CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022578Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	12-Jul-2010
From	Lesley-Anne Furlong
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 22578
Applicant	McNeil Consumer Healthcare
Date of Submission	6-Nov-2009
PDUFA Goal Date	9-Sep-2010
Proprietary Name / Established (USAN) names	Zyrtec Allergy/cetirizine HCl
Dosage forms / Strength	Orally disintegrating tablet/10 mg
Proposed Indication(s)	Temporarily relieve these symptoms due to hay fever or other upper respiratory allergies: • Runny nose • Sneezing • Itchy, watery eyes • Itching of the nose or throat
Recommended:	Approval, pending satisfactory labeling negotiations, chemistry review, and inspection of the manufacturing and clinical study sites

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1. Introduction

The applicant is proposing a new, citrus flavored, orally disintegrating tablet formulation of cetirizine HCl 10 mg ("cetirizine ODT" in this review) for over-the-counter use. The new formulation does not require swallowing a tablet. Cetirizine HCl is already available OTC in capsule, tablet, syrup, and chewable tablet formulations.

The application was supported by a successful bioequivalence (BE) trial comparing the proposed tablet to Zyrtec (cetirizine) 10 mg tablets. There were no serious adverse events in the BE trial. The most common adverse event reported in the BE trial was "sleepy," coded as somnolence. The proposed product and Zyrtec are appropriately labeled for this adverse event.

In addition, the applicant provided an update of postmarketing safety. No new safety issues were identified among the postmarketing reports.

The applicant proposed to add (b) (4) and "Melts in your mouth" on the principal display panel (PDP). The review team did not agree with the applicant's proposal to put (b) (4) on the PDP because (b) (4) implies a comparative claim that was not supported by data. The applicant agreed to remove (b) (4) and proposed the term (b) (4) The review team is uncertain wha (b) (4) will mean to a consumer and has asked the company to address consumer understanding with a consumer study. The term (b) (4) is not part of the name and is not required for labeling; therefore, taking time to understand the term and deciding whether it should go on labeling could be addressed by the applicant at a later date.

The Uses and Warnings sections of labeling are the same for cetirizine ODT and Zyrtec tablets. Directions for cetirizine ODT differ from directions for Zyrtec tablets by including the statements: "Tablet melts in mouth. Can be taken with or without water." These two statements are supported by the data provided in the submission. As with Zyrtec tablets, dosing is one tablet daily and the product is for adults and children who are six years old and older.

At the time this review was finalized, negotiations for labeling had not been completed. In addition, the chemistry review and inspections of the clinical and manufacturing sites were not completed. To date, no approvability issues have been identified by the review team. I recommend approval of the application pending a satisfactory outcome to labeling negotiations, the chemistry review, and the inspections.

2. Background

FDA first approved cetirizine HCl for prescription use in 1995; subsequently, FDA approved cetirizine HCl for OTC use on November 16, 2007.

Cetirizine HCl is available OTC in multiple OTC formulations

- 10 mg capsule, tablet, and chewable tablet
- 5 mg capsule, tablet, and chewable tablet
- 5 mg/5ml oral syrup children's formulation
- 5 mg tablet combined with pseudoephedrine hydrochloride 120 mg

Cetirizine has two OTC indications and each indication is packaged separately. The applicant is pursuing only the indication "symptoms due to hay fever or other upper respiratory allergies" in the present application; the second indication, "relieves itching due to hives," is not requested.

Cetirizine HCl remains available for prescription use for perennial allergic rhinitis in children ages 6 months to 23 months, as well as for uncomplicated skin manifestations of chronic idiopathic urticaria in children 6 months to 5 years of age.

In this application, efficacy and safety is supported by Study 1003 that shows that the new formulation is bioequivalent to an approved OTC tablet, Zyrtec. Safety is further supported by a summary of postmarketing safety data accumulated since January 16, 2007, the cutoff date for the four-month safety updated submitted in support of the OTC switch application of cetirizine in NDA 19835/S022.

3. CMC/Device

At the time this review was finalized, the chemistry review and the manufacturing site inspections were not completed; however, the chemistry team had not identified any approvability issues.

The proposed drug product is a citrus-flavored, white to off-white, round tablet with "Z10" debossed on one side. (b) (4) of the cetirizine is achieved by (b) (4). The drug product is packaged in blister cards in cartons containing 6, 12, 24, or 66 tablets.

The in vitro disintegration time of the ODT formulation was within 30 seconds, which is acceptable for an orally disintegrating tablet. Regarding the term (b) (4) proposed by the applicant for the principal display panel (PDP), in vitro dissolution testing in four different media did not show that the new formulation dissolved faster than the approved tablet. Zyrtec dissolved faster than the new formulation in water and in pH 6.8 phosphate buffer, and the new formulation dissolved faster than Zyrtec in acidic media (0.1 N HCl and pH 4.5 acetate buffer). There was no in vivo testing of dissolution; however, salivary pH is usually around 7[1], and therefore, the in vitro results suggest that dissolution in the mouth might in fact be slower for the new formulation compared with Zyrtec.

[1] Gonong's Review of Medical Physiology. 23rd edition (2010)

4. Nonclinical Pharmacology/Toxicology

There were no issues identified by the pharmacology/toxicology review team. The pharmacology/toxicology team recommended approval from a pharmacology/toxicology perspective.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology team has reviewed the application and finds it acceptable pending satisfactory DSI inspection of the study site for pivotal Study 1003. Proposed labeling was acceptable.

Study 1003 compared cetirizine ODT 10 mg to-be-marketed formulation to Zyrtec 10 mg, the reference listed drug. The study also evaluated the effects of water and a high-fat breakfast.

The results showed that, under fasted conditions, cetirizine ODT taken with or without water is bioequivalent to the approved Zyrtec tablet taken with water. A high-fat-breakfast decreased plasma cetirizine C_{MAX} by 37% and delayed T_{MAX} by 3 hours, which is comparable to the changes observed with approved Zyrtec products. (C_{MAX} was decreased by 38% and T_{MAX} was delayed by 3 hours for Zyrtec chewable tablets; C_{MAX} was decreased by 23% and T_{MAX} was delayed by 1.7 hours for Zyrtec tablets). Because Rx and current OTC labels do not restrict Zyrtec dosing relative to food, the clinical pharmacology team recommended no change in labeling.

Study 1003 is briefly summarized here; a detailed review can be found in the clinical pharmacology review.

Study 1003 was an open-label, single-dose, four-way randomized and five-way crossover study in healthy adults. Subjects received Treatments A, B, C, or D in the first four periods and Treatment E in Period 5. Twenty-eight subjects were enrolled.

In Part 1, subjects received the following treatments under fasting conditions:

- 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: A single 10 mg dose of the currently marketed U.S. cetirizine tablet (ZYRTEC®) with 240 mL water.
- Treatment D: A single 10 mg dose of the currently marketed Canadian cetirizine tablet (REACTINE®) with 240 mL water.

Subjects were randomized to a particular sequence of treatments. Dosing was separated by a 4 to 7 day washout interval.

In Part 2, subjects received the following treatment:

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

Table 1, Table 2, and Table 3 come from the clinical pharmacology review. Cetirizine ODT met statistical criteria for bioequivalence to marketed Zyrtec tablets, whether given with or without water. Table 1 shows the data for dosing with water, and Table 2 shows the data for dosing without water. Table 3 shows a significant food effect for C_{MAX}, but not for AUC. The same data are shown in graphic form in Figure 1.

Table 1. 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

Table 2. *Effect of Water:* Pharmacokinetic parameters and bioequivalence statistics single dose administration of cetirizine ODT (B) and 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)		

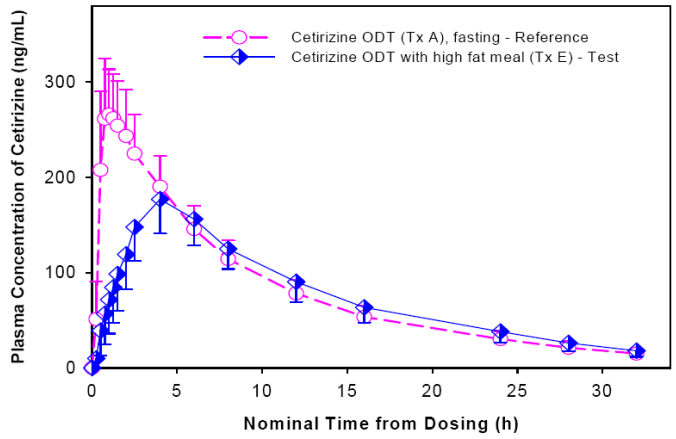
Treatment B = cetirizine HCl ODT 1 x 10 mg (without water) fasted
Treatment C = cetirizine HCl (Zyrtec) 1 x 10 mg (with water) fasted

Table 3. *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 1. 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

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

Efficacy was supported by Study 1003, which showed that cetirizine ODT was bioequivalent to the approved reference listed drug, Zyrtec 10 mg tablets. Cetirizine ODT may be taken with or without water. See Section 5 for a description of the design and results of Study 1003.

8. Safety

Safety was supported by the demonstration of bioequivalence of cetirizine ODT to the marketed Zyrtec 10 mg tablets. In addition, the safety database for the application included

- Safety data from Study 1003
- The company's safety data accrued since the most recent four-month safety update for Zyrtec sNDA 19-835 (17-Jan-2007 to 16-Jan-2009)
- FDA Adverse Event Reporting System (AERS) data (1-Jan-2007 to 31-Dec-2008)
- World Health Organization (WHO) Collaborating Centre for International Drug Monitoring, Uppsala (WHO-UMC) data (1-Jan-2007 to 20-May-2009)
- Data from the American Association of Poison Controls Centers (1-Jan-2007 to 15-Jun-2009)
- Data from the Drug Abuse Warning Network (DAWN) (1-Jan-2007 to 22-Jun-2009)
- Published literature from clinical trials (1-Jan-2007 to 22-Jun-2009)
- A four-month safety update submitted during the review cycle

I have evaluated the clinical reviewer's analysis of the above data and conclude that the safety data continue to support the safety of cetirizine for OTC use.

Adverse Events in the Clinical Development Program

Study 1003 exposed 28 healthy subjects to cetirizine ODT and two control formulations. Part 1 of the study was a four-way, randomized, single-dose, fasted crossover study. Part 2 of the study evaluated PK of cetirizine ODT after a high fat breakfast.

Twenty eight subjects completed Part 1, and 27 subjects completed Part 2 of the study. Twenty-one subjects were male; seven subjects were female. The mean age of subjects was 35 years old, with a range of 20 to 52 years. There were no deaths, serious adverse events (SAEs), or adverse events leading to discontinuation. Overall, 15 subjects reported adverse events. Somnolence was reported 19 times for 14 subjects, including 11 subjects following Treatment E (fed state). There were no significant blood chemistry or vital sign changes. ECGs were performed only at baseline. "Somnolence" was the MedDRA used to code the verbatim term "sleepy." It is likely that somnolence was drug-related as this is a labeled adverse event for cetirizine, and there was a cluster of reports around the expected T_{MAX} (see clinical review by Dr. Raffaelli).

Current labeling for Zyrtec and proposed labeling for cetirizine ODT address the issue of drowsiness. Labeling states that drowsiness may occur and contains precautionary language about driving, operating machinery, or using alcohol, sedatives, or tranquilizers.

Safety Findings in the Postmarketing Data

Overall, there were no unexpected safety findings in the review of postmarketing data for cetirizine. Exposure in the two year period covered by the postmarketing data was robust and is summarized in Table 4, which also provides numbers of case reports in three of the

databases reviewed by the applicant. The applicant estimates that worldwide exposure to cetirizine from January 2007 to January 2009 was (b) (4), representing about 36 million patient-years. Sales in the United States constitute approximately (b) (4) of the world market.

Table 4. Overview of Worldwide Exposure and Safety Data for Cetirizine in the Summary of Clinical Safety

Post Marketing Exposure (5 mg and 10 mg tablets and 5 mL doses sold/dispensed)	(b) (4)
Dosage units sold/dispensed in US (January 2007 - January 2009)	(b) (4)
• US OTC	
• US Rx	
Dosage units sold/dispensed outside US (January 2007 - December 2008)	(b) (4)
• ex-US OTC	(b) (4)
• ex-US Rx (based on an estimated (b) (4) doses/prescription)	(b) (4)
Clinical Bioequivalence Study	
Study CETALY1003 - Subjects, N	28
Reports with serious outcome, excluding deaths	0
Deaths	0
Company Database (January 17,2007 - January 16, 2009)	
Total cetirizine reports of adverse events	4778
• Reports with serious outcome, (excluding deaths)	621
• Deaths	52
FDA Safety Data (January 1,2007 - December 31, 2008)	
Reports from FDA Adverse Event Reporting System (AERS)	814
• Reports with serious outcome" (excluding deaths)	702
• Deaths	40
World Health Organization Collaborating Centre for International Drug Monitoring, Uppsala (WHO-UMC) Safety Data (January 1, 2007 - June 19,2009)	
Reports from WHO-UMC safety database	883
• Reports with serious outcome, (excluding deaths)	562
• Deaths	29
Published Safety Data (January 2007 to June 22, 2009)	
Controlled trial subjects, n	2431
• Reports with serious outcome, (excluding deaths)	4
• Deaths	0

Source: Summary of Clinical Safety, Module 2, Vol 1, p. 126

The postmarketing data are analyzed in detail by Dr. Raffaelli in his clinical review, and only the conclusions of the review will only be summarized.

The applicant's safety database contained 4778 case reports, of which 52 (1.1%) were deaths. Dr. Raffaelli evaluated all 52 MedWatch forms reporting death and found that most deaths

were of unknown cause or confounded. He identified two deaths as potentially related to cetirizine use. There was one case of a 23 year old male who took cetirizine and clemastine with alcohol and died after an eight-story fall. I agree with Dr. Raffaelli that cetirizine misuse may have contributed to this death. Both clemastine and cetirizine are sedating anithistamines and are appropriately labeled to avoid use with alcohol. The second case was a woman with several miscarriages while taking cetirizine. However, miscarriage is a common pregnancy outcome and occurs with or without concurrent drug use. It would therefore be difficult to make a case for a cetirizine contribution based on this case.

FDA Adverse Event Reporting System (AERS) data overlaps to a large extent with the applicant's database because of U.S. reporting requirements. The applicant and Dr. Raffaelli did not identify any significant trends in the AERS database.

World Health Organization (WHO) Collaborating Centre for International Drug Monitoring, Uppsala (WHO-UMC) data includes AERS data. The applicant and Dr. Raffaelli did not identify any new or unexpected safety signals.

The applicant and Dr. Raffaelli evaluated data from the three postmarketing databases above, as well as data from the American Association of Poison Controls Centers (AAPCC) and from the Drug Abuse Warning Network (DAWN), for signals for abuse or other misuse of cetirizine. Dr. Raffaelli agreed with the applicant that "there is no indication that abuse or misuse of cetirizine occurs to a significant degree."

The applicant searched three online databases for published literature from clinical trials involving treatment with cetirizine; Dr. Raffaelli did an independent literature search as well. Dr. Raffaelli's review contains a brief summary of each article. Both the applicant and Dr. Raffaelli concluded that the published literature supports the continued safety of cetirizine for OTC marketing.

The applicant submitted a four-month safety update during the review cycle. Dr. Raffaelli concluded in his review of the four-month safety update that "overall, there are no significant safety issues identified that would necessitate labeling changes."

On 7/8/2010, there were no open safety issues for cetirizine in FDA's repository for tracking safety issues ("DARRTS").

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

The proposed dosing directions are for adults and children 6 years of age and older. Because the product is bioequivalent to Zyrtec 10 mg, and Zyrtec 10 mg is labeled for children 6 years of age and older, the product is appropriately labeled for children 6 years of age and older. The applicant requested a waiver for children younger than 6 years of age. The primary

reviewer and I agreed with the request for a waiver and presented our assessment to FDA's Pediatric Review Committee (PeRC) on May 5, 2010. The PeRC agreed with the regulatory rationale for the waiver, as follows:

- For children 1 to < 2 years old, the disease/condition does not exist
- For children 2 to < 6 years old, the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of children in this age group.
- For children from 6 to 17 years old, the product is appropriately labeled based on studies and extrapolation

The regulatory rationale is consistent with the Agency's previous decision not to label cetirizine for children < 2 years old for (seasonal) allergic rhinitis because children generally need to be exposed to allergens for at least two seasons before they develop a seasonal allergy. In addition, for children < 2 years old, parents may not be able to properly diagnose an allergic rhinitis condition in this age group in an OTC environment.

The proposed product does not offer any additional meaningful therapeutic benefit over existing therapies for children 2 to < 6 years old; cetirizine syrup (1 mg/mL) and cetirizine chewable tablet (5 mg) are approved for children in this age range.

11. Other Relevant Regulatory Issues

The applicant has submitted a signed patent form, FDA Form 3542a, certifying that there are no relevant patents that claim the drug substance, drug product, or method of use.

The applicant certified that it did not use the services of anyone who was debarred in connection with the application.

The application contained a signed financial certification form (FDA Form 3454) certifying that there were no financial arrangements with the clinical investigators that could bias study outcomes.

The DSI inspection of the clinical site for Study 1003 and the manufacturing site inspection had not been completed at the time this review was finalized.

12. Labeling

The Division of Nonprescription Regulation Development (DNRD) and the Division of Medication Error Prevention and Analysis (DMEPA) provided labeling reviews. DNRD recommended the following changes:

- (b) (4) because the statement imply a comparative claim not supported by data; I concur.

- Revision of "melts in your mouth" to include [redacted] while I concur that the time for melting would be informative, the data to support [redacted] in the mouth are not in the submission. At the time this review was finalized, the applicant had requested [redacted]; the review team did not agree and has recommended using either "melts in your mouth" or providing a [redacted]

- Addition of days of the week and times when a person is available to respond to questions; I concur.

DNRD found the flag "original prescription strength" acceptable, and cleared the inclusion of the flag by the ODE IV immediate office (internal procedure). The flag "New Form" was also acceptable; however, it must be removed following 180 days of marketing.

DMEPA found the trade name acceptable. DMEPA provided additional formatting comments that had not yet been conveyed to the applicant at the time this review was finalized.

The applicant removed [redacted] and replaced it with [redacted] The review team expressed uncertainty about the meaning of [redacted] The Division Director recommended that the applicant test the term in a consumer study to find out how consumers understand the term, [redacted] At the time this review was finalized, this recommendation had been communicated to the applicant and DNRD was awaiting a response.

13. Recommendations/Risk Benefit Assessment

I recommend approval of the application pending a satisfactory outcome to labeling negotiations, the chemistry review, and the inspections of the manufacturing and clinical study sites.

The proposed product is bioequivalent to an approved OTC product Zyrtec, and the risk/benefit profile should therefore be the same. The review team has identified no new safety issues. Routine postmarketing surveillance is acceptable for postmarketing risk evaluation. I have no comments to convey to the applicant.

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/

LESLEYANNE A FURLONG
07/13/2010