

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022578Orig1s000

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

ONDQA (Biopharmaceutics) Review

NDA: 22-578 (000)
Submission Date: 11/06/09, 3/17/10, 7/22/10, 7/29/10, 8/25/10
Product: Zyrtec[®] (cetirizine HCl) Orally Disintegrating Tablets (10 mg)
Type of Submission: Original NDA Submission
Sponsor: McNeil Consumer Healthcare
Reviewer: Tapash K. Ghosh, Ph.D.

Background: The sponsor developed Cetirizine HCl Orally Disintegrating Tablets (ODT), which incorporates cetirizine HCl (b) (4) into an immediate-release orally disintegrating tablet dosage form. The cetirizine HCl (b) (4) form of the drug substance. The Zyrtec ODT tablets are indicated for temporary relief of symptoms of hay fever and other upper respiratory allergies (sneezing; runny nose; itchy, watery eyes; and itchy throat or nose). Each tablet contains 10 mg of cetirizine HCl, to be taken orally one tablet once daily.

The composition of Cetirizine HCl ODT, 10 mg intended for commercial distribution is provided in Table 1.

Table 1: Composition Statement of Cetirizine HCl ODT, 10 mg

Component	Reference to Quality standard	Function	mg/tablet
Cetirizine HCl (b) (4) ^{a, b, c}	In-house standard		(b) (4)
Mannitol (b) (4)	USP		
Mannitol	USP		
Microcrystalline Cellulose	NF		
Sucralose	NF		
Crospovidone	NF		
Colloidal Silicon Dioxide	NF		
Sodium Bicarbonate	USP		
Anhydrous Citric Acid	USP		
(b) (4) Citrus (b) (4) Flavor (b) (4)	(b) (4)		
Magnesium Stearate	NF		
Total Tablet Weight			

This document includes review of the sponsor's proposed dissolution method and specification.

Recommendation:

Via a t-con on 8/18/2010, the sponsor was notified the Agency's proposed dissolution specification of $Q = \text{[redacted]}^{(b)(4)}$ in 15 minutes and via e-mail dated 8/25/2010, the sponsor accepted the Agency's proposed dissolution specification.

The following dissolution specification will be the Agency approved dissolution specification using the following dissolution method for the Zyrtec[®] (cetirizine HCl) Orally Disintegrating Tablets (10 mg):

$$Q = \text{[redacted]}^{(b)(4)} \text{ in 15 minutes}$$

Apparatus: USP Apparatus 2 (paddle), 50 rpm
Medium: pH 6.5 phosphate buffer
Volume: 900 ml
Sampling Time: 15 minutes
Analytical method: Isocratic HPLC method utilizing UV detection at 230 nm

Tapash K. Ghosh, Ph. D.
Biopharmaceutics Primary Reviewer
Office of New Drugs Quality Assessment

FT Initialed by Patrick Marroum, Ph. D. _____

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22578	ORIG-1	MCNEIL CONSUMER HEALTHCARE DIV MCNEIL PPC INC	CETIRIZINE HCL ORALLY 10MG TABS

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/s/

TAPASH K GHOSH
08/27/2010

PATRICK J MARROUM
08/29/2010

CLINICAL PHARMACOLOGY REVIEW

NDA:	22-578
Application Type:	505(b)(1)
Proposed Name:	Zyrtec Orally Disintegrating Tablet (ODT)
Generic Name:	Cetirizine HCl
Therapeutic Class:	Anti-histamine
Indication:	Temporary relief of symptoms of hay fever and other upper respiratory allergies
Strength:	10 mg tablet
Proposed Dosing:	One tablet daily
Route of Administration:	Oral
Population:	6 years and older
Applicant:	McNeil Consumer Healthcare
OCP Division:	Division of Clinical Pharmacology 2
Clinical Division:	Office of Nonprescription Products (HFD-560)
Submission Date:	November 09, 2009
Primary Reviewer:	Arun Agrawal, Ph.D.
Team Leader (Acting):	Yun Xu, Ph.D.

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1 Executive Summary

McNeil Consumer Healthcare seeks approval for an orally disintegrating tablet (ODT) formulation of cetirizine HCl for the temporary relief of symptoms of hay fever and other upper respiratory allergies on the basis of bioequivalence (BE) with the Zyrtec[®] commercial tablet. The results of the BE trial showed that, under fasted conditions, Zyrtec ODT taken with or without water is bioequivalent to the already approved Zyrtec immediate release tablet taken with water. A high-fat-breakfast decreased plasma cetirizine C_{MAX} by 37% and delayed T_{MAX} by 3 hours. The extent of change in C_{MAX} and T_{MAX} is comparable to that of the previous approved Zyrtec products. Previous Rx and current OTC labels do not restrict Zyrtec dosing relative to food (Zyrtec labels). Therefore, Zyrtec ODT can be taken without regard to meals. There are no major clinical pharmacology and safety issues.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP 2) has reviewed NDA 22-578 submitted on November 09, 2009 and finds it acceptable pending on DSI inspection results of pivotal trial CETALY1003.

1.2 Background

Cetirizine hydrochloride, the active component of Zyrtec, is an orally active and selective H_1 receptor antagonist. The sponsor, McNeil Consumer Healthcare, has submitted this NDA (NDA 22-578) under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for a new proposed orally disintegrating tablet (ODT) formulation for Zyrtec (cetirizine HCl) 10 mg.

Zyrtec was first approved by FDA as a prescription product in 1995. The FDA approved Zyrtec for over-the-counter (OTC) use in November 2007 for the temporary relief of symptoms of hay fever or other upper respiratory allergies (runny nose, sneezing, itchy or watery eyes, itching of the nose or throat) and for the relief of itching due to hives (urticaria) in adults and children 6 years of age and older (5 and 10 mg tablets, 5 and 10 mg chewable tablets, and syrup 1 mg/mL dosage forms). In addition, the syrup formulation was approved for children ages 6 months to 5 years of age for the temporary relief of symptoms of hay fever or other respiratory allergies.

The sponsor has developed a new 10 mg ODT formulation to provide consumers a convenient option for dosing that does not require swallowing a whole tablet and may be dosed with or without water. This NDA requests approval of the 10 mg ODT, once a day, product for the temporary relief of symptoms of hay fever and other upper respiratory allergies. At this time sponsor does not plan to market this new formulation for part of the approved OTC indication: relief of itching due to hives (urticaria), and therefore, only labeling for the OTC allergy indication is submitted in this NDA.

This application relies on the safety and effectiveness of the reference listed drug (RLD), Zyrtec, 10 mg tablet, therefore, no efficacy and safety studies were conducted with cetirizine ODT tablets. The submission is mainly based on a clinical pharmacology

program. The sponsor conducted a pivotal bioequivalence (BE) trial (CETALY1003) comparing the cetirizine HCl ODT (10 mg) to-be-marketed formulation to RLD cetirizine HCl 10 mg conventional tablet. In addition, the effects of water and high-fat breakfast were also evaluated for cetirizine ODT in this trial.

1.3 Summary of Clinical Pharmacology Findings

1.3.1 Single-dose bioequivalence trial (CETALY1003)

This submission included pharmacokinetic data from the combined bioequivalence and food effect study. This was an open-label, single-dose, four-way randomized and five-way crossover study in healthy male and female adults. Twenty-eight (28) subjects were enrolled in this study and were randomized to a particular sequence of treatments. Subjects received Treatments A, B, C, or D in the first 4 periods and all subjects received Treatment E in Period 5. This study was conducted in 2 parts:

Part 1 of the study was a 4-way, randomized, crossover design, where subjects received the following treatments under fasting conditions, after an overnight fast of at least 10 hours:

- Treatment A: A single 10 mg dose of cetirizine ODT with 240 mL water.
- Treatment B: A single 10 mg dose of cetirizine ODT without water.
- Treatment C: (US marketed product): A single 10 mg dose of the currently marketed US cetirizine tablet (ZYRTEC®) with 240 mL water.
- Treatment D: (Canadian marketed product): A single 10 mg dose of the currently marketed Canadian cetirizine tablet (REACTINE®) with 240 mL water.

A total of 28 subjects entered the study and were randomized to a particular sequence of treatments and received Treatments A, B, C, and D over 4 periods. The dosing for each consecutive study period was separated by a 4 to 7 day washout interval. All 28 subjects completed Treatments A to D and all data were utilized for the analysis.

Part 2 of the study consisted of the following treatment administered after an overnight fast of at least 10 hours:

- Treatment E: A single 10 mg dose of cetirizine ODT administered approximately 30 minutes after the start of a high-fat breakfast with 240 mL water.

All procedures remained similar to Part 1, except subjects were given a high-fat breakfast approximately 30 minutes prior to administration of Treatment E (Period 5). One subject was dropped from the study by the investigator at check-in for Treatment E due to a positive alcohol test. Therefore, only 27

subjects were given Treatment E and all data from those 27 subjects were utilized for the analysis .

The study outline is presented in the following figure:



Pharmacokinetic Results:

Mean values of peak and overall exposure of cetirizine (C_{MAX} , AUC_{LAST} , AUC_{INF}) were similar for all fasted cetirizine treatments (Treatments A-D, Table 1). For the fasted cetirizine treatments (Treatments A-D), median T_{MAX} was approximately 1 hour post-dose. $T_{1/2}$ was similar for all the treatments (Treatments A-E). Percent of extrapolated AUC_{INF} (% AUC_{extrap}) was low for all the treatments (6.63-8.89%), indicating that the majority of the cetirizine exposure was captured during the sampling period of 32 hours post-dosing.

Table 1 Arithmetic mean (SD) pharmacokinetic parameters for total plasma cetirizine

	Treatment A	Treatment B	Treatment C	Treatment D	Treatment E
Pharmacokinetic Parameters	Mean \pm SD (CV%) (N=28)	Mean \pm SD (CV%) (N=28)	Mean \pm SD (CV%) (N=28)	Mean \pm SD (CV%) (N=28)	Mean \pm SD (CV%) (N=27)
C_{MAX} (ng/mL)	292 \pm 53.5 (18.3)	288 \pm 55.7 (19.3)	303 \pm 60.4 (19.9)	303 \pm 53.4 (17.6)	182 \pm 30.5 (16.8)
T_{MAX} (hr) ¹	1.00 (0.50,2.01)	1.13 (0.50,4.00)	1.00 (0.50,2.01)	0.89 (0.52,2.00)	4.01 (2.50,12.00)
AUC_{LAST} (ng*hr/mL)	2597 \pm 402 (15.5)	2556 \pm 453 (17.7)	2522 \pm 575 (22.8)	2593 \pm 449 (17.3)	2415 \pm 360 (14.9)
AUC_{INF} (ng*hr/mL)	2787 \pm 455 (16.3)	2722 \pm 525 ² (19.3)	2706 \pm 635 (23.5)	2792 \pm 515 (18.5)	2653 \pm 439 (16.5)
K_{EL} (1/hr)	0.0844 \pm 0.0143 (16.9)	0.0855 \pm 0.0155 ² (18.1)	0.0842 \pm 0.0138 (16.4)	0.0847 \pm 0.0151 (17.8)	0.0807 \pm 0.0134 (16.6)
$T_{1/2}$ (hr)	8.4 \pm 1.3 (15.6)	8.3 \pm 1.4 (16.8) ²	8.4 \pm 1.3 (15.0)	8.4 \pm 1.5 (17.2)	8.8 \pm 1.4 (16.3)
% AUC_{extrap} (%)	6.63 \pm 2.71 (40.9)	6.69 \pm 2.94 ² (43.9)	6.58 \pm 2.69 (40.9)	6.89 \pm 3.15 (45.8)	8.68 \pm 3.10 (35.7)
Treatment A: cetirizine HCl ODT 1 x 10 mg [with water] fasted Treatment B: cetirizine HCl ODT 1 x 10 mg [without water] fasted Treatment C: cetirizine HCl (ZYRTEC [®] , McNeil Consumer Healthcare) 1 x 10 mg [with water] fasted Treatment D: cetirizine HCl (REACTINE [®] , Keata Pharma Inc.) 1 x 10 mg [with water] fasted Treatment E: cetirizine HCl ODT 1 x 10 mg [with water] fed					
¹ T_{MAX} is presented as Median (Minimum, Maximum)					
² N=27					
Source: Table 14.2.2.1 , Table 14.2.2.2 , Table 14.2.2.3 , Table 14.2.2.4 , and Table 14.2.2.5 .					

Statistical comparisons for Treatment A versus C, and B versus C showed that cetirizine ODT with and without water was bioequivalent to Zyrtec administered with water in the fasted state (Table 2).

A significant food effect was observed with the cetirizine ODT formulation for C_{MAX} , but not for AUC (Table 2). Mean C_{MAX} after Treatment E (cetirizine ODT, fed) was 37% lower of that after Treatment A (cetirizine ODT, fasted); median T_{MAX} was delayed by approximately 3 hours with food. The extent of change in C_{MAX} and T_{MAX} is comparable to that of the previous approved Zyrtec products (Zyrtec labels).

Table 2 Statistical comparisons of pharmacokinetic parameters for total plasma cetirizine*

Treatment Comparison (Test vs Reference)	Parameter	Treatment LS Means		% Mean Ratio	Confidence Intervals (90% Confidence)
		Test	Reference		
A vs C	AUC _{LAST} (ng*hr/mL)	2566	2468	103.96	100.48 - 107.56
	C _{MAX} (ng/mL)	287	298	96.34	91.77 - 101.13
	AUC _{INF} (ng*hr/mL)	2749	2643	104.02	100.28 - 107.90
B vs C	AUC _{LAST} (ng*hr/mL)	2519	2468	102.07	98.66 - 105.61
	C _{MAX} (ng/mL)	283	298	95.16	90.65 - 99.90
	AUC _{INF} (ng*hr/mL)	2708	2643	102.46	98.73 - 106.33
E vs A	AUC _{LAST} (ng*hr/mL)	2389	2570	92.97	89.23 - 96.87
	C _{MAX} (ng/mL)	179	287	62.55	58.95 - 66.36
	AUC _{INF} (ng*hr/mL)	2618	2753	95.11	91.13 - 99.27
Treatment A: cetirizine HCl ODT 1 x 10 mg [with water] fasted Treatment B: cetirizine HCl ODT 1 x 10 mg [without water] fasted Treatment C: cetirizine HCl (ZYRTEC [®] , McNeil Consumer Healthcare) 1 x 10 mg [with water] fasted Treatment D: cetirizine HCl (REACTINE [®] , Keata Pharma Inc.) 1 x 10 mg [with water] fasted Treatment E: cetirizine HCl ODT 1 x 10 mg [with water] fed Parameters were ln-transformed prior to analysis. The LS means for treatment A are not the same for each comparison since different statistical models were used. Source: Table 14.2.2.7 , Table 14.2.2.8 , and Table 14.2.2.9 .					

*28 subjects for Treatments A-D and 27 subjects for Treatment E

1.3.2 Conclusions:

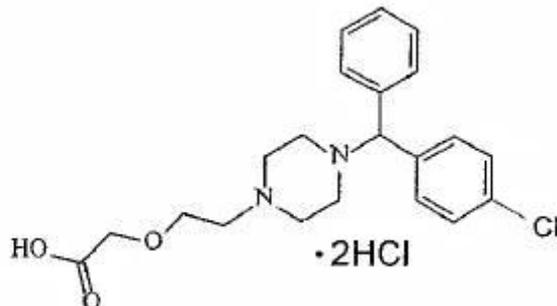
- Cetirizine 10 mg ODT when taken with or without water in the fasted state is bioequivalent to 10 mg of the currently marketed cetirizine reference product, Zyrtec taken with water.
- The rate, but not the extent of cetirizine ODT absorption, was affected by a high-fat meal, resulting in a C_{MAX} which was 37% lower than that in the fasted state. The time to peak exposure was delayed by 3 hours with food. These data are consistent with previously observed food effects for Zyrtec products [C_{MAX} was decreased by 23% and T_{MAX} was delayed by 1.7 hours for Zyrtec tablets; C_{MAX} was decreased by 38% and T_{MAX} was delayed by 3 hours for Zyrtec chewable tablets].
- Previous Rx and current OTC labels do not restrict Zyrtec dosing relative to food. Therefore, Zyrtec ODT can be taken without regard to meals.

2 Question Based Review

2.1 General Attributes

2.1.1 What are the general attributes of cetirizine HCl ODT formulation?

The drug substance, cetirizine dihydrochloride, is commonly referred to as cetirizine hydrochloride or cetirizine HCl. The molecular formula is $C_{21}H_{25}ClN_2O_3 \cdot 2HCl$. The molecular weight is 461.82. The chemical structure is provided below:



Cetirizine HCl has three ionizable moieties resulting in pKa values of 2.2, 2.9 and 8.0. At physiological pH, it predominantly exists as a zwitterion or an anion. Cetirizine HCl is a white or almost white powder that is freely soluble in water, practically insoluble in acetone and in methylene chloride. It has a pH of 1.2 to 1.8 and a relatively high melting range of 214°C to 221°C. The analyses of cetirizine powder did not show any change in crystalline form or any tendency to exhibit polymorphism.

Formulation

Cetirizine HCl is a bitter drug substance that requires (b) (4) when used in a dosage form that disintegrates in the oral cavity. Therefore, an ODT formulation was developed that disintegrates rapidly and passes a pleasant taste and mouth-feel. The 10 mg cetirizine ODT formulation is provided as a citrus flavored, white to off-white, round, flat-faced, beveled edge tablet, which weighs 325 mg. The drug product will be debossed with “Z10” on one side of the tablet. The ODT consists of cetirizine HCl (b) (4) (a (b) (4) form of the drug substance) incorporated in an immediate-release tablet. The ODT formulation will be packaged in 6 counts child-resistant peelable blister package that will be commercially distributed in cartons. The overall composition of cetirizine HCl ODT 10 mg tablet is given below:

Component	Reference to Quality standard	Function	mg/tablet
Cetirizine HCl (b) (4), b, c	In-house standard	(b) (4)	(b) (4)
Mannitol (b) (4)	USP		
Mannitol (b) (4)	USP		
Microcrystalline Cellulose	NF		
Sucralose	NF		
Crospovidone	NF		
Colloidal Silicon Dioxide	NF		
Sodium Bicarbonate	USP		
Anhydrous Citric Acid	USP		
(b) (4) Citrus (b) (4) Flavor (b) (4)	(b) (4)		
Magnesium Stearate	NF		
Total Tablet Weight			325

Disintegration Time

The disintegration time of cetirizine ODT formulation was within 30 seconds as stated below:

Method: USP Disintegration <701>, disks, 1.0 mm distance, ATM-679

The cetirizine disintegration specification is set to comply with the FDA Guidance for Industry on Orally Disintegrating Tablets, December 2008. All registration batches comply with the proposed specification at release and through six months stability. See [Table 3.2.P.5-15](#).

Table 3.2.P.5-15. Disintegration Results

Batch	Release Disintegration Times Determined by Electronic Endpoint (sec)	Stability Disintegration Time Range Determined by Electronic Endpoint (sec)
C05136	26, 20, 22, 14, 20, 16	11 – 26
C12909	20, 22, 18, 16, 14, 22	12 – 24
C12910	17, 15, 23, 15, 19, 25	11 – 27
C29451	20, 14, 20, 10, 18, 20	10 – 25

Dissolution Profile

A comparison of dissolution profiles of cetirizine HCl ODT and Zyrtec IR tablet showed that the dissolution rate for cetirizine ODT is slower in water than the dissolution rate for Zyrtec tablet. This phenomenon was attributed to the presence of the (b) (4) that is used for (b) (4) cetirizine in the ODT formulation. The (b) (4) is soluble in acidic media and swells or becomes permeable at neutral pH. Thus, the dissolution rate

for cetirizine HCl ODT is slightly slower in water and in pH 6.8 phosphate buffer relative to the commercial Zyrtec IR tablet, and is equivalent to the commercial Zyrtec IR tablet in 0.1 N HCl.

2.2 General Clinical Pharmacology

2.2.1 What is known about the pharmacokinetics of Cetirizine HCl?

Previous studies in adults have demonstrated that cetirizine undergoes rapid absorption where the maximum plasma concentration was reached at ~1 hour following oral administration of tablets, chewable tablets, and syrup. Comparable bioavailability was found between the tablet and syrup dosage forms. No accumulation was observed following multiple dosing of cetirizine HCl (10 mg tablets once daily for 10 days) in healthy subjects. Cetirizine pharmacokinetics is linear for oral doses ranging from 5 to 60 mg. The mean plasma protein binding of cetirizine hydrochloride is 93%, independent of concentration in the range of 25 to 1000 ng/mL, which includes the therapeutic plasma concentrations. The mean elimination half-life is 8.3 hours and the apparent total body clearance for cetirizine is ~53 mL/min following oral administration of cetirizine in healthy subjects. The plasma PK parameters of cetirizine obtained in the bioequivalence study submitted with this supplement are not different from that known previously (Zyrtec labels).

2.3 General Biopharmaceutics

2.3.1 What is the bioequivalence of the proposed Zyrtec 10 mg ODT following single dose administration to the reference approved Zyrtec 10 mg tablet?

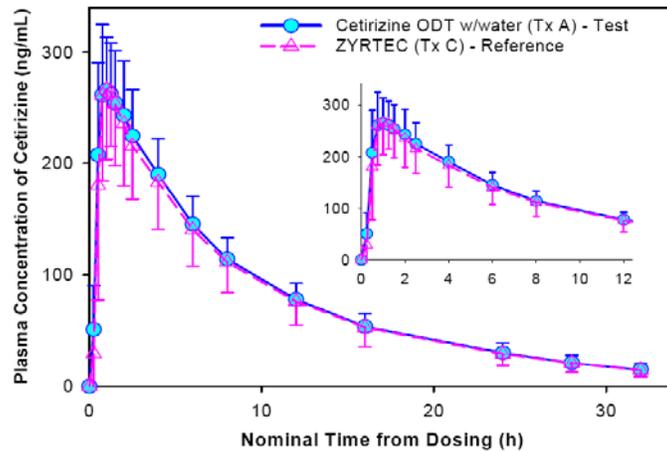
The bioequivalence of Zyrtec 10 mg ODT with the Zyrtec 10 mg reference tablet was demonstrated with or without water under fasted conditions by the observation that the 90% CIs for the ratios of the geometric means for AUC_{LAST} , AUC_{INF} and C_{MAX} were within the limits for bioequivalence (80-125%) for cetirizine ODT (Tables 3-4; Figures 1-2). A significant food effect was observed with the cetirizine ODT formulation for C_{MAX} , but not for AUC (Table 5, Figure 3).

Table 3 Pharmacokinetic parameters and bioequivalence statistics of cetirizine following single dose administration of a 10 mg ODT (A) and 10 mg Zyrtec tablet (C) in healthy subjects

PK parameters	Geometric Least Squares Mean		Test : Reference ratio	
	Test (A)	Reference (C)	% LS Means Ratio	90% Confidence Intervals
AUC _{LAST} (ng*hr/mL)	2566	2468	104	100.5 – 107.6
AUC _{INF} (ng*hr/mL)	2749	2643	104	100.3 – 107.9
C _{MAX} (ng/mL)	287	298	96.3	91.8 – 101.1
T _{MAX} (hr) ^a	1.0 (0.50, 2.0)	1.0 (0.50, 2.0)		

Treatment A = cetirizine HCl ODT 1 x 10 mg (with water) fasted
 Treatment C = cetirizine HCl (Zyrtec) 1 x 10 mg (with water) fasted

Figure 1 Mean plasma cetirizine concentrations following single dose administration of a 10 mg ODT (A) and 10 mg Zyrtec tablet (C) in healthy subjects



Treatment A: cetirizine HCl ODT 1 x 10 mg [with water] fasted
 Treatment C: cetirizine HCl (ZYRTEC®, McNeil Consumer Healthcare) 1 x 10 mg [with water] fasted

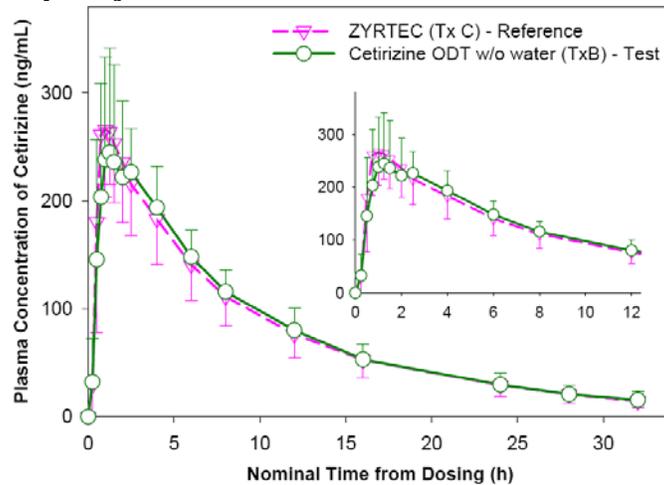
Statistical comparisons for Treatment A versus C showed that cetirizine ODT with water was bioequivalent to Zyrtec administered with water in the fasted state.

Table 4 Pharmacokinetic parameters and bioequivalence statistics of cetirizine following single dose administration of a 10 mg ODT (B) and 10 mg Zyrtec tablet (C) in healthy subjects

PK parameters	Geometric Least Squares Mean		Test : Reference ratio	
	Test (B)	Reference (C)	% LS Means Ratio	90% Confidence Intervals
AUC _{LAST} (ng*hr/mL)	2519	2468	102	98.7 – 105.6
AUC _{INF} (ng*hr/mL)	2708	2643	102	98.7 – 106.3
C _{MAX} (ng/mL)	283	298	95.2	90.7 – 99.9
T _{MAX} (hr) ^a	1.1 (0.50, 4.0)	1.0 (0.50, 2.0)		

Treatment B = cetirizine HCl ODT 1 x 10 mg (without water) fasted
 Treatment C = cetirizine HCl (Zyrtec) 1 x 10 mg (with water) fasted

Figure 2 Mean plasma cetirizine concentrations following single dose administration of a 10 mg ODT (B) and 10 mg Zyrtec tablet (C) in healthy subjects



Treatment B: cetirizine HCl ODT 1 x 10 mg [without water] fasted
 Treatment C: cetirizine HCl (ZYRTEC®, McNeil Consumer Healthcare) 1 x 10 mg [with water] fasted

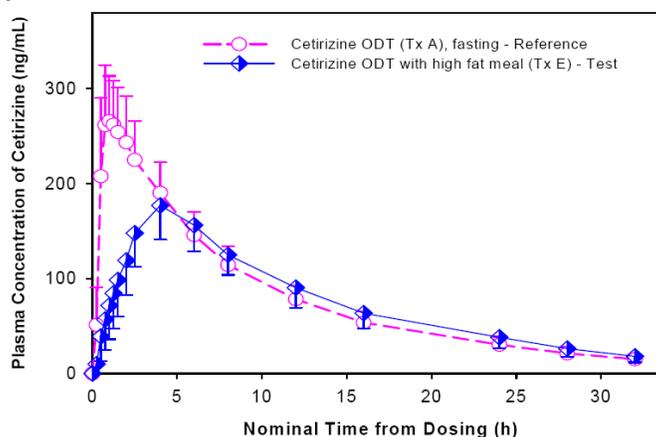
Statistical comparisons for Treatment B versus C showed that cetirizine ODT without water was bioequivalent to Zyrtec administered with water in the fasted state.

Table 5 *Effect of Food: Pharmacokinetic parameters and bioequivalence statistics of cetirizine following single dose administration of a 10 mg ODT (E) and 10 mg ODT (A) in healthy subjects*

PK parameters	Geometric Least Squares Mean		Test : Reference ratio	
	Test (E)	Reference (A)	% LS Means Ratio	90% Confidence Intervals
AUC _{LAST} (ng*hr/mL)	2389	2570	93	89.2 – 96.9
AUC _{INF} (ng*hr/mL)	2618	2753	95	91.1 – 99.3
C _{MAX} (ng/mL)	179	287	63	59.0 – 66.4
T _{MAX} (hr) ^a	4.0 (2.50, 12.0)	1.0 (0.50, 2.0)		

Treatment E = cetirizine HCl ODT 1 x 10 mg (with water) fed
 Treatment A = cetirizine HCl ODT 1 x 10 mg (with water) fasted

Figure 3 *Mean plasma cetirizine concentrations following single dose administration of a 10 mg ODT (E) and 10 mg ODT (A) in healthy subjects*



Treatment E: cetirizine HCl ODT 1 x 10 mg [with water] fed
 Treatment A: cetirizine HCl ODT 1 x 10 mg [with water] fasting

A significant food effect was observed with the cetirizine ODT formulation for C_{MAX}, but not for AUC. Mean C_{MAX} after Treatment E (cetirizine ODT, fed) was decreased by 37% as compared to Treatment A (cetirizine ODT, fasted); median T_{MAX} was delayed by 3 hours with food. This is consistent with previously reported food effect on C_{MAX} and T_{MAX} for Zyrtec products (Zyrtec labels).

2.3.2 Did the sponsor use to-be-marketed formulation in the bioequivalence trial CETALY 1003?

Yes. The ODT formulation proposed for registration is the same as that used in the bioequivalence trial (CETALY1003).

2.4 Analytical Section

2.4.1 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

Yes. All bioanalytical assays fulfilled the regulatory criterion [refer to the FDA guidance for industry “Bioanalytical Method Validation (Final-May 2001)"] of not exceeding 15% ((20% for the lowest Quality Control Samples (QCSs)) for precision and accuracy. Study samples were analyzed in runs containing calibrators and QC samples, as recommended in the FDA guidance.

The bioanalytical laboratory at (b) (4) determined the concentrations of cetirizine in human plasma (K₃ EDTA) by HPLC-MS/MS detection using a validated method. The limit of reliable quantification was 0.5 ng/mL. The dynamic calibration range was 0.5 to 400 ng/mL and required a 50 µL human plasma aliquot containing K₃ EDTA. Interday precision and accuracy of the method were evaluated using the results of the QCSs assayed daily alongside the clinical samples. QCSs accuracy was between 98% and 100.4% of the nominal concentrations. No interfering peaks were observed showing selectivity/specificity of the method. Overall recovery of the QCSs was 93.3%. Following table summarizes the details of the method validation:

Table 2.7- 1. Bioanalytical Methods Summary for Plasma Analysis of Cetirizine HCl in CETALY 1003

Parameter	Value
Analyte	Cetirizine in K3EDTA human plasma
Lower Limit of Quantitation	0.5 ng/mL
Linear Range	0.5 ng/mL to 400 ng/mL
Accuracy (QC Samples)	98 - 100.4% of nominal concentrations
Precision (Inter-Run %CV QC Samples)	3.02 - 5.38%
Specificity	No interfering peaks were observed
Overall Recovery (QC Samples)	93.3%

VALIDATION SUMMARY TABLE FOR THE DETERMINATION OF CETIRIZINE

Report location	Central Data Room at (b) (4)
Method description	Method BTM-1125-R0 is an LC/MS/MS method developed for the determination of cetirizine in human plasma using cetirizine-d ₄ as the internal standard (IS). Cetirizine and the internal standard were extracted by protein-precipitation from human plasma. Reversed-phase HPLC separation was achieved with a Waters Atlantis T3 column (50 x 2.1 mm, 3 micron). MS/MS detection was set at mass transitions of 389.3→165.3 m/z for cetirizine and 393.3→165.3 m/z for cetirizine-d ₄ (IS) in Turboionspray Positive mode.
Sample volume	50 µL
Regression	Linear
Weighting factor	1/x ²
Analyte	Cetirizine
Internal standard	Cetirizine-d ₄
Linearity	r ² ≥0.9979
Lower limit of quantitation	0.5 ng/mL
Average recovery of drug (%)	93.3
Average recovery of internal standard (%)	95.7
Dynamic range	0.5-400 ng/mL
QC concentrations	1.5 ng/mL, 45 ng/mL, 300 ng/mL
QC Intraday precision range (%CV)	Day 1: 1.8-4.5
	Day 2: 1.1-2.9
	Day 3: 1.1-3.7
QC Intraday accuracy range (%Nominal)	Day 1: 100.7-103.4
	Day 2: 101.0-105.1
	Day 3: 100.7-103.8
QC Interday precision range (%CV)	1.8-3.5
QC Interday accuracy range (%Nominal)	100.8-104.1
Bench-top stability	At least 6 hours at room temperature
Stock solution stability	To be determined. (Refer to Section 6)
Processed sample stability	At least 69 hours at room temperature
Freeze/Thaw stability	3 freeze (-20°C)/thaw cycles
Long-term storage stability	To be determined. (Refer to Section 6)
Dilution integrity	4000 ng/mL diluted 20 times for cetirizine
Selectivity	No interfering peaks were detected in blank human plasma at the retention times of cetirizine and cetirizine-d ₄ (IS).

2.5 Labeling Recommendations

From Clinical Pharmacology perspective, there are no changes to the submitted label.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22578	ORIG-1	MCNEIL CONSUMER HEALTHCARE DIV MCNEIL PPC INC	CETIRIZINE HCL ORALLY 10MG TABS

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

/s/

ARUN K AGRAWAL
06/29/2010

YUN XU
07/01/2010

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	22-578	Brand Name	Zyrtec ODT
OCP Division (I, II, III, IV, V)	II	Generic Name	Cetirizine HCl
Medical Division	DNCE	Drug Class	Antihistamine
CP/PM Reviewer	Arun Agrawal, Ph.D.	Indication(s)	Allergy
CP Team Leader (Acting)	Partha Roy, Ph.D.	Dosage Form	ODT Tablet
Pharmacometrics Team Leader		Dosing Regimen	Cetirizine HCl 10 mg ODT Tablet, QD
Date of Submission	06 November, 2009	Route of Administration	Oral
Estimated Due Date of OCP Review		Sponsor	McNeil Consumer Health
Medical Division Due Date		Priority Classification	Standard
PDUFA Due Date	09 September, 2010		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			Data submitted for study: CETALY1003
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	█		(b) (4) (b) (4)
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
<i>Patients-</i>				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				

In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		CETALY1003
replicate design; single / multi dose:				
Food-drug interaction studies	X	1		CETALY1003
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		3		CETALY1003

On initial review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	To-be-marketed form used in the pivotal study
2	Has the applicant provided metabolism and drug-drug interaction information?	x			Reference to previous NDAs

3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?			X	Data provided on a CD
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Partial waiver requested
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study			X	

information) from another language needed and provided in this submission?				
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IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

None

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

BACKGROUND

Cetirizine HCl is an orally active and selective H1 receptor antagonist. It is a racemic mixture of two enantiomers which are stable and do not interconvert. McNeil Consumer Healthcare has submitted this NDA (NDA 22-578) under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for a new proposed orally disintegrating tablet (ODT) formulation for Zyrtec® (cetirizine HCl) 10 mg.

Cetirizine HCl (Zyrtec) was first approved by FDA as a prescription product in 1995. The FDA approved Zyrtec for over-the-counter (OTC) use on November 16, 2007 for the temporary relief of symptoms of hay fever or other upper respiratory allergies (runny nose, sneezing, itchy, watery eyes, itching of the nose or throat) and for the relief of itching due to hives (urticaria) in adults and children 6 years of age and older (5 mg and 10 mg tablet, 5 mg and 10 mg chewable tablet, and syrup 1 mg/mL dosage forms). In addition, the syrup formulation was approved children ages 2 to 5 years of age for the temporary relief of symptoms of hay fever or other respiratory allergies.

McNeil has developed a new 10 mg ODT formulation to provide consumers a convenient option for dosing that does not require swallowing a whole tablet and may be dosed with or without water. This NDA requests approval of the 10 mg ODT product for the temporary relief of symptoms of hay fever and other upper respiratory allergies. At this time sponsor does not plan to market this new formulation for the OTC indication: relief of itching due to hives (urticaria), and therefore, only labeling for the OTC allergy indication is submitted in this NDA.

This application relies on the safety and effectiveness of the reference listed drug (RLD), Zyrtec, 10 mg tablet, therefore, no efficacy/safety study was conducted with cetirizine ODT tablets.

CLINICAL PHARMACOLOGY PROGRAM

A bioequivalence and food effect study (CETALY1003) was conducted to support this NDA. This was a randomized, open-label, single-dose, crossover study in healthy male and female adults. Twenty-eight (28) subjects were enrolled in this study and were randomized to a particular sequence of treatments. Subjects received Treatments A, B, C, or D in the first 4 periods and all subjects received Treatment E in Period 5.

This study had 2 parts. Part 1 of the study was a 4-way, randomized, crossover study design, where subjects received the following treatments under fasting conditions, after an overnight fast of at least 10 hours:

- Treatment A: A single 10 mg dose of cetirizine ODT with 240 mL water.
- Treatment B: A single 10 mg dose of cetirizine ODT without water.
- Treatment C: (US marketed product): A single 10 mg dose of the currently marketed US cetirizine tablet (ZYRTEC®) with 240 mL of water.
- Treatment D: (Canadian marketed product): A single 10 mg dose of the currently marketed Canadian cetirizine tablet (REACTINE®) with 240 mL of water.

Part 2 of the study consisted of the following treatment administered after an overnight fast of at least 10 hours:

- Treatment E: A single 10 mg dose of cetirizine ODT administered approximately 30 minutes after the start of a high-fat breakfast with 240 mL of water.

Dropouts were not to be replaced unless the number of subjects completing Part 1 was less than 24 subjects or the number of subjects completing Part 2 was less than 18 subjects.

In each period, subjects checked into the site on the evening before dosing. The enrolled subjects were randomized to a particular sequence of treatments for Part 1, and received Treatments A, B, C, and D over 4 periods. The dosing for each consecutive study period was separated by a 4 to 7 day washout interval.

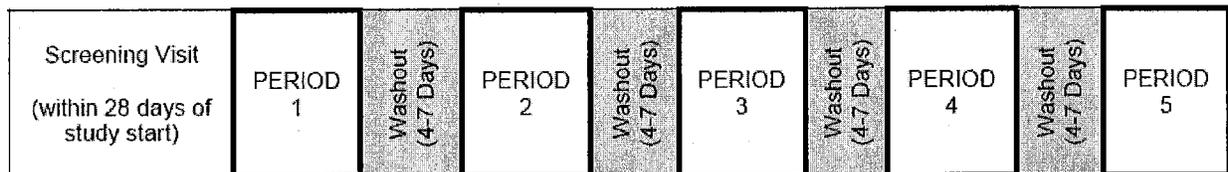
All treatments were administered to subjects after an overnight fast of at least 10 hours followed by pharmacokinetic (PK) blood sampling for 32 hours in each period for both parts of the study. After dosing, subjects continued to fast for an additional 4 hours until lunch was served at approximately noon. After the Hour 2 blood sample was collected, subjects were provided 120 mL of water to maintain adequate hydration.

In Part 2, all procedures remained similar to Part 1, except subjects were given a high-fat breakfast approximately 30 minutes prior to administration of Treatment E (Period 5). The caloric content of the meal was according to the Food and Drug Administration (FDA) guidance for Food-Effect Bioavailability Studies.¹ Subjects consumed the meal in 30 minutes or less, and the treatment was administered approximately 30 minutes after the start of the meal.

Blood samples (4 mL) were collected during each study period, predose (0 hr), and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 4, 6, 8, 12, 16, 24, 28, and 32 hours after the dose. Plasma was split into 2 aliquots, harvested, and stored frozen at -20°C until assayed for cetirizine using a validated bioanalytical assay with liquid chromatographic separation and tandem mass detection (LC/MS/MS) method.

A total of 355 mL of blood was collected for males, and up to 370 mL of blood was collected for females (total of 340 mL for plasma cetirizine concentrations, 15 mL for screening clinical laboratory testing, and 15 mL for serum pregnancy at check-in). The duration of the study after screening was approximately 43 days.

The study outline is presented in the following figure:



Sponsor's Results and Conclusions:

Pharmacokinetic Results:

A summary of pharmacokinetic parameters for all treatments is presented in Table 1 below.

Table 1: Summary of Pharmacokinetic Parameters by Treatment					
	Treatment A	Treatment B	Treatment C	Treatment D	Treatment E
Pharmacokinetic Parameters	Mean ± SD (CV%) (N=28)	Mean ± SD (CV%) (N=28)	Mean ± SD (CV%) (N=28)	Mean ± SD (CV%) (N=28)	Mean ± SD (CV%) (N=27)
C_{MAX} (ng/mL)	292 ± 53.5 (18.3)	288 ± 55.7 (19.3)	303 ± 60.4 (19.9)	303 ± 53.4 (17.6)	182 ± 30.5 (16.8)
T_{MAX} (hr) ¹	1.00 (0.50,2.01)	1.13 (0.50,4.00)	1.00 (0.50,2.01)	0.89 (0.52,2.00)	4.01 (2.50,12.00)
AUC_{LAST} (ng*hr/mL)	2597 ± 402 (15.5)	2556 ± 453 (17.7)	2522 ± 575 (22.8)	2593 ± 449 (17.3)	2415 ± 360 (14.9)
AUC_{INF} (ng*hr/mL)	2787 ± 455 (16.3)	2722 ± 525 ² (19.3)	2706 ± 635 (23.5)	2792 ± 515 (18.5)	2653 ± 439 (16.5)
K_{EL} (1/hr)	0.0844 ± 0.0143 (16.9)	0.0855 ± 0.0155 ² (18.1)	0.0842 ± 0.0138 (16.4)	0.0847 ± 0.0151 (17.8)	0.0807 ± 0.0134 (16.6)
$T_{1/2}$ (hr)	8.4 ± 1.3 (15.6)	8.3 ± 1.4 (16.8) ²	8.4 ± 1.3 (15.0)	8.4 ± 1.5 (17.2)	8.8 ± 1.4 (16.3)
% AUC_{extrap} (%)	6.63 ± 2.71 (40.9)	6.69 ± 2.94 ² (43.9)	6.58 ± 2.69 (40.9)	6.89 ± 3.15 (45.8)	8.68 ± 3.10 (35.7)
Treatment A: cetirizine HCl ODT 1 x 10 mg [with water] fasted Treatment B: cetirizine HCl ODT 1 x 10 mg [without water] fasted Treatment C: cetirizine HCl (ZYRTEC [®] , McNeil Consumer Healthcare) 1 x 10 mg [with water] fasted Treatment D: cetirizine HCl (REACTINE [®] , Keata Pharma Inc.) 1 x 10 mg [with water] fasted Treatment E: cetirizine HCl ODT 1 x 10 mg [with water] fed					
¹ T_{MAX} is presented as Median (Minimum, Maximum) ² N=27					
Source: Table 14.2.2.1, Table 14.2.2.2, Table 14.2.2.3, Table 14.2.2.4, and Table 14.2.2.5.					

Bioequivalence analysis results are presented in Table 2.

Table 2: Statistical Analysis of Plasma Total Cetirizine Pharmacokinetic Parameters					
		Treatment			
		LS Means			
Treatment Comparison (Test vs Reference)	Parameter	Test	Reference	% LS Means Ratio	Confidence Intervals (90% Confidence)
A vs C	AUC _{LAST} (ng*hr/mL)	2566	2468	103.96	100.48 - 107.56
	C _{MAX} (ng/mL)	287	298	96.34	91.77 - 101.13
	AUC _{0-INF} (ng*hr/mL)	2749	2643	104.02	100.28 - 107.90
B vs C	AUC _{LAST} (ng*hr/mL)	2519	2468	102.07	98.66 - 105.61
	C _{MAX} (ng/mL)	283	298	95.16	90.65 - 99.90
	AUC _{0-INF} (ng*hr/mL)	2708	2643	102.46	98.73 - 106.33
E vs A	AUC _{LAST} (ng*hr/mL)	2389	2570	92.97	89.23 - 96.87
	C _{MAX} (ng/mL)	179	287	62.55	58.95 - 66.36
	AUC _{0-INF} (ng*hr/mL)	2618	2753	95.11	91.13 - 99.27

Treatment A: cetirizine HCl ODT 1 x 10 mg [with water] fasted
 Treatment B: cetirizine HCl ODT 1 x 10 mg [without water] fasted
 Treatment C: cetirizine HCl (ZYRTEC[®], McNeil Consumer Healthcare) 1 x 10 mg [with water] fasted
 Treatment D: cetirizine HCl (REACTINE[®], Keata Pharma Inc.) 1 x 10 mg [with water] fasted
 Treatment E: cetirizine HCl ODT 1 x 10 mg [with water] fed
 Parameters were ln-transformed prior to analysis. The LS means for treatment A are not the same for each comparison since different statistical models were used.

Source: Table 14.2.2.7, Table 14.2.2.8, and Table 14.2.2.9.

Mean values of peak and overall exposure of cetirizine (C_{MAX}, AUC_{LAST}, AUC_{INF}) were similar for all fasted cetirizine treatments (Treatments A - D). For the fasted cetirizine treatments (Treatments A - D), median T_{MAX} was approximately 1 hour postdose. T_{1/2} was similar for all treatments. Percent of AUC_{INF} which is extrapolated (%AUC_{extrap}) was low for all treatments (6.63 – 8.89%), indicating that the majority of the cetirizine exposure was captured during the sampling interval.

Mean C_{MAX} after Treatment E (cetirizine ODT with water, fed) was 63% (based upon LS means ratio) of that after Treatment A (cetirizine ODT with water, fasted); median T_{MAX} was increased by approximately 3 hours with food.

Statistical comparisons for Treatments A versus C and B versus C showed that cetirizine ODT with and without water was bioequivalent to ZYRTEC[®] administered with water in the fasted state.

A significant food effect was observed with the cetirizine ODT formulation for C_{MAX}, but not for AUC. This is consistent with previously reported food effect on peak concentrations for the reference product (ZYRTEC[®]).¹

Conclusion:

- Cetirizine 10 mg ODT when taken with or without water in the fasted state is bioequivalent to 10 mg of the currently marketed cetirizine reference product, (ZYRTEC®).
- The rate, but not extent of cetirizine ODT absorption, was affected by a high-fat meal, resulting in a C_{MAX} which was 63% of that in the fasted state.
- Single, 10 mg, oral doses of cetirizine ODT, administered under fed and fasted conditions, were generally safe and well-tolerated by the healthy male and female subjects.

Clinical Pharmacology Reviewer's comments:

NDA 22-578 is fileable.

Food effect greater than previously known. This will be a review issue and may impact labeling.

This BE study is the pivotal study and therefore, we will request a DSI audit:

Study # CETALY1003

Clinical Site: MDS Pharma Services, 1930 Heck Avenue, Building 2, Neptune, NJ 07753; Investigator: Sandra M. Connolly, MD (Clinical Report No. AA79661); Phone: 732-502-8900; Fax: 732-502-9484

Analytical Site:

(b) (4)



ZYRTEC ODT (Cetirizine HCl) NDA 22-578

Sponsor: McNeil Consumer Health (J&J)

Zyrtec for the temporary relief of
symptoms of hay fever and other upper
respiratory allergies

Filing Meeting

Arun Agrawal, Ph.D.
Clinical Pharmacology
Jan 5, 2010



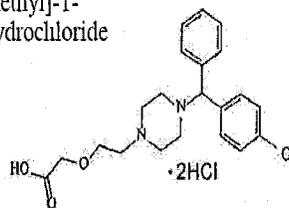
Overview

- Reference name: Cetirizine hydrochloride

(±)-[2-[4-[(4-chlorophenyl) phenylmethyl]-1-piperazinyl] ethoxy] acetic acid, dihydrochloride

- A metabolite of hydroxyzine

- MW: 461.82



- White, crystalline powder, freely soluble in water

- Racemic mixture of two stable enantiomers that do not interconvert



Overview (contd.)

- An orally active and selective peripheral H1-receptor antagonist
- First approved in 1995
 - Approved for SAR in adults and children \geq 2 years old
 - Approved for PAR in adults and children \geq 6 months old
 - Approved for OTC use in 2007 for adults and children \geq 2 years old
 - Approved for OTC use for the relief of itching due to hives (urticaria)
- New NDA submitted for a 10 mg ODT formulation
 - to provide consumers a convenient option for dosing

3



Overview (contd.)

- Cetirizine HCl is bitter in taste
- ODT contains cetirizine HCl (b) (4) of the drug substance) incorporated in an IR tablet
- 10 mg ODT formulation is provided as a citrus flavored tablet to give pleasant taste and weighs 325 mg
- In vitro data suggest that ODT disintegrates in 10-27 seconds
- ODT is described as (b) (4) " and "Melts in Your Mouth CITRUS FLAVOR" on the principal display panel
- ODT is not intended to be chewed

4



Current NDA 22-587:

Evaluated the BE of the 10 mg cetirizine HCl ODT taken with and without water to the currently marketed reference product, Zyrtec

Also evaluated the effect of a high-fat-breakfast on the BA of cetirizine HCl from the ODT formulation

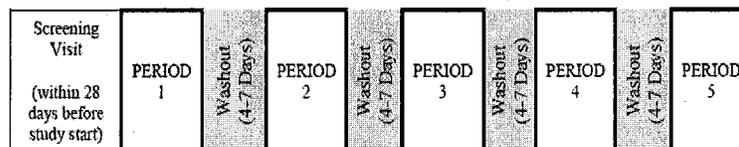
Safety data from this study

5



Design of Clin Pharm (Bioequivalence) Study

Study CETALY1003 had a randomized, open-label, single-dose, five-way crossover design (see diagram below).



Fixed sequence, four-way randomized, five-way crossover

6



Design of Clin Pharm BE Study (contd.)

All 28 healthy subjects received Treatments A, B, C, D and E (n=27)*. The study was conducted in two parts :

- Treatment A: A single 10 mg dose of cetirizine ODT with 240 mL water.
 - Treatment B: A single 10 mg dose of cetirizine ODT without water.
 - Treatment C: (US marketed product): A single 10 mg dose of the currently marketed US cetirizine tablet (Zyrtec) with 240 mL of water.
 - Treatment D: (Canadian marketed product): A single 10 mg dose of the currently marketed Canadian cetirizine tablet (Reactine) with 240 mL of water.**
- Part 1
- Treatment E: A single 10 mg dose of cetirizine ODT administered approximately 30 minutes after the start of a high-fat breakfast with 240 mL of water.
- Part 2

* One subject was dropped due to positive alcohol screen at check-in for Treatment E 7

** For registration in Canada



Blood Sampling for PK

Blood samples (4 mL) were collected during each study period, pre-dose (0 hr), and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 4, 6, 8, 12, 16, 24, 28, and 32 hours after the dose. Plasma was split into two aliquots, harvested and stored frozen at -20°C until assayed for cetirizine using validated bioanalytical methods.

A total of 355 mL of blood per subject was collected for males and up to 370 mL of blood was collected for females (total of 340 mL for plasma total cetirizine concentrations, 15 mL for screening clinical laboratory testing, and 15 mL for serum pregnancy at check-in). The duration of the study after screening was approximately 43 days.

Sponsor's Findings

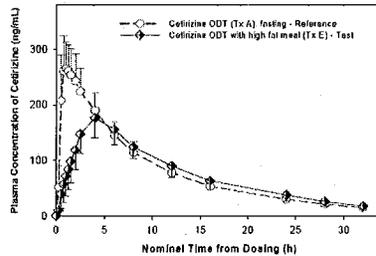
- Systemic exposures (AUC and C_{max}) met the BE criteria between 10 mg ODT Cetirizine tablets (taken with or without water) and 10 mg Zyrtec tablets (taken with water) in the fasted state

9

Sponsor's Findings (contd.)

-High-fat-breakfast resulted in delayed T_{max} (by 3 hr) and 37% lower C_{max} than the fasted state for ODT, however, the AUCs met the BE criteria

Figure 11.4.1.1-4 Mean Plasma Cetirizine Concentrations: Comparison of Treatments E and A



Treatment E: cetirizine HCl ODT 1 x 10 mg [with water] fast
Treatment A: cetirizine HCl ODT 1 x 10 mg [with water] fast

These findings are consistent with reported food effects on T_{max} (delayed by 1.8 hr), C_{max} (decreased by 30%) and AUC (no effect) of cetirizine for the reference product Zyrtec

10



Bioanalytical Issues

- No key concerns been found
- Method validation and analytical reports are in
- Request DSI audit
 - Samples analyzed by [REDACTED] (b) (4)
 - [REDACTED] (b) (4) Validation report for method [REDACTED] (b) (4)
 - Bioanalytical report [REDACTED] (b) (4)

11



Mid-cycle Deliverables and Preliminary Conclusions

- Mid-cycle deliverables:
 - Assess clinical pharmacology analyses
 - Key review questions: study was not completely randomized
- Fileable from Clinical Pharmacology perspective
 - Request DSI audit

12

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22578	ORIG-1	MCNEIL CONSUMER HEALTHCARE DIV MCNEIL PPC INC	CETIRIZINE HCL ORALLY 10MG TABS

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

/s/

ARUN K AGRAWAL
01/08/2010

PARTHA ROY
01/08/2010