of the treatments are summarized in Table 2. Individual cetirizine Cmax, AUCt and AUC(inf) values following the administration of the treatments are shown in Figures 2 and 3, respectively.

**APPEARS THIS WAY  
ON ORIGINAL**

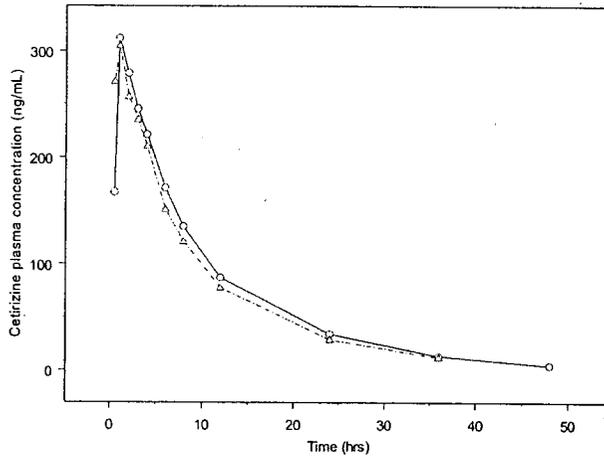


Figure 1. Mean cetirizine plasma concentration-time profiles following single administration of TRT A:10 mg Zyrtec commercial tablet (circles); TRT B: 10 mg Zyrtec chewable tablet taken WITH water (triangles).

Table 2. Mean ( $\pm$ SD) pharmacokinetic parameters of cetirizine following single administration of the treatments

Treatment	Mean (SD) PK Parameters				
	Cmax (ng/mL)	Tmax (hr)	AUCt (ng*hr/mL)	AUCinf (ng*hr/mL)	T1/2 (hr)
Commercial tablet with water	329 (80)	1.3 (0.6)	3180 (743)	3300 (756)	9.1 (1.7)
Chewable tablet WITH water	330 (67)	1.0 (0.8)	2940 (529)	3040 (534)	9.0 (1.4)

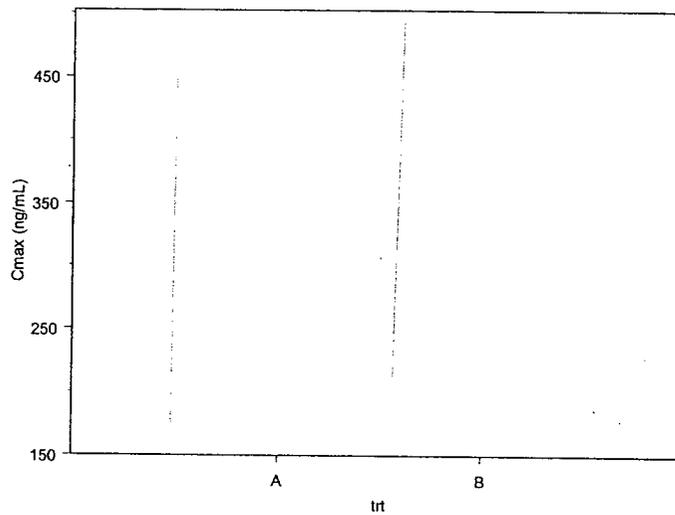
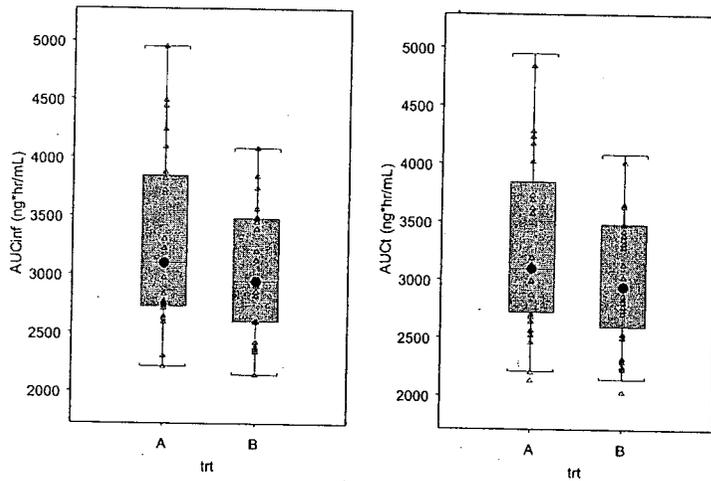


Figure 2. Individual cetirizine Cmax values following single administration of the treatments: TRT A:10 mg Zyrtec commercial tablet; TRT B: 10 mg Zyrtec chewable tablet taken WITH water.

APPEARS THIS WAY  
ON ORIGINAL



**Figure 3.** Individual cetirizine AUCinf and AUCt values following single administration of the treatments. TRT A: 10 mg Zyrtec commercial tablet; TRT B: 10 mg Zyrtec chewable tablet taken WITH water.

The point estimates and the 90% CIs for the log-transformed Cmax and AUC(I) for cetirizine are presented in Table 3.

**Table 3.** Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of cetirizine following single administration of the treatments

Comparison	PK parameter	Point estimates	90% confidence intervals
		Sponsor's findings	Sponsor's findings
Chewable WITH water/ Commercial with water	Cmax	101.2	95.4-107.5
	AUCt	93.2	89.4-97.1
	AUCinf	93	89.3-96.9

**CONCLUSION**

- The 10 mg Zyrtec chewable tablet taken WITH was BE to the 10 mg Zyrtec commercial tablet taken with water. The 90% CI for the ratio of the log-transformed Cmax, AUCt and AUCinf were within the 80-125 goal post for BE.

**APPEARS THIS WAY  
ON ORIGINAL**

**“A Comparative Bioavailability Study of Cetirizine Chewable Tablet Following a Single Dose Under Fed and Fasted Conditions”**

**Protocol:** A1431021  
**Study Dates:** 29 Apr 2003 to 16 May 2003  
**Phase:** I  
**Investigator(s):** Candace R. Bramson, M.D.

**Objectives**

- To estimate the effect of a high-fat meal on the bioavailability of cetirizine chewable tablet following a single dose administration with water under fed and fasted conditions.

**Study Population**

Twenty-four healthy subjects (12 men and 12 women), ranging in age from 18 to 51 years (mean 35.3 years) and ranging in weight from 54.3 to 99.1 kg (mean 76.1 kg) entered the study. The demographic characteristics of the subjects enrolled in the study are described below:

Subject Characteristic	Total Population	
	(N = 24)	Percentage or Statistic
<b>Sex</b>		
Male	12	50.0
Female	12	50.0
<b>Race</b>		
White, Non-Hispanic	18	75.0
Black, Non-Hispanic	4	16.7
Hispanic (White or Black)	2	8.3
Asian or Pacific Islander	0	0.0
American Indian or Alaskan Native	0	0.0
Other	0	0.0
<b>Age at Day 1 (Years)</b>		
Mean		35.3
Standard Deviation		10.3
Median		34.6
Min-Max		18-51
<b>Screening Weight (kg)</b>		
Mean		76.1
Standard Deviation		11.8
Median		76.85
Min-Max		54.3-99.1

**STUDY DESIGN, TREATMENT AND ADMINISTRATION**

This was a randomized, open-label, single-dose, 2-way crossover bioavailability/food effect study of cetirizine hydrochloride chewable tablets conducted in healthy subjects. Each of the 24 subjects were to receive the following 2 treatments separated by 1 week as follows:

Treatment	Dose	Dosing Regimen	Duration of Treatment	Route
Cetirizine Chewable Tablet	10 mg	1 × 10-mg tablet/fasted state	Single Dose	Oral
Cetirizine Chewable Tablet	10 mg	1 × 10-mg tablet/fed state	Single Dose	Oral

Subjects under fasting condition continued fasting for at least 4 hours after administration of 10 mg cetirizine chewable tablet with 240 mL of water. Subjects under fed condition

**BEST POSSIBLE COPY**

consumed the standardized meal completely over 30 minutes and the 10 mg cetirizine chewable tablet with 240 mL of water was administered immediately after the meal. The standardized meal consisted of 2 eggs fried in butter, 2 strips of bacon, 4 oz of hash brown potatoes, 2 slices of toast with 2 pats of butter, and 8 oz of whole milk.

#### FORMULATION

The following batch numbers of the drug treatments were used in this study:

Treatment	Strength	Lot	Formulation
Cetirizine	10 mg chewable tablet (UCB Pharma)	11629-G1	10910-DEB

#### PHARMACOKINETIC MEASUREMENTS

Blood samples for cetirizine determination were collected at the following times: 0 (just prior to dosing), 0.5, 1, 2, 3, 4 (prior to meal), 6, 8, 12, 24, 36, and 48 hours after drug administration.

#### Analytical Method

Plasma samples were assayed for cetirizine HCl using a HPLC/UV (lower limit of quantification, LLQ= ~~0.1~~).

#### SAFETY MEASUREMENTS

Safety was evaluated in this study by monitoring of adverse events, laboratory safety data, physical examinations, and vital sign evaluations.

#### DATA ANALYSIS

##### Pharmacokinetic Data Analysis

Pharmacokinetic parameters were determined using the non-compartmental pharmacokinetic analysis using WinNonlin Pro 2.1

##### Statistical Analysis

Bioavailability of cetirizine chewable tablets following administration with food relative to fasting was assessed by comparison of cetirizine pharmacokinetic parameter values. Parameter values were evaluated by analysis of variance (ANOVA) using a model incorporating sequence, subject within sequence, period, and treatment effects. Results of ANOVA were used to calculate 90% confidence intervals for the treatment ratios (test/reference) of least-squares mean parameter values. Absence of a food effect would be concluded if the 90% confidence intervals for the ratios for C<sub>max</sub> and AUC, based on log transformation, both lie within the 80% to 125% range. Secondary parameter value comparisons were also conducted.

**APPEARS THIS WAY  
ON ORIGINAL**

## RESULTS

### Analytical Method

The limit of quantitation for cetirizine: \_\_\_\_\_

**Stability and % of Recovery:** The mean recovery of cetirizine was 66.2% and the mean recovery for the standard was 46.5%

**Freeze/Thaw of Plasma:** Not reported

**Bench Top Stability:** Not reported

### In-Study Validation

Table 1. Assay performance (Pre-study validation) for Cetirizine

Cetirizine	
Linearity	Satisfactory: Standard curve range from 1' _____
Accuracy	Satisfactory: %bias: +1' _____
Inter-day Precision	Satisfactory: %CV1.1 at 1' _____
Specificity	Satisfactory: sample chromatograms submitted

### Pharmacokinetic Results

Twenty-four subjects entered and 23 completed the study. One subject (10011017) withdrew on Day 3 due to personal reasons. He received a single dose of 10 mg cetirizine chewable tablet, fasted on Day 1.

The mean plasma concentration-time profiles for cetirizine following administration of the treatments are shown in Figure 1. The mean pharmacokinetic parameters for cetirizine following administration of the treatments are summarized in Table 2. Individual cetirizine C<sub>max</sub>, AUC<sub>t</sub> and AUC<sub>(inf)</sub> values following the administration of the treatments are shown in Figures 2 and 3, respectively. Figure 3 shows the individual T<sub>max</sub> values as a function of treatment.

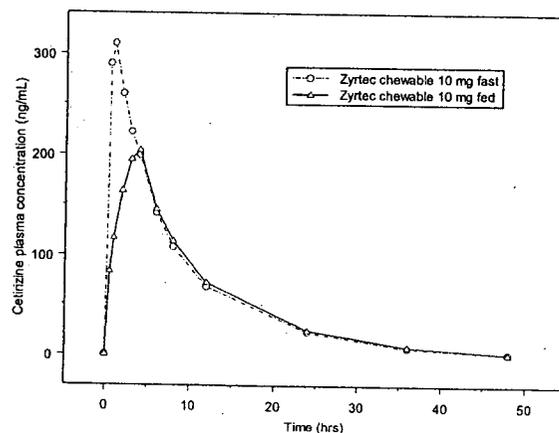


Figure 1. Mean cetirizine plasma concentration-time profiles following single administration of zyrtec chewable tablet under fed and fast conditions.

Table 2. Mean ( $\pm$ SD) pharmacokinetic parameters of cetirizine following single administration of the treatments

Treatment	Mean (SD) PK Parameters				
	Cmax (ng/mL)	Tmax (hr)	AUCt ( $\mu$ g*hr/mL)	AUCinf ( $\mu$ g*hr/mL)	T1/2 (hr)
Chewable tablet under fasting	333 (50)	0.82 (0.44)	2.65 (0.4)	2.75 (0.4)	8.6 (3.3)
Chewable tablet under fed	208 (28)	3.6 (0.6)	2.38 (0.4)	2.48 (0.4)	8.3 (1.7)

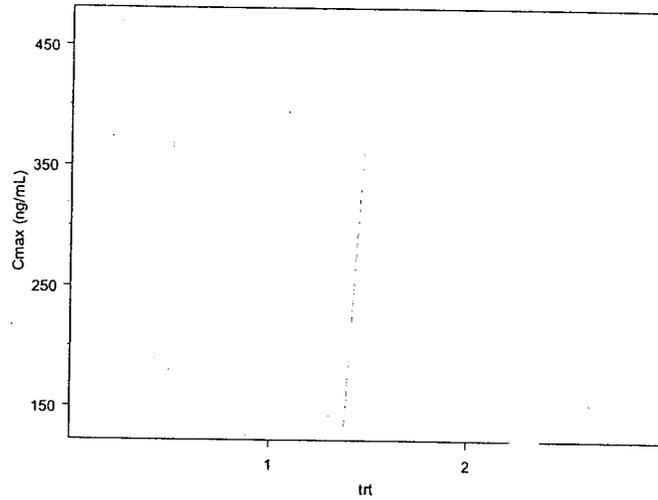


Figure 2. Individual cetirizine Cmax values following single administration of the treatments: TRT 1:10 mg Zyrtec chewable tablet under fast conditions; TRT 2: 10 mg Zyrtec chewable tablet under fed conditions.

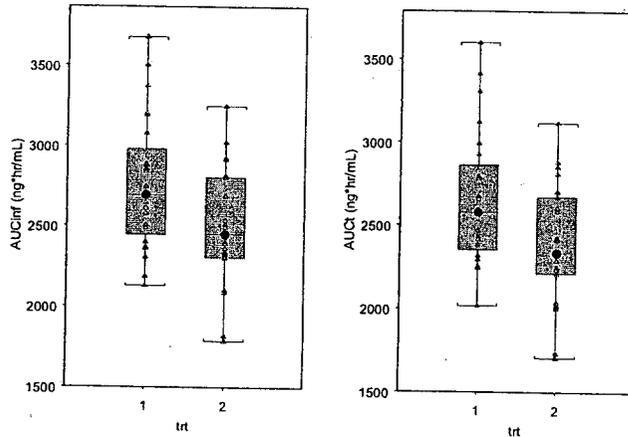
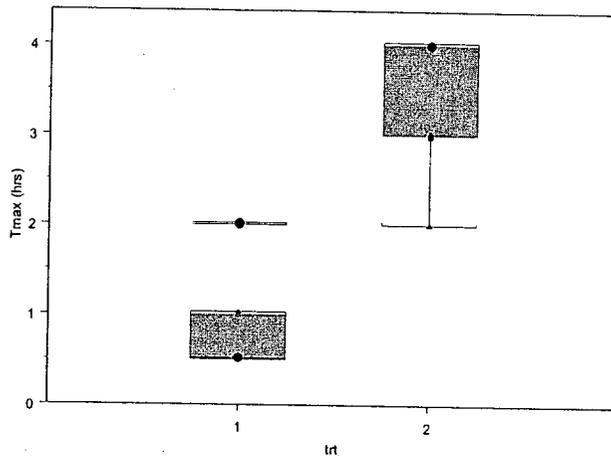


Figure 3. Individual cetirizine AUCinf and AUCt values following single administration of the treatments. TRT 1:10 mg Zyrtec chewable tablet under fast conditions; TRT 2: 10 mg Zyrtec chewable tablet under fed conditions.

APPEARS THIS WAY  
ON ORIGINAL



**Figure 4.** Individual cetirizine Tmax values following single administration of the treatments. TRT 1: 10 mg Zyrtec chewable tablet under fast conditions; TRT 2: 10 mg Zyrtec chewable tablet under fed conditions.

The point estimates and the 90% CIs for the log-transformed Cmax and AUC(I) for cetirizine are presented in Table 3.

**Table 3.** Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of cetirizine following single administration of the treatments

Comparison	PK parameter	Point estimates	90% confidence intervals
		Sponsor's findings	Sponsor's findings
Chewable under fed/ chewable under fasting	Cmax	63.1	59.8-66.6
	AUCt	91.4	88-94.9
	AUCinf	91.4	87.9-94.9

### CONCLUSION

- The mean AUCinf following Zyrtec chewable tablet under fed conditions was 10% lower than that under fasting conditions.
- The mean Cmax following Zyrtec chewable tablet under fed conditions was 37.8% lower than that under fasting conditions.
- The mean Tmax following Zyrtec chewable tablet under fed conditions increased 2.8 hrs compared to that under fasting conditions.
- The approximately 40% decrease in the Cmax and increase in Tmax of 3 hours of Zyrtec chewable tablet when given with a high fat meal compared to fasting conditions may not be clinically relevant. Therefore, Zyrtec chewable table can be taken without regard of meals.

**APPEARS THIS WAY  
ON ORIGINAL**

## Office of Clinical Pharmacology and Biopharmaceutics

### New Drug Application Filing and Review Form

#### General Information About the Submission

	Information		Information
NDA Number	21-621	Brand Name	Zyrtec Chewable Tablet
OCPB Division (I, II, III)	II	Generic Name	Cetirizine Hydrochloride
Medical Division	DPADP	Drug Class	Antihistamine
OCPB Reviewer	Sandra Suarez-Sharp	Indication(s)	Treatment of SAR, PAR CU
OCPB Team Leader	Emmanuel Fadiran	Dosage Form	Chewable Tablet
PM Reviewer		Dosing Regimen	Adult and children 12 years and older: 5 or 10mg per day depending on symptom severity. Most patients in clinical trials started at 10mg. Children 6 to 11 Years: 5 or 10 mg once daily depending on symptom severity. Children 2 to 5 Years: 2.5 mg (1/2 teaspoon) once daily. The dosage in this age group can be increased to a maximum dose of 5mg per day given as 1 teaspoon (5mg) syrup or one 5mg chewable tablet once daily, or as 1/2teaspoon (2.5mg) given every 12hours.
Date of Submission	May 5, 2003	Route of Administration	Oral
Estimated Due Date of OCPB Review	December, 2003	Sponsor	Pfizer
PDUFA Due Date	March 5, 2004	Priority Classification	Standard
Division Due Date	February, 2004		

#### 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	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<b>Healthy Volunteers-</b>				
single dose:				
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				

renal impairment:				
hepatic impairment:				
<b>PD:</b>				
Phase 2:				
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:	x	6	2	
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>	X	1	1	
<b>Dissolution:</b>				
<b>(IVIVC):</b>				
Bio-wavier request based on BCS				
BCS class				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		6	3	
<b>Filability and QBR comments</b>				
	"X" if yes	<b>Comments</b>		
Application filable ?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?	X	Comments have been sent to firm (or attachment included). FDA letter date if applicable. • Information from published literature has shown that the coadministration of formulations containing betacyclodextrins (BCD) with some oral formulations may change the oral BA of the coadministered drug (drug in formulation not containing BCD). Please provide information related to this issue with Zyrtec chewable tablets.		
<b>QBR questions (key issues to be considered)</b>	1. Is zyrtec chewable tablet bioequivalent to the tablet formulation in the presence and absence of water? 2. Are the proposed dissolution methods and specifications supported by the submitted information?			
<b>Other comments or information not included above</b>				
<b>Primary reviewer Signature and Date</b>				
<b>Secondary reviewer Signature and Date</b>				

CC: NDA 21-585, HFD-870 (Electronic Entry or Lee), HFD-570 (Jackson), HFD-870 (Fadiran, ,Hunt, Malinowski)), CDR (B. Murphy)

**APPEARS THIS WAY  
ON ORIGINAL**

**CPB INFORMATION CONTENT IN SUBMITTED NDA**

Study Title/Description	Tabular listing/PK summary	Analytical method	PK parameters (means and individual values)	Statistical analysis
A1431018 (with water)	√	√	√	√
A1431019 (without water)	√	√	√	√
A1431016	√	√	√	√
A1431014	√	√	√	√
A1431007	√	√	√	√
UCB-A00332	√	√	√	√

**CONCLUSION:** Submission is filable.

**COMMENTS TO SPONSOR:**

- Information from published literature has shown that the coadministration of formulations containing betacyclodextrins (BCD) with some oral formulations may change the oral BA of the coadministered drug (drug in formulation not containing BCD). Please provide information related to this issue with Zyrtec chewable tablets.

**APPEARS THIS WAY  
ON ORIGINAL**

-----  
**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  
12/18/03 11:10:12 AM  
BIOPHARMACEUTICS

Emmanuel Fadiran  
12/18/03 11:50:11 AM  
BIOPHARMACEUTICS  
I concur

APPEARS THIS WAY  
ON ORIGINAL

## Clinical Pharmacology and Biopharmaceutics Review

---

### CETIRIZINE HYDROCHLORIDE 5 MG, 10 MG CHEWABLE TABLETS

**NDA:** 21-621  
**Sponsor:** Pfizer Pharmaceuticals  
**Type:** Filing meeting  
**Drug:** Cetirizine HCl  
**Submission date:** May 5, 2003  
**Draft review:** Jul 07, 2003  
**Review date:**  
**Reviewer:** Sandra Suarez-Sharp, Ph.D.

### INTRODUCTION

Cetirizine hydrochloride is an orally administered H<sub>1</sub>-antagonist that is approved by FDA for the symptomatic treatment of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria in adults and children 2 years of age and older. The recommended dose of cetirizine hydrochloride is 5 mg or 10mg once daily for those 6 years and older and 2.5 mg once daily for those 2 to 5 years old. Cetirizine hydrochloride is available in tablet and syrup formulations. Pfizer, along with its co-development partner UCB S.A. (Belgium), has developed a grape-flavored cetirizine hydrochloride chewable tablet providing either 5 mg or 10 mg of cetirizine hydrochloride in an immediate-release form. The chewable tablet is designed for once-daily administration in adults and children either with or without water.

### BACKGROUND

A New Drug Application for cetirizine hydrochloride chewable tablets was submitted for FDA's consideration on May 5, 2003. This NDA has been submitted in CTD format and has been cross-referenced with previously-approved NDA 19-835 and DMF — with regard to drug substance chemistry, manufacturing and controls information. Some information contained in the NDA is specified below:

1. CMC information: six months stability data for the primary stability lots.
2. Bridging of the commercial manufacturing and packaging sites to the primary stability lot manufacturing and packaging site.
3. Drug product dissolution method based on the Zyrtec immediate release tablet method. The sponsor also included the information requested at the pre-NDA meeting:
  - Dissolution data generated (individual and mean values) for all the media/conditions used during the development of the method.
  - Dissolution profile comparisons (applied F2 test) between the 5 and 10-mg chewable tablets.
4. Two pivotal bioequivalence studies and four supportive pharmacokinetic studies (See Table 1). SAS transport datasets with associated documentation for the pharmacokinetic parameters for both pivotal studies is included.

Table 1. PK studies submitted to support the filing of NDA 21-621

Protocol	Title	No. Subjects	Comparators
A1431019	Phase 1, Open, 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	25	Cetirizine HCl Chewable Tablet 10mg (To-Be-Marketed) Zyrtec Commercial Tablet 10mg
A1431018	Phase 1, Open, Randomized, 2-way Crossover Pivotal Bioequivalence Study Comparing the Cetirizine Chewable Tablet Taken Without Water to the Commercial Zyrtec (Cetirizine) Tablet Taken With Water in Healthy Subjects	24	Cetirizine HCl Chewable Tablet 10mg (To-Be-Marketed) Zyrtec Commercial Tablet 10mg
A1431016	Phase 1 Open, Randomized, 3-way Crossover Bioequivalence Study of Two Formulations of Cetirizine Chewable Tablet taken without water versus Zyrtec (Cetirizine) Tablet taken with water in Healthy Subjects	18	Cetirizine HCl Chewable Tablet 10mg (To-Be-Marketed) Formulation A <sup>1</sup> Zyrtec Commercial Tablet 10mg
A1431014	Phase 1 Open, Randomized, 2-way Crossover Bioequivalence Study of a New Formulation of Cetirizine Chewable Tablet versus Zyrtec (Cetirizine) Tablet in Healthy Subjects	14	Cetirizine HCl Chewable Tablet 10mg (To-Be-Marketed) Zyrtec Commercial Tablet 10mg
A1431007	A Phase I, Open, Randomized, 3-Way Crossover, Single Dose Bioequivalency Study of Two Formulations of Cetirizine Chewable Tablets versus Zyrtec (Cetirizine) Tablet in Healthy Subjects	24	Formulation A <sup>1</sup> Formulation B <sup>1</sup> Zyrtec Commercial Tablet 10mg
UCB-A00332	Randomized, Monocentre, Open Label, Three-way Crossover, Bioequivalence Study of Cetirizine 10 mg Chewable Tablet Taken Without or With 240 mL of Water, with Cetirizine 10 mg Reference Tablet (ZYRTEC®), after Single Oral Administration in 20 Healthy Subjects	20	Cetirizine HCl Chewable Tablet 10mg (To-Be-Marketed) Zyrtec EU Commercial Tablet 10mg (European Union formulation)

Betacyclodextrin (Betadex, NF) (BCD) is included in the formulation of Zyrtec chewable tablets. Each zyrtec chewable tablet (10 mg strength) contains of BCD. In aqueous solution,

In solution (e.g. saliva), cetirizine and betadex form a weak complex that fully dissociates upon dilution in the gastric fluid and does not affect performance (such as BA). However, complexation between betadex and cetirizine does not occur in dry blends containing of cetirizine and up to of betadex.

Published articles have shown the potential for BCD to interact with certain poor water soluble drugs, such as some vitamins. It is also known that not all drugs interact with BCD and the degree of interaction depends on several factors, such as the size of the molecule, its physicochemical characteristics, and the amount of BCD in the formulation.

However, this is not the case for cetirizine in the chewable tablet,

Up to date, the Agency does not have enough information as of what is the maximum amount of BCD allowed in a formulation, so that no formulation-formulation interactions are present.

The sponsor has not considered the issue about interaction of Zyrtec chewable tablet with other formulations.

**BEST POSSIBLE COPY**

## COMMENTS TO SPONSOR

The following comment should be sent to the sponsor:

- Information from published literature has shown that the coadministration of formulations containing betacyclodextrins (BCD) with some oral formulations may change the oral BA of the coadministered drug (drug in formulation not containing BCD). Please provide information related to this issue with Zyrtec chewable tablets.

## CONCLUSION

The submission is filable from a CPB stand point.

## RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics, the Division of Pharmaceutical Evaluation II (OCPB/DEP-II) has reviewed the NDA package submission (NDA 21-621) for Zyrtec Chewable Tablets 5 and 10 mg received on May 5, 2003. The OCPB/DEP-II is of the opinion that the submission is filable. The above comment should be conveyed to the sponsor.

Sandra Suarez-Sharp, Ph.D.  
Pharmacokinetics Reviewer, DPEII, OCPB

Concurrence:

Emmanuel Fadiran Ph. D.  
Team Leader, DPEII, OCPB

cc:

HFD-570 Div., Nicklas, Jackson  
HFD-870 Malinowski, Hunt, Fadiran, Suarez-Sharp

**APPEARS THIS WAY  
ON ORIGINAL**

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

*General Information About the Submission*

	Information		Information
NDA Number	21-621	Brand Name	Zyrtec Chewable Tablet
OCBP Division (I, II, III)	II	Generic Name	Cetirizine Hydrochloride
Medical Division	DPADP	Drug Class	Antihistamine
OCBP Reviewer	Sandra Suarez-Sharp	Indication(s)	Treatment of SAR, PAR CU
OCBP Team Leader	Emmanuel Fadiran	Dosage Form	Chewable Tablet
PM Reviewer		Dosing Regimen	Adult and children 12 years and older: 5 or 10mg per day depending on symptom severity. Most patients in clinical trials started at 10mg. Children 6 to 11Years: 5 or 10 mg once daily depending on symptom severity. Children 2 to 5Years: 2.5 mg (½ teaspoon) once daily. The dosage in this age group can be increased to a maximum dose of 5mg per day given as 1 teaspoon (5mg) syrup or one 5mg chewable tablet once daily, or as ½teaspoon (2.5mg) given every 12hours.
Date of Submission	May 5, 2003	Route of Administration	Oral
Estimated Due Date of OCPB Review	December, 2003	Sponsor	Pfizer
PDUFA Due Date	March 5, 2004	Priority Classification	Standard
Division Due Date	February , 2004		

*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	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<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:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD:</b>				
Phase 2:				
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:	x	6		
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>				
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		6		
<b>Filability and QBR comments</b>				
	<b>"X" if yes</b>	<b>Comments</b>		
<b>Application filable ?</b>	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
<b>Comments sent to firm ?</b>	X	Comments have been sent to firm (or attachment included). FDA letter date if applicable. • No comments at this time		
<b>QBR questions (key issues to be considered)</b>	1. Is zyrtec chewable tablet bioequivalent to the tablet formulation in the presence and absence of water? 2. Are the proposed dissolution methods and specifications supported by the submitted information?			
<b>Other comments or information not included above</b>				

Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

CC: NDA 21-585, HFD-870 (Electronic Entry or Lee), HFD-570 (Jackson), HFD-870 (Fadiran, , Hunt, Malinowski), CDR (B. Murphy)

**CPB INFORMATION CONTENT IN SUBMITTED NDA**

Study Title/Description	Tabular listing/PK summary	Analytical method	PK parameters (means and individual values)	Statistical analysis
A1431018 (with water)	√	√	√	√
A1431019 (without water)	√	√	√	√
A1431016	√	√	√	√
A1431014	√	√	√	√
A1431007	√	√	√	√
UCB-A00332	√	√	√	√

**CONCLUSION:** Submission is filable.

**APPEARS THIS WAY  
ON ORIGINAL**

-----  
**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  
7/22/03 01:19:40 PM  
BIOPHARMACEUTICS

Emmanuel Fadiran  
7/22/03 02:42:30 PM  
BIOPHARMACEUTICS  
I concur

APPEARS THIS WAY  
ON ORIGINAL