

## CLINICAL REVIEW

NDA # 21-621, -cetirizine, chewable tablet

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**Table 8. Study A1431019**

### Summary of Pharmacokinetic Parameters

	AUC <sub>0-t</sub> (ng*h/mL)	AUC <sub>0-inf</sub> (ng*h/mL)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	T <sub>1/2</sub> (h)
Commercial Tablet With Water	3180 ± 743	3300 ± 756	329 ± 80	1.3 ± 0.6	9.1 ± 1.7
Chewable Tablet With Water	2940 ± 529	3040 ± 534	330 ± 67	1.0 ± 0.8	9.0 ± 1.4

Source: Table 5.2.1

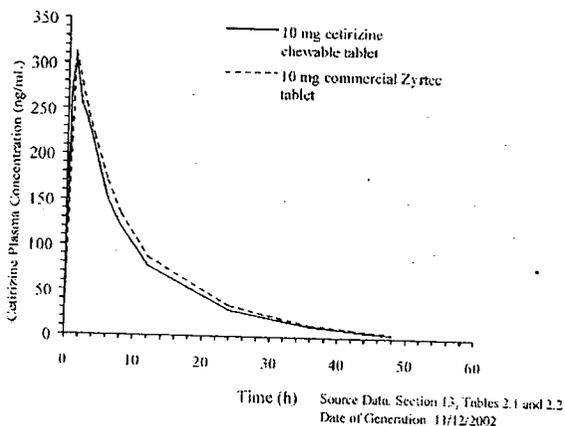
**Table 9.**

### Summary of Statistical Comparisons of Cetirizine Pharmacokinetics

10 mg Cetirizine HCl				
	Commercial Tablet With Water	Chewable Tablet With Water	Chewable/Commercial	
Pharmacokinetic Parameter	Adjusted Geometric Means		Ratio (%)	
			90% Confidence Limits (%)	
AUC <sub>0-inf</sub> (ng*hr/mL)	3218.34	2993.05	93.0	(89.25, 96.91)
AUC <sub>0-t</sub> (ng*hr/mL)	3104.03	2892.51	93.2	(89.39, 97.14)
C <sub>max</sub> (ng/mL)	319.34	323.28	101.2	(95.35, 107.48)

Source: Tables 5.2.1, 5.3; Section 11, Item 11, Tables 1-3.4.

**Figure 1. Mean Plasma Concentrations of Cetirizine Following Administration of 10 mg Commercial Zyrtec Tablet Taken With Water and 10 mg of a Cetirizine Chewable Tablet Taken With Water**



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### 1.1.2.4 Safety Outcomes

There were no deaths, serious adverse events, or withdrawals due to adverse events. The rate of mild-moderate adverse events was similar in the two treatment groups and all of the AEs were consistent with those reported in the package labeling for Zyrtec. These AEs are outlined in Table 10 below.

**Table 10. Study A143019**

#### Treatment-Emergent Adverse Events

Adverse Event (Preferred Term)	Commercial Tablet With Water		Chewable Tablet With Water	
	All Causalities	Treatment- Related	All Causalities	Treatment- Related
<b>Body As a Whole/Total Number</b>	<b>6</b>	<b>3</b>	<b>10</b>	<b>5</b>
abdominal pain	0	0	1	1
allergic reaction	2	0	2	0
asthenia	1	1	2	2
back pain	0	0	1	0
chills	0	0	1	1
headache	4	3	4	1
infection	0	0	1	0
moniliasis	0	0	1	0
pain	2	0	1	0
<b>Digestive/Total Number</b>	<b>1</b>	<b>0</b>	<b>2</b>	<b>0</b>
dry mouth	0	0	2	0
nausea	1	0	0	0
<b>Hemic and Lymphatic/Total Number</b>	<b>1</b>	<b>0</b>	<b>1</b>	<b>0</b>
ecchymosis	1	0	1	0
<b>Nervous/Total Number</b>	<b>6</b>	<b>5</b>	<b>4</b>	<b>3</b>
confusion	1	1	0	0
dizziness	1	1	0	0
somnolence	4	3	4	3
<b>Respiratory/Total Number</b>	<b>1</b>	<b>0</b>	<b>3</b>	<b>0</b>
rhinitis	1	0	3	0
<b>Skin and Appendages/Total Number</b>	<b>1</b>	<b>1</b>	<b>0</b>	<b>0</b>
rash	1	1	0	0
<b>Urogenital/Total Number</b>	<b>1</b>	<b>1</b>	<b>1</b>	<b>1</b>
metrorrhagia	1	1	1	1
<b>Total adverse events</b>	<b>20</b>	<b>11</b>	<b>25</b>	<b>9</b>
<b>Subjects with adverse events</b>	<b>12 (50.0%)</b>	<b>8 (33.3%)</b>	<b>16 (64.0%)</b>	<b>7 (28.0%)</b>
<b>Total subjects available for adverse events</b>	<b>24</b>	<b>24</b>	<b>25</b>	<b>25</b>

Headache and somnolence were the most frequently reported AEs. Four patients in each treatment group complained of each symptom.

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Nine patients had abnormal laboratory values. One patient had a minimally elevated total and indirect bilirubin, both of which increased slightly after treatment (1.2->1.7 mg/dL and 1.1->1.7 mg/dL) and were not repeated. This 36 year-old female also had protein and white cells in her urine at the end of the study. One 47 year-old male had 6% eosinophils in his peripheral smear (upper limit of normal in this laboratory) that increased to 9% after treatment. All of the other patients had abnormalities limited to the urinalysis. Two young women had 6-14 WBC/HPF in the urine at baseline and at day 10. Two female patients with blood in the urine were noted to be menstruating at the time. Three subjects (2 females and 1 male) developed low levels of pyruia (up to 29 WBC/HPF) during the study. Two of the last three were treated with the commercial tablet first and one was treated with the chewable tablet first. None of the laboratory abnormalities was thought to be clinically significant by the investigators.

There were no clinically important changes in vital signs during the study.

### 1.1.3. Discussion and Conclusions

This is a pivotal bioequivalence study in 25 healthy volunteers. The 10-mg cetirizine chewable tablets, taken with water, were bioequivalent to the 10-mg cetirizine commercial product (tablet to swallow) taken with water. The  $AUC_{0-inf}$ ,  $AUC_{0-t}$ , and  $C_{max}$  for the chewable tablet all fell within 80-125% of the values obtained for the commercial product. Adverse events were mild and equally distributed between the two treatment groups. Laboratory abnormalities were also mild and distributed evenly between treatment groups. One subject with an elevated bilirubin after treatment had minimally abnormal values before treatment.

### 1.2. Study # A1431018.

Phase I, Open-Label, 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

#### 1.2.1 Protocol

##### 1.2.1.1 Administrative

Study Dates: June 3, 2002 to June 21, 2002.

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

Principal Investigator: Dr. Candace R. Bramson

##### 1.2.1.2 Objective/Rationale

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.

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### 1.2.1.3 Overall Design

This was a randomized, open-label, two-way crossover, single dose study with a 7-day washout between the two treatment periods. Each subject was randomly assigned according to a computer-generated randomization code provided by Pfizer to one of two treatment regimens. After fasting at least 8 hours, they received either 10 mg Cetirizine commercial tablet with water and seven days later 10 mg Cetirizine chewable tablet without water, or they received the chewable tablet first followed by the swallowed formulation. Patients fasted and were prevented from lying down for 4 hours after the dose.

Each treatment period was followed by 48 hours of blood drawing for PK analysis. (The subjects remained in the clinic under observation for the first 9 hours.) In addition, at 48 hours baseline blood hematology and chemistries were repeated. Adverse events were recorded at 1, 4, 12, 24, 36, and 48 hours.

### 1.2.1.4 Study Population

The subjects were 25 healthy men and women, 18-55 years of age, with a BMI of 18-30 kg/m<sup>2</sup>.

Exclusion criteria included other diseases (other than seasonal allergy) 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. In addition, subjects with a potential for abnormal saliva production (Sjögrens) were excluded.

## 1.2.2. Results

### 1.2.2.1 Subject Disposition

Twenty-four patients were recruited and enrolled. All were followed to the end of the study. None was withdrawn due to adverse events. The Demographic characteristics of the study population are summarized in Table 11.

**Table 11. Demographic Characteristics of Study Population (A1431018)**

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

Source: Table 2.1 and Section 11, Item 1, Appendix B.

Ethnic Group: White – 11 male, 11 female; Black - 1 female; 'Other' – 1 male.

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### 1.2.2.3. Pharmacokinetics

Bioequivalence was established between the 10 mg cetirizine HCl commercial Zyrtec tablet taken with water and the 10 mg cetirizine HCl chewable tablet taken without water based on 90% confidence limits for the ratio of their  $AUC_{0-\infty}$ ,  $AUC_{0-t}$  and  $C_{max}$  falling within the 80%, 125 % limits. The pharmacokinetic data are summarized in tables 12 and 13 and figure2, all of which are copied from the sponsor's submission.

**Table 12. (Study A1431018)**  
**Arithmetic Mean  $\pm$  SD Cetirizine Pharmacokinetic Parameter Values Following a Single 10 mg Administration of Commercial Zyrtec® (Cetirizine) Tablet Taken With Water and the Cetirizine Chewable Tablet Taken Without Water**

	$AUC_{0-t}$ (ng*h/mL)	$AUC_{0-\infty}$ (ng*h/mL)	$C_{max}$ (ng/mL)	$T_{max}$ (h)	$T_{1/2}$ (h)
Commercial Tablet With Water	3020 $\pm$ 466	3130 $\pm$ 475	330 $\pm$ 78.2	1.3 $\pm$ 0.7	9.3 $\pm$ 1.8
Chewable Tablet Without Water	2960 $\pm$ 346	3060 $\pm$ 344	321 $\pm$ 77.3	1.6 $\pm$ 0.9	8.9 $\pm$ 1.6

Source: Table 5.2.1

**Table 13.**  
**Summary of Statistical Analyses of Pharmacokinetic Values For Commercial Zyrtec (Zyrtec ®) vs Cetirizine Chewable Tablet Formulation**

10 mg Cetirizine HCl				
	Commercial Tablet With Water	Chewable Tablet Without Water	Chewable/ Commercial	
Pharmacokinetic Parameter	Adjusted Geometric Means		Ratio (%)	90% Confidence Limits (%)
$AUC_{0-\infty}$ (ng*hr/mL)	3095.49	3043.26	98.31	(95.43, 101.29)
$AUC_{0-t}$ (ng*hr/mL)	2989.23	2935.48	98.20	(95.29, 101.20)
$C_{max}$ (ng/mL)	319.56	310.85	97.28	(94.30, 100.35)

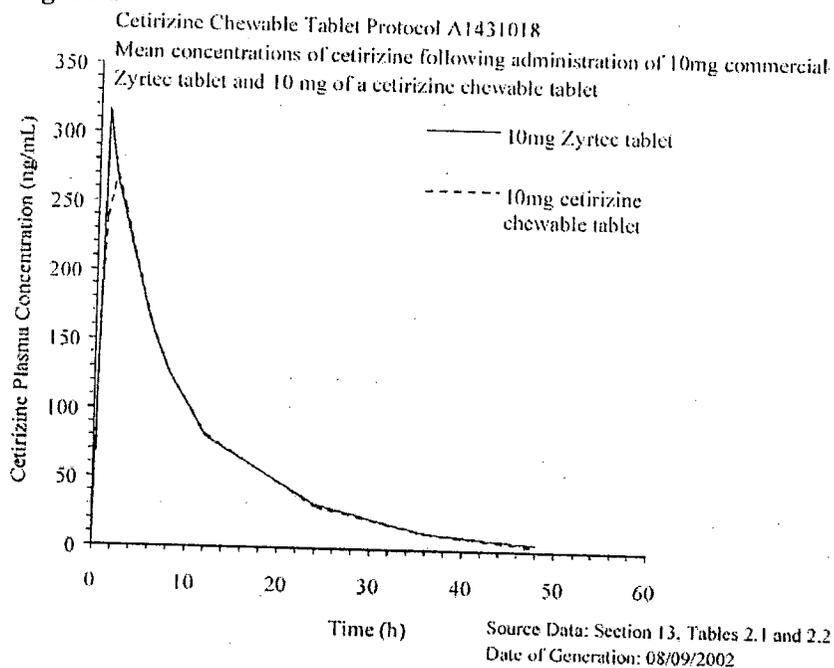
Source: Table 5.3; Section 11, Item 11, Tables 1, 2, 3.1-3.4

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Figure 2



### 1.2.2.4 Safety Outcomes

The safety profile of the cetirizine chewable tablet was similar to the commercial Zyrtec® tablet. There were no deaths, serious adverse events (SAEs), or discontinuations due to AEs reported in this study. All AEs were mild-to-moderate in severity with no reports of severe AEs

The most common adverse events were somnolence and headache. Somnolence occurred in 5 patients taking the commercial product and 6 who received the chewable tablet. Headache occurred in 3 and 8 patients respectively. Adverse events recorded in this study are listed in Table 14.

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Table 14. Study A143018

### Treatment-Emergent Adverse Events

Adverse Event (Preferred Term)	Commercial Tablet With Water		Chewable Tablet Without Water	
	All Causalities	Treatment- Related	All Causalities	Treatment- Related
<b>Body As a Whole/Total Number</b>	<b>7</b>	<b>5</b>	<b>10</b>	<b>4</b>
abdominal pain	1	1	0	0
accidental injury	1	0	1	0
allergic reaction	1	0	0	0
asthenia	2	2	0	0
back pain	0	0	2	0
headache	3	2	8	3
photosensitivity reaction	1	1	1	1
<b>Respiratory/Total Number</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>0</b>
pharyngitis	0	0	1	0
<b>Digestive/Total Number</b>	<b>3</b>	<b>3</b>	<b>2</b>	<b>2</b>
diarrhea	1	1	1	1
dry mouth	2	2	1	1
<b>Metabolic &amp; Nutritional/Total Number</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>
edema	1	0	0	0
<b>Special Senses/Total Number</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>1</b>
taste perversion	0	0	1	1
<b>Musculoskeletal/Total Number</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>
myalgia	1	0	0	0
<b>Nervous/Total Number</b>	<b>5</b>	<b>4</b>	<b>6</b>	<b>3</b>
somnolence	5	4	6	3
<b>Skin and Appendages/Total Number</b>	<b>1</b>	<b>1</b>	<b>1</b>	<b>1</b>
dry skin	1	1	1	1
<b>Urogenital/Total Number</b>	<b>1</b>	<b>0</b>	<b>2</b>	<b>0</b>
dysmenorrhea	0	0	1	0
menstrual disorder	1	0	1	0
<b>Total adverse events</b>	<b>21</b>	<b>14</b>	<b>25</b>	<b>11</b>
<b>Subjects with adverse events</b>	<b>11 (45.8%)</b>	<b>8 (33.3%)</b>	<b>15 (62.5%)</b>	<b>10 (41.7%)</b>
<b>Total subjects evaluated</b>	<b>24</b>	<b>24</b>	<b>24</b>	<b>24</b>

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Laboratory abnormalities were infrequent and mild in nature. Six patients had an abnormality recorded at some time during the study (4 treated with the commercial product and 2 treated with the chewable tablet), but in only 2 cases was the baseline normal. Two patients had red cells in the urine that were not present at baseline and one patient had a low peripheral lymphocyte count at the end of the study.

There were no clinically important changes in vital signs during the study.

### **1.2.3 Discussion and Conclusions**

In this pivotal trial, bioequivalence was demonstrated between the commercial Zyrtec tablet taken with water and the chewable tablet taken without water. The toxicity profiles were similar in the two treatment groups and there were no severe or serious toxicities.

### **1.3. Study #A1431021.**

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

##### **1.3.1. Protocol**

###### **1.3.1.1. Administrative**

Study Dates: April 29, 2003 – May 16, 2003

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

Principal Investigator: Dr. Candace R. Bramson was the principal investigator.

###### **1.3.1.2. Objectives**

The objective of this study was to estimate the effect of a high-fat meal on the bioavailability of the cetirizine chewable tablet following a single dose administration with water under fed and fasted conditions.

###### **1.3.1.3. Overall Design**

This was a randomized, open-label, single-dose, 2-way crossover bioavailability/food effect study of cetirizine hydrochloride chewable tablets conducted in healthy subjects. Twenty-four subjects who fulfilled the entry criteria were to receive one 10-mg cetirizine chewable tablet in the morning in random order on Days 1 and 8 under fed and fasted conditions.

###### **1.3.1.4. Study Population**

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

Exclusion criteria included other diseases (other than seasonal allergy) or 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.

###### **1.3.1.5. Study Procedures**

The subjects fasted for 8 hours prior to the administration of the drug. The fed group ate a high-fat breakfast prior to ingesting the drug with 240 mls water. The fasted group

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continued to fast for an additional 4 hours after ingestion of the test product. Subjects stayed in the clinic for dinner.

Blood was collected over the 48 hours following the dose for PK analysis. Adverse events were recorded at 1, 4, 12, 24, 36, and 48 hours. Vital signs, an ECG and clinical laboratory evaluations (hematology, chemistry, urinalysis) were obtained at baseline and at 24 hours.

### 1.3.2. Results

#### 1.3.2.1. Patient Population

Twenty-four subjects entered and 23 completed the study. One subject (#17) withdrew on Day 3 due to personal reasons. He received a single dose of 10 mg cetirizine chewable tablet while fasting on Day 1. The demographic characteristics of the study populations are summarized in Table 15.

**Table 15. Demographic Characteristics (Study A143021)**

Characteristic		
Sex (n, %)	Male	12 (50)
	Female	12 (50)
Race (n (%))	White	18 (75)
	Black	4 (16.7)
	Hispanic	2 (8.3)
Age (mean $\pm$ SD)		35.3 $\pm$ 10.3
Range		18 - 51
BMI (mean $\pm$ SD)		25.7 $\pm$ 3.5
Range		20.2 - 30

#### 1.3.2.2. Pharmacokinetic Outcomes

Based on  $t_{max}$  and  $C_{max}$  values, rate of cetirizine absorption following administration of 10-mg cetirizine chewable tablets with a high-fat meal was slower than that observed in fasting subjects. The mean  $t_{max}$  value with food was 2.8 hours longer and the mean  $C_{max}$  value was 37% lower relative to those in fasting subjects. The 90% confidence interval for the ratio of treatment  $C_{max}$  values, based on log-transformed values, was not within the 80% to 125% range. The pharmacokinetic data are summarized in table 16 and figure 3 which are copied from the sponsor's submission.

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**Table 16. Statistical Analysis of PK Data from study A143021**

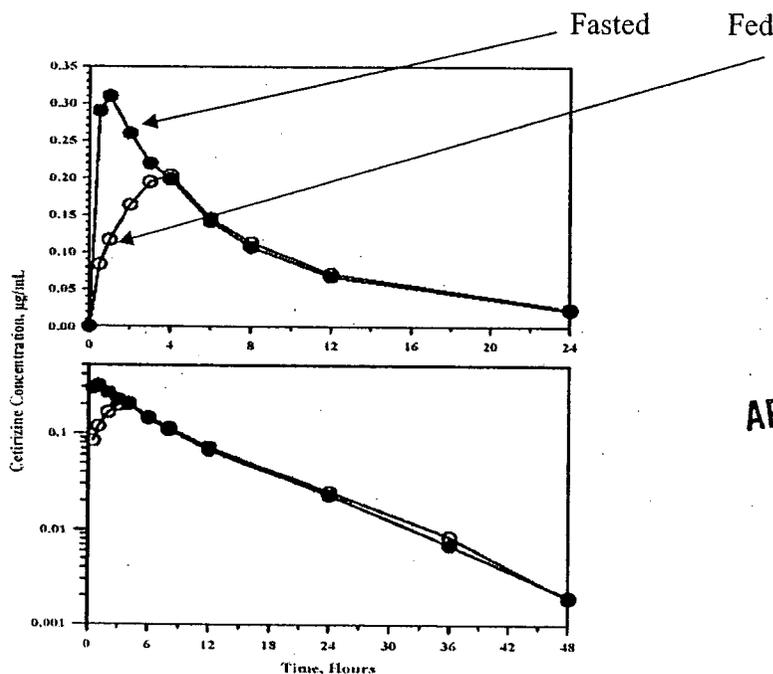
Parameter	Least-Squares Mean Values		Ratio	90% Confidence Interval
	Tablets Fasting (Reference)	Tablets With Food (Test)		
N	24	23		
C <sub>max</sub> , ng/mL	329	208	63.1	59.8 to 66.6
AUC(0-t <sub>lqc</sub> ), µg·hr/mL	2.62	2.39	91.4	88.0 to 94.9
AUC(0-∞), µg·hr/mL	2.72	2.49	91.4	87.9 to 94.9
t <sub>max</sub> , hr	0.817	3.60		Not Applicable
t <sub>1/2</sub> , hr	8.64	8.32		Not Applicable

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).

90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.

Based on AUC(0-∞) values, extent of cetirizine exposure following administration of 10-mg cetirizine chewable tablets with a high-fat meal was similar to that observed for fasting subjects. The mean AUC(0-∞) value with food was 9% lower relative to fasting subjects and the 90% confidence interval for the ratio of treatment AUC(0-∞) values, based on log-transformed values, was within the 80% to 125% range. Cetirizine elimination t<sub>1/2</sub> values were similar for each treatment averaging approximately 8.5 hours.

**Figure 3. Blood Levels of Cetirizine**



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### 1.3.2.3. Safety Outcomes

There were no deaths due to adverse events. There were no serious adverse events, however there was one severe event. One patient could not sleep for several nights due to back pain after taking the chewable tablet with food. The sponsor assessed the event as definitely not related to treatment. The adverse events are listed in Table 17.

**Table 17. Summary of Treatment-Emergent Adverse Events (A1431021)**

Adverse Event	10 mg Cetirizine Chewable Tablet, Fasted (N=24)		10 mg Cetirizine Chewable Tablet, Fed (N=23)	
	All Causality	Treatment Related	All Causality	Treatment Related
<b>BODY AS A WHOLE</b>	7	3	7	2
Headache	4	3	5	2
Pain	1	0	3	0
Fever	1	0	1	0
Asthenia	0	0	1	0
Back Pain	1	0	0	0
Chest Pain	1	0	0	0
Flu Syndrome	0	0	1	0
<b>NERVOUS SYSTEM</b>	2	2	4	1
Somnolence	2	2	2	0
Dizziness	0	0	2	1
Insomnia	1	0	0	0
<b>DIGESTIVE SYSTEM</b>	1	0	4	1
Flatulence	1	0	2	1
Nausea	0	0	2	0
Diarrhea	0	0	1	1
<b>RESPIRATORY SYSTEM</b>	1	0	1	0
Cough	0	0	1	0
Pharyngitis	1	0	0	0
Rhinitis	0	0	1	0
Sinusitis	0	0	1	0
Dysmenorrhea	2	0	0	0
Vasodilatation	0	0	1	0
Lymphadenopathy	1	0	0	0
Sweating	0	0	1	0
Ear Pain	1	0	0	0
<b>Total adverse events</b>	17	5	25	5
<b>Subjects with adverse events</b>	10 (41.7%)	5 (20.8%)	11 (47.8%)	4 (17.4)
<b>Total subjects evaluated</b>	24	24	23	23

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Laboratory tests and ECGs were performed only during screening. No labs were obtained after treatment.

### 1.3.3. Discussion and Conclusions

In 24 subjects the AUC for 10 mg chewable cetirizine was equivalent in the fasted and fed state. There was a slight delay in the systemic absorption of cetirizine when it was taken after a high-fat meal. However, the overall exposure was the same in the two conditions. The spectrum of adverse events was similar to that found in the other studies with somnolence and headache being the most common. However, there were no placebo-treated subjects or subjects treated with the commercial Zyrtec tablet, so that no conclusions about the safety of the chewable formulation of cetirizine can be drawn from this study alone. It would appear, however, that acceptable efficacy and safety can be expected from the chewable tablet regardless of recent food intake.

### 1.4 Study #A1431016 .

Phase I Open-Label, 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

#### 1.4.1 Protocol

##### 1.4.1.1 Administrative

Study Dates: September 19, 2001 to October 17, 2001

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

Principal Investigator: Dr. Candace R. Bramson was the principal investigator.

##### 1.4.1.2 Objectives

The purpose of this pilot study was to assess the bioequivalence of two formulations of a cetirizine chewable tablet when taken without water to the commercial Zyrtec® (cetirizine HCl) tablet taken with water.

##### 1.4.1.3 Overall Design

This was a single center, open-label, single dose, randomized, 3-way crossover study of cetirizine HCl. Subjects were randomized to receive both the Pfizer and UCB chewable 10 mg cetirizine HCl tablets without water and the commercially available Zyrtec® (cetirizine) tablet with water.

*Reviewer: The product described in this report as UCB chewable is actually the to-be-marketed product. The product labeled "Pfizer chewable" was a mono-layer pill, produced in small quantities only and not developed further after this study.*

Appendix

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### 1.4.1.4 Study Population

The study was conducted in 18 normal healthy male and female volunteers between the ages of 18 and 55 years and  $\leq 230$  lbs.

Exclusion criteria included other diseases; drug, alcohol, or tobacco consumption; gastrectomy or Sjögren's syndrome.

### 1.4.1.5. Study Procedures

After an 8-hour fast patients were given 10 mg of one of the test preparations. The chewable tables were given without water and the commercial tablet was given with 240 cc water. Subjects were not allowed to lie down or eat for 4 hours after the dose. They stayed in the study clinic for 9 hours and then returned at 12, 24, 36, & 48 hours for blood draws.

Efficacy was not assessed. Safety procedures included AEs, vital signs at all time points, and routine hematology, chemistry, and urinalysis at the beginning and the end of the study.

## 1.4.2 Results

### 1.4.2.1 Study Population

Eighteen subjects were enrolled and 17 completed the study. One patient was withdrawn after receiving the commercial tablet due to the onset of pregnancy. In addition, the PK samples for 6 subjects were accidentally destroyed. Therefore, the adverse event evaluation includes 17 patients, but the PK evaluation of the chewable tablet includes only 14. Only six patients receiving the chewable tablet had the entire laboratory evaluation. The demographic characteristics of the study population are summarized in Table 18, which is copied from the sponsor's submission.

**Table 18. Demographic Characteristics of Study Population – All Subjects (A143016)**

	Male	Female	Total
Number of Subjects	3	15	18
Mean Age (years)	41.3	36.9	37.6
Range	29–49	24–48	24–49
Mean Weight (kg) $\pm$ SD	81.9 $\pm$ 8.2	65.5 $\pm$ 9.2	68.3 $\pm$ 10.8
Mean Height (cm) $\pm$ SD	185.7 $\pm$ 4.0	163.4 $\pm$ 4.5	167.1 $\pm$ 9.5
Ethnic Group			
White	2	11	13
Black	1	3	4
Hispanic	0	1	1

Source: Table 2.1

## CLINICAL REVIEW

NDA # 21-621, -cetirizine, chewable tablet

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### 1.4.2.2 Pharmacokinetics

Bioequivalence was demonstrated between the commercial Zyrtec® (cetirizine) tablet when taken with water and both the Pfizer chewable and UCB chewable cetirizine tablet formulations when taken without water, with the 90% confidence limits for AUC and C<sub>max</sub> completely within the 80, 125 % limits. The pharmacokinetic data are summarized in Table 19 and 20, which are copied from the sponsor's submission.

**Table 19. Arithmetic Mean ± SD Pharmacokinetic Parameters (A1431016)**

	AUC <sub>0-t</sub> (ng•hr/ml)	AUC <sub>0-inf</sub> (ng•hr/ml)	C <sub>max</sub> (ng/ml)	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)
Zyrtec Commercial	3172 ± 560	3266 ± 569	378 ± 70	1.18 ± 0.49	8.12 ± 1.25
Pfizer Chewable Tablet	2920 ± 664	3020 ± 660	360 ± 62	1.21 ± 0.67	7.39 ± 1.58
UCB Chewable Tablet	2830 ± 715	2930 ± 738	357 ± 72	1.18 ± 0.58	7.74 ± 1.69

Source: Table 5.2.1

**Table 20. Summary of Statistical Analysis of Cetirizine Pharmacokinetics\* (A1431016)**

Parameter	10 mg Cetirizine Adjusted Geometric Means		Ratio (%)	90% CL	
	Commercial Tablet	Chewable Formulations Pfizer and UCB			
AUC <sub>0-inf</sub> (ng•hr/ml)	3290.1	Pfizer	2982.6	90.7	86.6, 94.9
		UCB	2926.8	89.0	83.9, 94.4
AUC <sub>0-t</sub> (ng•hr/ml)	3172.1	Pfizer	2876.7	90.7	86.2, 95.4
		UCB	2845.9	89.7	84.0, 95.8
C <sub>max</sub> (ng/ml)	370.2	Pfizer	354.7	95.8	89.1, 103.1
		UCB	354.5	95.8	87.1, 105.3

Source: Table 5.3; Ratio = Chewable/Commercial; CL = Confidence Limits

\*"UCB" is the to-be-marketed product

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## CLINICAL REVIEW

NDA # 21-621, -cetirizine, chewable tablet

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### 1.4.2.3 Safety Outcomes

There were no deaths, serious adverse events or withdrawals due to adverse events. The most common events were headache, somnolence, and respiratory infection. There were 5 headaches in patients treated with the commercial tablet compared with 3 in the patients treated with the chewable tablet. There were no cases of somnolence and 2 cases of respiratory infection in patients treated with the commercial tablet compared with 2 and 5 in the patients treated with the chewable tablet. Adverse events are listed in Table 21.

**Table 21. Treatment-Emergent Adverse Events (A1430016)**

		Cetirizine 10 mg Commercial Tablet with Water		Cetirizine 10 mg Chewable Tablet without Water	
		All-Cause	Drug- Related	All Cause	Drug Related
<b>Body as a Whole</b>	Headache	5	1	1	0
	Abdominal Pain	0	0	0	0
	Asthenia	1	1	0	0
	Back Pain	0	0	1	0
	Flu Syndrome	0	0	0	0
<b>Digestive</b>	Nausea	1	0	0	0
	Gastrointestinal Disorder	0	0	0	0
	Dry Mouth	0	0	0	0
	Tooth Abnormality	0	0	1	0
<b>Metabolic</b>	Abnormal Liver Function	0	0	1	1
<b>Musculoskeletal</b>	Myalgia	1	0	0	0
<b>Nervous</b>	Somnolence	0	0	0	0
<b>Respiratory</b>	Pharyngitis	0	0	0	0
	Respiratory Disorder	1	0	1	0
	Respiratory Infection	2	0	1	1
<b>Skin</b>	Dry Skin	1	1	0	0
	Herpes Simplex	0	0	1	0
	Rash	0	0	1	1
<b>Etc</b>	Taste Perversion	1	1	0	0
	Dysmenorrhea	0	0	2	0
<b>Total adverse events</b>		13	4	13	2
<b>Subjects with adverse events</b>		10 (55.5%)	4 (22.2%)	8 (47.1%)	2 (11.8%)
<b>Total subjects</b>		18	18	17	17

One patient (#17) with a history of abnormal liver function in the past had an elevation of hepatic enzymes during the treatment phase of the study. The hepatic enzyme levels are shown in Table 22 which is copied from the sponsor's submission.

## CLINICAL REVIEW

NDA # 21-621, -cetirizine, chewable tablet

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**Table 22. Liver Function in Patient with Abnormal Hepatic Enzymes (A1431016)**

	ALT	AST	Alkaline Phosphatase
Normal Limits	9-80 U/L	2-56 U/L	30-130 U/L
Criteria*	>3 ULN	>3 ULN	>3 ULN
Baseline	60 U/L	36 U/L	84 U/L
Day 19	120 U/L	59 U/L	149 U/L
Day 22	96 U/L	39 U/L	143 U/L

Source: Section 13, Tables 3 and 17. \*These laboratory results did not meet the threshold criteria for clinical significance for inclusion in tables 7.1, 7.2 or 7.3.

*Reviewer: Because of the study design it is impossible to determine if one or the other doses was related to the elevated enzymes. The last dose of active drug was given on day 15. Therefore, all three doses had been given by day 19.*

There were no clinically significant changes in laboratory values from baseline to last observation except for the subject (PID 5004-0017). Four female subjects experienced abnormal urinalyses at the conclusion of the study, which were not considered clinically significant.

### 1.4.3 Discussion and Conclusions

This is a small bioequivalence study that replicated study A1431018. Bioequivalence was demonstrated for the 10-mg dose of the chewable formulation as compared with the commercial tablet. The number of patients was so small (17 treated with the chewable tablet) that the low incidence of adverse events is to be expected. Even somnolence, which is the most common adverse event in most studies would be expected in only 2 subjects and random selection could explain the absence of any cases of somnolence in this study. The case of abnormal liver function is of concern as the enzymes were clearly normal before the study, increased during the study and returned to normal in the follow-up period. On the other hand, this is the only instance of abnormal liver function tests in the 124 patients.

### 1.5 Study # A1431014

Phase I, Open-Label, Randomized 2-way Crossover Bioequivalence Study of a New Formulation of Cetirizine Chewable Tablet versus Zyrtec (Cetirizine) Tablet in Healthy Subjects

#### 1.5.1 Protocol

##### 1.5.1.1 Administration

Study Dates: June 14, 2001 – June 29, 2001

The study was conducted at Pfizer Global Research & Development in Ann Arbor, Michigan. Dr. Candace R. Bramson was the principal investigator.

## CLINICAL REVIEW

NDA # 21-621, -cetirizine, chewable tablet

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### 1.5.1.2 Objectives

The objective of this pilot study was to assess the bioequivalence between a new 10 mg cetirizine HCl chewable tablet and the commercial 10 mg cetirizine HCl (Zyrtec)

### 1.5.1.3 Overall Design

This was a randomized, open-label, two-way crossover single dose study of cetirizine. The commercial Zyrtec tablet was compared to the chewable tablet administered with 240 ml water. Study subjects were healthy 18-55 year-old volunteers with no other diseases or difficulty with swallowing or intestinal absorption. Subjects fasted for 8 hours before and 4 hours after receiving the 10-mg dose of cetirizine. After the dose blood was drawn for PK evaluation for 48 hours.

## 1.5.2. Results

### 1.5.2.1. Study Population

Fourteen subjects were enrolled and 14 completed the study. There were 5 men and 9 women with a mean age of 33.4 years (range 20-49). All subjects were Caucasians.

### 1.5.2.2. Pharmacokinetics

Bioequivalence was demonstrated between the commercial cetirizine HCl tablet and the UCB cetirizine chewable tablet formulation based on 90% confidence limits for the ratios of their AUC<sub>0-inf</sub>, AUC<sub>0-t</sub>, and C<sub>max</sub> within the 80% to 125% limits. The pharmacokinetic data are summarized in Table 22.

Table 23. Study A142014

Summary of Statistical Analyses of Cetirizine HCl Pharmacokinetics for Commercial Zyrtec (Zyrtec®) Tablet vs UCB Chewable Tablet

Parameter	10 mg Cetirizine HCl Adjusted Means		Ratio (%)	Difference	90% CI
	UCB Chewable Tablet	Zyrtec® Tablet			
AUC <sub>0-inf</sub> (ng•hr/ml)	2482.01	2726.01	91		86, 96
AUC <sub>0-t</sub> (ng•hr/ml)	2383.31	2617.73	91		85, 97
C <sub>max</sub> (ng/ml)	266.24	289.50	92		86, 98
T <sub>max</sub> (hr)	0.93	1.04		-0.11	-0.33, 0.11
T <sub>1/2</sub> (hr)	8.87	9.33		-0.46	-1.48, 0.57

Source: Table 5.3. Geometric means for AUC and C<sub>max</sub>, arithmetic means for T<sub>max</sub> and T<sub>1/2</sub>. Ratio = UCB/Commercial. CI = Confidence Interval

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NDA # 21-621, -cetirizine, chewable tablet

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### 1.5.2.3. Safety Outcomes

There were no deaths, serious adverse events (SAE), severe adverse events or withdrawals due to adverse events (AE) reported in this study. The incidence of AEs was comparable for the two formulations. A total of 3 treatment-emergent adverse events in 3 subjects were seen with the commercial tablet, compared to 5 treatment-emergent events in 2 subjects with the chewable tablet. In the Commercial Zyrtec Tablet group 1 subject complained of a headache, one described arthralgia, and one complained of dysmenorrhea. In subjects receiving the chewable tablet there was one case each of nausea, vomiting, arthralgia, somnolence and dizziness. Adverse events are listed in Table 24, which is copied from the sponsor's submission.

**Table 24. Adverse Events in Study A1431014**

		Cetirizine 10 mg Commercial Tablet		Cetirizine 10 mg UCB Chewable Tablet	
		All Causality	Treatment- Related	All Causality	Treatment- Related
<b>Body as a Whole</b>					
	Headache	1	1	0	0
<b>Digestive</b>					
	Nausea	0	0	1	0
	Vomiting	0	0	1	0
<b>Musculoskeletal</b>					
	Arthralgia	1	0	1	0
<b>Nervous</b>					
	Somnolence	0	0	1	1
	Dizziness	0	0	1	0
<b>Urogenital</b>					
	Dysmenorrhea	1	0	0	0
<b>Total Number of AE's</b>		3	1	5	1
<b>Total Subjects with AE's</b>		3	1	2	1
<b>Total Number of Subjects</b>		14	14	14	14

Source: Table 6.1.1 - 6.1.3, 6.2.1 - 6.2.3, 6.3

### 1.5.3 Discussion and Conclusions

This is a small bioequivalence study comparing the chewable cetirizine tablet to commercial Zyrtec. The list of adverse events was no different in frequency of type from the type of adverse events seen with the commercial product.

Appendix

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**1.6. Study # A1431007**

**Phase I, Open-Label, Randomized, 3-way Crossover, Single Dose Bioequivalence Study of Two Formulations of Cetirizine Chewable Tablets versus Zyrtec (Cetirizine) Tablet in Healthy Subjects.**

The to-be-marketed formulation is not used in this study and it will not be reviewed in detail. Briefly, this study was designed to test the bioequivalence of chewable tablet containing BCD and one that did not contain BCD. The tablets were monolayer precursors of the to-be-marketed formulation. Twenty four healthy adults were enrolled in this open label, randomized, 3-way crossover study. The treatments are described as Formulation A, Formulation B and commercial cetirizine. Bioequivalence between the two chewable formulations and the commercial product were demonstrated as shown in table 25.

**Table 25. Study A143007**

**Summary of Statistical Analyses of Commercial Tablet (Zyrtec®) vs Pfizer Chewable Tablets: Formulation A (with BCD) and Formulation B (without BCD)**

Pharmacokinetic Parameter	Adjusted Geometric Means		Ratio % Chewable Formulation A,B/ Zyrtec®	90% Confidence Limits (%)
	Chewable Formulations, A,B	Zyrtec®		
AUC 0-12h (ng*hr/ml)	Formulation A= 2948.2	2957.5	A= 99.7	A= (95.6, 104.0)
	Formulation B= 2939.9		B= 99.4	B= (95.3, 103.7)
AUC 0-t (ng*hr/ml)	Formulation A = 2849.4	2846.1	A= 100.1	A= (95.7, 104.7)
	Formulation B = 2847.1		B= 100.0	B= (95.6, 104.6)
C max (ng/ml)	Formulation A= 326.1	336.7	A= 96.9	A= (91.4, 102.6)
	Formulation B= 348.4		B= 103.5	B= (97.7, 109.6)

Source: Table 5.3

There were no deaths or serious adverse events in this study.

**1.7 Study # UCB A00332**

Randomized, mono-center, 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.

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**1.7.1 Protocol****1.7.1.1. Administrative**

Study Dates: April 25, 2002 to June 20, 2002

Study Site: SGS Biopharm SA Research Unit, Antwerp, Belgium

Principal Investigator: Steven Ramael, MD

**1.7.1.2 Objectives**

The primary objective is to assess the bioequivalence of the new cetirizine 10 mg chewable table as compared with the commercial product sold in Europe.

To assess the safety and tolerability of the chewable tablet.

**1.7.1.3 Overall Design**

This was a phase I, open-label, randomized, 3-way 6-sequence crossover, bioequivalence, single-dose study, conducted in one center. The study consisted of 3 treatment periods of 48 hours during which identical procedures were followed. A wash-out period of at least 7 days separated each period. During each study period, the subjects received in fasted conditions one of the following treatments:

- ⊃ One 10 mg cetirizine (CTZ) film-coated tablet (Zyrtec) with 240 mL water;
- ⊃ One 10 mg CTZ chewable tablet without water (chewed);
- ⊃ One 10 mg CTZ chewable tablet with 240 mL water (swallowed without chewing).

*Reviewer: The first of these products is a film-coated tablet not marketed in the USA.*

During the observation period blood was drawn for PK studies over 48 hours, and adverse events were recorded.

**1.7.1.4 Subjects**

Subjects were normal volunteers 18-55 years of age.

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NDA # 21-621, -cetirizine, chewable tablet

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### 1.7.2 Results

#### 1.7.2.1 Subjects

Twenty patients were enrolled and 19 completed the study. One patient received all of the treatments, but did not have all of the required samples for the PK analysis. The demographic characteristics of the study population are summarized in table 26.

**Table 26. Demographic Characteristics (UCB A00332)**

	All N=20	Males N=10	Females N=10
Age (mean years $\pm$ SD) (Range)	38.0 $\pm$ 8.1 (21-54)	41.0 $\pm$ 8.2 (25-54)	35.0 $\pm$ 7.0 (21-45)
BMI (mean kg/m <sup>2</sup> $\pm$ SD) (Range)	23.18 $\pm$ 2.51 (18.4-27.7)	23.96 $\pm$ 2.68 (18.4-27.7)	22.4 $\pm$ 2.17 (19.7-27.4)

#### 1.7.2.3 Pharmacokinetics

Since the comparator drug for this study is not marketed in the United States the PK results will not be reviewed.

#### 1.7.2.4 Safety Outcome

There were no deaths, serious adverse events or withdrawals due to adverse events. All adverse events are listed in Table 27.

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## CLINICAL REVIEW

NDA # 21-621, -cetirizine, chewable tablet

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**Table 27. Adverse Events with UCB A00332 (Chewable tablet)**

	Chewable Tablet without Water		Chewable Tablet with Water	
	Total	Possible Drug related	Total	Possible Drug related
<b>GASTROINTESTINAL</b>				
Abdominal pain	0	0	1	0
Constipation	0	0	1	0
Diarrhoea	0	0	1	0
Dry mouth	1	1	0	0
Dyspepsia	0	0	1	0
Toothache	1	0	0	0
<b>GENERAL</b>				
Fatigue	2	2	3	1
Feeling abnormal	1	1	0	0
<b>MUSCULOSKELATAI</b>				
Neck pain	0	0	0	0
Pain in limb	1	0	0	0
<b>NERVOUS SYSTEM</b>				
Dizziness	1	1	1	0
Headache	6	2	3	1
Somnolence	3	2	3	2
Syncope	0	0	1	0
<b>VASCULAR</b>				
Haematoma	1	0	0	0
Orthostatic hypotension	1	1	0	0
<b>OTHER</b>				
Acne	1	0	0	0
<b>Total Adverse Effects</b>	<b>19</b>	<b>10</b>	<b>15</b>	<b>6</b>
<b>Number of Patients with Adverse Effects</b>	<b>18</b>	<b>9</b>	<b>12</b>	<b>6</b>
	<b>(75%)</b>	<b>(45%)</b>	<b>(60%)</b>	<b>(30%)</b>
<b>Total subjects evaluated</b>	<b>20</b>	<b>20</b>	<b>20</b>	<b>20</b>

Most of the subjects were had values within normal range for the laboratory parameters at both screening and discharge. A few deviations from the normal range were observed, but none of them was considered clinically significant by the Investigator. Hematocrit was the most frequently out-of-range parameter: 2 subjects had elevated hematocrit at screening and 5 subjects shifted from normal to elevated hematocrit from screening to discharge.

### 1.7.3. Discussion and Conclusion

This study was conducted in Europe and compared the to-be-marketed chewable tablet to the commercially available tablet. The commercial tablet used in this study is not available in the United States and the study was not used to evaluate the PK data. The list of adverse events is similar to those reported in the other studies. However, the incidence of adverse events in the chewable tablets taken without water is higher than that found in study A143016) although the difference does not reach statistical significance in this small group of patients ( $p = 0.30$  for total adverse events, and  $p = 1.6$  for drug-associated events).



## CLINICAL REVIEW

NDA # 21-621, -cetirizine, chewable tablet

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### **CITATIONS**

1. Simmons FE. Prospective, long-term safety evaluation of the H1-receptor antagonist cetirizine in very young children with atopic dermatitis. *J Allergy Clin Immunology* 1999; 104:433-440.
2. Stevenson J, Cornah D, Philippe E, Vanderheyden V, Billard C, Bax M, BsnHout A, Long0-term evaluation of the impact of the H1-receptro antagonist cetirizine on the behavioral, cognitive, and psychomotor development of very young children with atopic dermatitis. *Ped Res* 2002; 52:251-257.
3. Simmons, FE, Silas P, Portnoy JM, Catuogno J, Chapman D, Olufade AO. Safety of cetirizine in infants 6 to 11 months of age: A randomized, double-blind, placebo-controlled study. *J Allergy Clin Immunology* 2003; 111:1244-1248.

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**MEDICAL OFFICER 45-DAY FILING REVIEW**  
**Division Of Pulmonary and Allergy Drug Products (HFD-570)**

APPLICATION: NDA # 21,621                      TRADE NAME: Zyrtec®  
 APPLICANT/SPONSOR: Pfizer Pharmaceuticals              USAN NAME: Cetirizine  
 MEDICAL OFFICER: Carol H. Bosken, MD  
 TEAM LEADER: Lydia Gilbert-McClain, MD              CATEGORY: Antihistamine  
 DUE DATE: July 15, 2003                      ROUTE: Oral

**SUBMISSIONS REVIEWED IN THIS DOCUMENT**

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
May 15, 2003	5/16/2003	Original NDA	Electronic submission

**RELATED APPLICATIONS**

<u>Stamp Date</u>	<u>Application Type</u>	<u>Application Type</u>	<u>Approval Date</u>
May 1, 1984	IND	Original IND for tablets	N/A
Aug 17, 1992	IND	Original IND for syrup	N/A
Dec 22, 1992	IND	IND for combination with pseudoephedrine	N/A
April 17, 2002	IND	Original IND for chewable tablets	N/A
July 1, 1988	NDA 19,835	Original NDA for tablets	Dec 8, 1995
Jan 14, 1993	NDA 20,346	Original NDA Syrup	Sept 26, 1993
Jan 19, 2000	NDA 21,151	NDA for combination with pseudoephedrine	Aug 10, 2001

**REVIEW SUMMARY:** Cetirizine hydrochloride (Zyrtec®) was approved for seasonal and perennial allergic rhinitis 1995. The current application for a chewable tablet is based on bioequivalence. In the two pivotal trials the AUC for the chewable formulation was 3104 and 2989 ng·hr/ml compared to 2892 and 2935 ng·hr/ml for the commercial tablet. Adverse events after these single dose exposures were similar to those seen in the larger clinical trials for the commercial tablet. In the 100 patients reported in this submission who were given the chewable formulation that is to be marketed, 16% complained of headache 13% complained of somnolence and 5% developed fatigue/asthenia. Comparable percentages for the commercial tablet were 16%, 11%, and 6% respectively. The proposed label will be used for all of the Zyrtec products. A description of the chewable tablet formulation is the only addition.

**OUTSTANDING ISSUES:** None

**RECOMMENDED REGULATORY ACTION**

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

**APPEARS THIS WAY  
ON ORIGINAL**

## I. Introduction

Cetirizine hydrochloride (Zyrtec®, Pfizer) is approved for the treatment of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), and chronic idiopathic urticaria (CIU) in patients two years old and up. The dose is 5-10 mg once a day for patients over 5 years old and 2-5 mg for patients 2-5 years old. Both tablets and syrup formulations are approved. The sponsor is now seeking approval for a grape-flavored chewable tablet for patients who do not want to swallow tablets or syrup. The application is supported by the results of five bioequivalence trials performed in 125 healthy adults.

## II. Proposed Dosage and Administration

A chewable tablet containing 5 or 10 mg cetirizine to be taken once a day with or without water.

However, cetirizine — with mannitol so the two substances have been put into separate layers in the tablet to minimize contact “using carefully selected excipients”.

*Reviewer: In study A1431016 Two different chewable tablet formulations are tested. According to table 2 in section 2.7.1.1.2 these are G02273AA (Pfizer labs) and DEV-AG.10910 (UCB Pharma) and DEV-AG.10910 is the to-be-marketed formulation. Apparently the final formulation is coming from UCB Pharma. This is confirmed in table 2 in study A1431016 where only DVE-AG.10910 is tested and is identified as the to-be-marketed formulation.*

## III. Summary of Pre-clinical Data

A. No new chemistry, PK, or carcinogenicity/mutagenicity data is submitted.

B. Biopharmaceutics

The results of two pivotal and four supporting bioequivalence studies are submitted.

Pivotal Studies:

In both pivotal studies (A1431019, A1431018) 10 mg of cetirizine chewable tablet was compared to the commercial product (10-mg tablet). In trial A1431019 the chewable tablet was taken with water and in A1431018 the chewable tablet was taken without water. In both studies the subjects were healthy adults, age 37.1 and 37.6 years respectively, and they were evenly split between men and women. In both studies the subjects were given a single dose of the test product and blood was drawn 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. Comparison of the AUC and  $C_{max}$  of the two products showed bioequivalence as shown in the table below:

Table 1.

## Bioequivalence Assessment: Pivotal Studies

Study ID	Parameter	Adjusted Geometric Means		Ratio (%)	90% CI (%)
		Reference	Test		
A1431019	C <sub>max</sub> , ng/mL	319.34	323.28	101.2	95.35, 107.48
	AUC(0-t), nγ hr/mL	3104.03	2892.51	93.2	89.39, 97.14
	AUC(0-8), nγ hr/mL	3218.34	2993.05	93.0	89.25, 96.91
A1431018	C <sub>max</sub> , ng/mL	319.56	310.85	97.28	94.30, 100.35
	AUC(0-t), nγ hr/mL	2989.23	2935.48	98.20	95.29, 101.20
	AUC(0-8), nγ hr/mL	3095.49	3043.26	98.31	95.43, 101.29

Ratio = Ratio of geometric mean values (100% x test/reference); 90% CI = 90% confidence interval; C<sub>max</sub> = Maximum plasma concentration; AUC(0-t) = Area under plasma concentration-time profile from zero to time t for last quantifiable concentration; AUC(0-8) = area under plasma concentration-time profile from zero to infinity; Reference = Commercial Zyrtec tablet

*Reviewer: None of the trials included measurements after taking the chewable formulation after eating.*

## C. Adverse Event Experience

The most common adverse events that occurred in the pivotal studies are listed in table 2. In study A1431018 headache was more common in patients taking the chewable formulation than in those receiving the tablet.

Table 2

	A1431019		A1431018	
	Chewable Tablet	Ref	Chewable Tablet	Ref
Number of subjects	25	24	24	24
Total events (treatment related)	25 (9)	20 (11)	25 (11)	21 (14)
Total subjects with events	16	12	15	11
Headache	4 (1)	4 (3)	8 (3)	3 (2)
Somnolence	4 (3)	4 (3)	6 (3)	5 (4)
Backache	1 (0)	0 (0)	2 (0)	0 (0)
Dry mouth	2 (0)	0 (0)	1 (1)	2 (2)
Allergic Reaction	2 (0)	2 (0)	0 (0)	1 (0)
Rhinitis	3 (0)	1 (0)	0 (0)	0 (0)

When the five trials that used the proposed commercial chewable tablet formulation were combined (Pivotal trials A1431019 & A1431018, and supportive trials A1431016, A1431014, and UCB-A00332; 100 subjects received the chewable formulation and 99 received the commercial tablet) the distribution of adverse events was quite similar to those noted on the approved label. (Note: A1431007 did not test the formulation that is to be marketed.) There were no deaths or serious adverse events. Table 2 shows the combined events and compares them to the percentage of events that are listed on the approved label. Only headache was seen more frequently in the current submission. However, headache occurred in almost identical proportions of subjects taking the tablets as those taking the chewable tablet formulation. One subject each was removed from protocol A1431016 due to pregnancy and elevated liver enzymes. This last patient was said to have elevated enzymes in the past. The enzyme levels were of the order of 1.5 x ULN and were, therefore, not included in the tabulation of AEs. The only other laboratory abnormality that was seen was red and white blood cells in the urine, but this was not seen after ingestion of the chewable formulation more frequently than after the commercial tablet.

Table 3. Percentage of subjects with specified adverse events.

	Current Submission (A1431019, 018, 016, 014, UBC)		Approved Label – Adults		Approved Label – Children	
	10 mg Chewable Tablet (n=100)	10 mg Ref. Tablet (n=99)	10 mg Ref. Tablet	placebo	10 mg Ref. Tablet	placebo
Headache	16.0	16.0	---	---	14.0	12.3
Somnolence	13.0	11.0	13.7	6.3	4.2	1.3
Asthenia/fatigue	5.0	6.0	5.9	2.6	---	---
Dry mouth	3.0	2.0	5.0	2.3	---	---
Rhinopharyngitis	4.0	0.0	2.0	1.9	2.8	2.9
Dizziness	2.0	4.0	2.0	1.2	---	---
Abdominal pain	2.0	1.0	---	---	5.6	1.9
Total	53	48				

*Reviewer: Headache is a very common complaint found in most placebo populations. The aberration is probably in the studies summarized in the approved label.*

IV. Clinical trials for efficacy and safety were not performed for this submission

V. Labeling claims

It is proposed that the label for Zyrtec® contain a description for all of the products (i.e., tablet, chewable tablet, and syrup). To this end the original label is submitted with minor changes. There is a description of the product and the statement that “Comparable bioavailability was also found between the Zyrtec tablet and the Zyrtec chewable tablet taken with or without water.” No additional data has been added to the label.

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

VI. Financial Disclosure

All of the investigators are employees of Pfizer

VII. Pediatric use information

Zyrtec tablets and syrup are approved for patients down to 2 years of age. No information is provided for the chewable formulation for children, All of the subjects in the bioavailability studies were over 18 years old.

VII. Fileability

The application is submitted as an eNDA with CTD presentation. All of the elements are present except for a micro and clinstat folder which are not applicable. The cover letter was submitted in print form. There is a comprehensive table of contents with hyperlinks to each section.

VIII. Audit

None required

IX. Consults

None required

X. Patent Information & Certification

Found in 1.4.1 & 1.4.2

XI. Debarment Certification

Found in 1.4.3

XII. Field copy certification (if applicable)

Found in 1.4.4

XIII. User Fee Cover Sheet

Found in 1.4.5

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Carol Bosken  
7/21/03 11:18:22 AM  
MEDICAL OFFICER

Lydia McClain  
7/21/03 11:29:00 AM  
MEDICAL OFFICER  
I concur

**APPEARS THIS WAY  
ON ORIGINAL**