CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-578
Priority or Standard	Standard
Submit Date(s)	November 6, 2009
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PDUFA Goal Date	September 9, 2010
Division / Office	DNCE/ODE IV
Reviewer Name(s)	Ryan Raffaelli, M.D.
Review Completion Date	July 7, 2010
Established Name	Cetirizine
(Proposed) Trade Name	Zyrtec® (b) (4)
Therapeutic Class	Anti-histamine
Applicant	McNeil Consumer Healthcare
Formulation(s)	10 mg oral disintegrating tablet
Dosing Regimen	One tablet daily
Indication(s)	Temporary relief of hay fever and upper respiratory allergies
Intended Population(s)	6 years to adult

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The applicant provided adequate safety and efficacy data to support the proposed 10 mg oral disintegrating tablet (ODT) formulation for Zyrtec® for the following indication:

- Temporary relief of allergic rhinitis symptoms due to hay fever or other upper respiratory allergies (runny nose, itchy, watery eyes, sneezing, and itching of the nose or throat) in children and adults 6 years of age and older.

No new indications were proposed for this drug product and no new efficacy trials were performed. The applicant relied on the demonstration of bioequivalence to an approved cetirizine product for efficacy in the treatment of symptoms of allergic rhinitis. The directions for use are similar to those of other approved cetirizine drug products, and appear adequate.

Based on my review of the clinical data, I recommend APPROVAL of this application pending labeling changes based on all recommendations (See **Section 9.2**), and a satisfactory inspection of the clinical trial facility.

1.2 Risk Benefit Assessment

McNeil Consumer Healthcare is seeking the FDA's approval of the proposed 10 mg oral disintegrating tablet (ODT) formulation of Zyrtec® (cetirizine hydrochloride) for OTC status as a convenient, alternative dosing formulation. Cetirizine is currently approved and marketed in several other formulations for OTC use, and has a good safety profile in this setting. Approved OTC indications are for relief of symptoms of allergic rhinitis in adults and children down to 2 years of age, and relief of itching due to hives down to 6 years of age. Cetirizine is labeled for prescription use in children down to 6 months of age for relief of symptoms of allergic rhinitis and chronic idiopathic urticaria (hives). The applicant is currently seeking only the allergic rhinitis indication (down to 6 years). Ten (10) mg dosage strengths for cetirizine products are approved down to 6 years of age. No new indications are proposed; therefore, no new clinical trials were performed other than bioequivalence to an approved cetirizine product. There are no submitted plans to manufacture lower dosage strengths (5 mg) of this ODT formulation, as there are other formulations (syrup and chewable tablet) that provide this lower strength. There are other similar, available products in the same class of drugs (loratadine) that are marketed OTC for the same indication.

Efficacy

The applicant relied on the demonstration of bioequivalence to an approved cetirizine product for efficacy in the relief of symptoms of allergic rhinitis. Adequate data from clinical trials submitted with the original NDAs were referenced to support the efficacy of cetirizine for the proposed indication.

A food-effect trial comparing administration of cetirizine to healthy volunteers after a high-fat meal and under fasting conditions determined that the C_{max} is decreased by 37% while the AUC remains unchanged in the fed subjects (See **Section 4.4.3**). Also, the T_{max} is delayed by three hours over the T_{max} for the cetirizine tablet following food intake. This delay is similar to that of the approved chewable tablet formulation (See **Section 5.3** and **Table 7**). Yet, this reviewer and the clinical pharmacology review team agree that the changes in C_{max} and T_{max} following food intake do not significantly affect the overall efficacy of cetirizine for once-daily use. According to the prescription insert for the tablet, the onset of action of a single 10 mg dose in clinical trials occurred within 20 minutes in 50% of adult subjects, and within one hour in 95% of subjects. Taking the product after eating may delay the time to effect, but the difference may not be clinically significant for daily use.

Safety

The applicant relies primarily on the data from clinical trials and from postmarketing databases as well as a review of literature. Clinical trial data were previously submitted and evaluated for safety in support of the original single-ingredient cetirizine NDAs. Safety data submitted in this application include:

- Analysis of all OTC post marketing adverse events received by McNeil for cetirizine products (January 2007 to November 2009).
- Summary and analysis of adverse events reported to the FDA from the Adverse Event Reporting System (AERS) (January 2007 to December 2008).
- Summary and analysis of adverse events reported to the World Health Organization's (WHO) International Drug Monitoring Program (January 2007 to May 2009).
- Analysis of reports in the American Association of Poison Control Center (AAPCC) database (January 2007 to June 2009).
- A report of the Drug Abuse Warning Network (DAWN) for cetirizine (January 2007 to June 2009).
- A review of medical literature relevant to the safety of cetirizine (January 2007 to June 2009).

The types of adverse events for OTC cetirizine that were noted in the bioequivalence trial, postmarketing safety databases, and the medical literature are generally similar to those noted in clinical trials that supported original approval of the prescription (R_x) to OTC switches. The most common adverse events reported overall were "drug

ineffective," "somnolence," "wrong drug administered," "overdose," "drug exposure during pregnancy," "pruritis," "dizziness," "hypersensitivity," and "fatigue." There is no conclusive evidence of a causal relationship between the use of cetirizine and any previously unidentified serious or life-threatening adverse events from postmarketing experience. There was no new clustering of unlabeled AEs. Cetirizine products have been used OTC worldwide for several years without revealing new or significant safety signals. Four safety topics, arrhythmia, convulsion, thrombocytopenia and somnolence were identified as pertinent in early discussions of the R_x to OTC switches of 2nd-generation antihistamines (see below). There are no new conclusive data that these four AEs or any of the reported AEs should preclude approval of this proposed ODT formulation.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

None recommended.

2 Introduction and Regulatory Background

2.1 Product Information

The applicant is proposing a new orally disintegrating tablet formulation of cetirizine HCl. Cetirizine is currently marketed OTC for children 2 years old to adult in several formulations (5 mg and 10 mg tablet, 5 mg and 10 mg chewable tablet, and syrup 1 mg/mL) under the tradename, Zyrtec®. Cetirizine is a second generation anti-histamine that antagonizes peripheral H1 receptors with greater affinity than its parent compound, hydroxyzine[1].

The indications for current OTC Zyrtec® products:

- Temporary relief of symptoms (runny nose; sneezing; itchy, watery eyes; and itching of the nose or throat due to hay fever or other upper respiratory allergies) associated with allergic rhinitis (AR)
    - Seasonal and perennial AR in children 2 years old to adult
- Temporary relief of skin manifestations associated with chronic idiopathic urticaria (CIU), or hives, in children 6 years old to adult

1 http://www.clinicalpharmacology-ip.com/Forms/drugoptions.aspx?cpnum=110&n=Cetirizine (accessed November 23, 2009)

Allergic rhinitis and hives are OTC indications that consumers are able to self-diagnose and self-treat. The proposed product is intended to provide an alternative and convenient option for dosing that does not require swallowing a tablet, and may be dosed with and without water. The applicant proposes this product will provide the temporary relief of symptoms due to AR. At this time, they do not plan to claim an indication for relief of itching due to CIU. The proposed dosing regimen is for children 6 years old to adult to take one tablet (10 mg) once daily, and not more than one tablet in 24 hours.

2.2 Currently Available Treatments for Proposed Indications

The drugs listed in **Table 1** have been approved under either the OTC monograph[2] or original NDAs. Fexofenadine and loratadine market orally disintegrating tablet dosage forms. Only a few examples of monograph-allowed antihistamines are included, and many are marketed in combination drug products. First generation antihistamines are thought to cause more drowsiness than the second generation drug substances. OTC drug products that deviate from the monograph (e.g. extended-release, combined with non-monograph ingredient) are marketed under a NDA. Monograph antihistamines are generally labeled down to 6 years old. However, professional labeling is allowed for children from 2 – 5 years old.

Table 1: Examples of Available Antihistamine Drugs with Same Indication

Generic Name	Class	Forms	Status
loratadine	2nd generation antihistamine	several	OTC
fexofenadine	2nd generation antihistamine	several	R_x
chlorpheniramine*	1st generation antihistamine	several	OTC
dexbrompheniramine*	1st generation antihistamine	several	OTC
diphenhydramine*	1st generation antihistamine	several	Both
doxylamine*	1st generation antihistamine	tablet	OTC
clemastine	1st generation antihistamine	syrup; tablet	Both

**Monograph-allowed active ingredients*
Source: www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm and 21 CFR 341.12

2.3 Availability of Proposed Active Ingredient in the United States

Zyrtec® was approved for prescription use on December 8, 1995, and first approved for OTC use on November 16, 2007. **Table 2** lists the regulatory history for all cetirizine products since its original approval. At a meeting in May 2001, the Joint Advisory Committees on Nonprescription Drug Products and Pulmonary-Allergy Drug Products concluded that cetirizine demonstrates a safety profile suitable for use in an OTC setting. The background information, transcript and meeting minutes can be found at

[2] 21 CFR 341.12

http://www.fda.gov/ohrms/dockets/ac/cder01.htm (accessed June 21, 2010). There have been no significant safety concerns following the switch to OTC. Further review of post-marketing safety issues since the switch to OTC will be addressed in **Section 8.** There have been no key labeling changes since the switch.

As this is a new formulation of an already approved drug, see **Table 3** for current Zyrtec® OTC dosing. Zyrtec® remains "prescription only" for AR in children 6 months to 2 years old, and for itching from hives in children 6 months to 6 years old.

Table 2: Approval History of Zyrtec® Products

Approval	NDA#	Formulation	Indications	Population
Dec 8, 1995	19-835	5, 10 mg tablet	SAR, PAR, CIU	Adults Children ≥ 12y
Sept 27, 1996	20-346	1 mg/mL syrup	SAR, PAR, CIU	Adults Children ≥ 6y
May 15, 1998	sNDA 19-835/S-005 sNDA 20-346/S-002	Tablets Syrup	SAR, PAR, CIU	Adults Children 2 – 6y
Aug 10, 2001	21-150	W/ pseudoephedrine 120 mg (Zyrtec®-D)	Relief of nasal & non-nasal symp. w/ SAR and PAR	Adults Children ≥ 12y
Oct 21, 2002	sNDA 19-835/S-015 sNDA 20-346/S-008	Tablets Syrup	SAR, PAR, CIU	Adults Children ≥ 6mo
Mar 16, 2004	21-621	Chewable Tablets	SAR, PAR, CIU	SAR: Adults & Children ≥ 2y PAR/CIU: Adults & Children ≥ 6mo
Nov 16, 2007	sNDA 19-835/S-022 sNDA 21-621/S-005 22-155	Tablets Chewable Tablets Syrup	AR, itching w/ hives Tab/chewable: Full OTC switch Syrup: partial OTC switch	AR/hives: Adults & Children ≥ 6y AR:Children 2 – 5y

Sources: Adapted from **Table 1**, p. 9 - Medical Officer Review (Lolita Lopez, M.D., September 4, 2007) and www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Table 3: Current Recommended Dosage for OTC Cetirizine (Zyrtec®)

Age Group	Recommended Dose
Adults & children ≥12 years	5 or 10 mg once daily depending on symptom severity.
Children 6 – 11 years	5 or 10 mg once daily depending on symptom severity.
Children 2 – 5 years	2.5 mg (syrup) once daily. May increase to 5 mg once daily or 2.5 mg twice daily depending on symptom severity.
Renal or hepatic impairment	Ask a Doctor before use
Geriatric patients > 65 years	Ask a Doctor before use

Sources: Current Zyrtec® OTC label and www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

2.4 Important Safety Issues With Consideration to Related Drugs

Antihistamines are known for their sedative effects. Second generation antihistamines (cetirizine, fexofenadine and loratadine) are thought to cause a lesser degree of somnolence compared to the first generation drugs. However, cetirizine appears to be the most-sedating of the second generation drugs.

Terfenadine (withdrawn in 1998) and astemizole (discontinued in 1999) are second generation antihistamines with similar structure to cetirizine. The two former drug products are associated with increased risk of ventricular arrhythmia due to QT prolongation at high serum levels. Concomitant use of other drugs that inhibit certain hepatic microsomal enzymes causes higher serum concentration of these antihistamines. There are no reports of cetirizine, as the single suspect drug, associated with or causing QT prolongation or arrhythmia. Hekkala, *et al*[3] specifically exposed subjects with long QT syndrome to cetirizine, found no apparent effect, and suggested that cetirizine could be used safely as an antihistamine in these patients.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

There was no presubmission activity for this formulation. Prior to the original R_x-to-OTC switch of cetirizine, there were discussions between the FDA and the applicant to decide on an appropriate OTC target population. The FDA was concerned that parents would have difficulty diagnosing AR in children 6 months to 2 years or hives in children less than 6 years, without the input of a physician. Following the 2001 Advisory Committee Meeting, 6 years of age was chosen as a minimum for the hives indication. Currently, NDAs 19-835 (tablet), 21-621 (chewable tablet) and 22-155 (syrup) are approved for Zyrtec® OTC for two indications (**Table 2**). Zyrtec® syrup (NDA 20-346) is approved for hives in children 6 months to 6 years, and for AR in children 6 months to 2 years, both by prescription use only. No new indications are proposed for the current application.

2.6 Other Relevant Background Information

The non-clinical development of cetirizine began in Europe by UCB, a Belgian pharmaceutical company. It has been marketed globally for two decades. It is now available worldwide for OTC use in children down to 2 years of age. The foreign brands marketed under Johnson & Johnson are approved for OTC use in children 12 years old to adult (10 mg daily), and in children 6-12 years old (5 mg twice daily) for the indications, AR and relief of itching from hives. Formulations are marketed under the trade names Zyrtec®, Reactine®, Benadryl® (UK), and Sinutab®.

[3] Hekkala A-M, H Swan, H Väänänen, M Viitasalo, L Toivonen, 2007, The Effect of Antihistamine Cetirizine on Ventricular Repolarization in Congenital Long QT Syndrome, *J Cardiovasc Electrophysiol,* 18(7): 691-695

The package leaflet for the European Union harmonized label contains several items not in the U.S. version of the Zyrtec® insert:

- Consumers with hereditary disorders of galactose intolerance, lactase deficiency and glucose-galactose malabsorption should not take the product.
    - The lactose excipient in current, foreign marketed products is not included in the proposed product's inactive ingredients.
- Persons with epilepsy are asked to consult their physician before use.
- Pregnant women are asked to avoid use.

Reviewer's comments: Information is not available as to why epileptics are asked to consult with their physicians before use. The U.S. R_x insert states that convulsions are a potentially severe adverse event, but very rarely reported. In Dr. Lopez' review of the R_x-to-OTC switch (September 4, 2007), and in a postmarketing safety review by the Division of Drug Risk Evaluation (DDRE), seizures were no more reported for cetirizine than loratadine in OTC use, and there was no consensus determination that cetirizine would not be appropriate for OTC marketing based on risk of seizures. Convulsions as an adverse event (AE) will be further addressed below.

Cetirizine is a pregnancy category B drug without adequate pregnancy data. OTC labeling recommends that pregnant women ask a health professional before use.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, the submission was of high quality. Although an electronic submission would have been preferred, the paper submission was easy to navigate and well organized. The applicant submitted three amendments that included safety data; a 120 day update and two updated AE reports that were necessary following two programming errors that resulted in incorrect data tabulation in the WHO and AAPCC safety databases. None of the adjusted data resulted in changes to the overall conclusions. The applicant also submitted electronic safety datasets for the bioequivalence trial.

3.2 Compliance with Good Clinical Practices

There was one clinical bioequivalence trial performed in support of this application. The trial took place at MDS Pharma Services in Neptune, NJ. The MDS Pharma Services IRB reviewed the protocol prior to trial initiation. The operations are reported to be in compliance with 21 CFR 56 and the ICH Good Clinical Practices guideline. The research was ethically conducted in accordance with guidelines from the Medical Research Council of Canada (Reactine®, marketed in Canada, was used as a second

comparator), 21 CFR 312, the requirements of Directive 2001/20/EC (Europe), and the Declaration of Helsinki (2000). The informed consent was reviewed and approved by the IRB. The trial site was audited by the Quality Assurance division of MDS Pharma Services. Four additional independent audits were undertaken to ensure compliance with U.S. federal regulations and standard operating procedures of MDS Pharma Services.

Subjects were free to withdraw from the trial at any time. Subjects could be removed by the Investigator if it was in the subject's best interest. Safety data that included a physical examination, vital signs, adverse event assessment and concomitant medication assessment were required, if possible, upon withdrawal from the trial. Compliance to treatment was ensured by dosing medication in a closed clinical setting with close monitoring of subjects.

There was a single subject protocol violation. Subject 14 tested positive for alcohol and was removed from the trial. This subject did not complete the early termination safety procedures. There were nine protocol deviations for timing of blood draws between 5 and 13 minutes in length both before and after the pre-assigned draw times. The applicant did not feel that these affected the results. The deviations were scattered throughout the blood sampling timeframes of several trial subjects. Subject 5 had four deviations in various periods with three different test products. Subject 25 had two deviations with two test products prior to the T_{max}, approximately one hour post-dose under fasting conditions (four hours post-dose under fed conditions). Three other subjects (8, 9 and 27) had one deviation. According to the clinical pharmacology reviewer, a sampling window of 30 minutes is generally acceptable. It is unlikely that these deviations affected the results of the trial. Also, the Zyrtec® 10 mg tablet used as a control drug was manufactured by Pfizer in Brooklyn, NY, not in Puerto Rico as originally stated in the protocol.

A DSI inspection/audit was requested by the clinical pharmacology review team since the bioequivalence clinical trial was pivotal for this application. Both the clinical site – MDS Pharma Services, and the analytical site – (b) (4). will be audited. The results of the audit were not available at the time this review was finalized. Final approval of the proposed product is contingent on satisfactory inspections.

3.3 Financial Disclosures

Form 3454 was submitted certifying that the applicant has not entered into any financial arrangements with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the trial as defined in 21 CFR 54.2(a). None of the clinical investigators disclosed any proprietary or financial interests in the drug product or the applicant. The integrity of the trial results appears sound.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Findings are based on preliminary discussions with the pertinent discipline reviewers. See the full reviews for detail. A microbiology review was not necessary for this application.

4.1 Chemistry Manufacturing and Controls

The final CMC review is pending at the time this review was finalized. Inspection of the manufacturing site is pending. All excipients are included in official drug compendia, and none are novel.

4.3 Nonclinical - Pharmacology/Toxicology

No new nonclinical/toxicology data were submitted with this application. The applicant refers to the original NDA (19-835) for pertinent information. The R_x package insert includes nonclinical data. The pharmacology/toxicology review is pending at the time this review was finalized.

4.4 Clinical Pharmacology

A bioequivalence and food effect trial (CETALY 1003) was conducted to support this NDA. A description of the mechanism of action, pharmacodynamics and pharmacokinetics of cetirizine was obtained from the prescription label for current, approved formulations. The clinical pharmacology review team finds both the bioequivalence of cetirizine ODT to the approved immediate release tablet in the fasted state, and the biovailability in the fed state, to be acceptable for approval pending the DSI inspection results of the CETALY 1003 trial.

4.4.1 Mechanism of Action

Cetirizine is a metabolite of hydroxyzine, and a second generation anti-histamine defined by its selective inhibition of peripheral H_1 receptors. Animal models have shown negligible anticholinergic or antiserotonergic effects. The drug has no measurable affinity for non-H_1 receptors. There does not appear to be an effect on cerebral H_1 receptors in animals, with limited transport across the blood-brain barrier.

4.4.2 Pharmacodynamics

Briefly summarizing from the prescription label, 5 and 10 mg doses in adult and pediatric subjects inhibited skin wheal and flare caused by intradermal injection of histamine. The onset of activity occurred within one hour in 95% of subjects, and

persisted for at least 24 hours. Four clinical trials in healthy adult males, taking doses up to 60 mg daily, failed to show any clinically meaningful increase in QTc. Trials were also performed to evaluate the effect on QTc by a combination of cetirizine and drugs considered to increase the plasma concentration by inhibiting hepatic microsomal enzymes (e.g. ketoconozole, macrolide antibiotics). There was no effect. In a pediatric clinical trial (6-11 years old), random ECGs before and during a two week trial of 5 or 10 mg cetirizine daily did not show an increase in QTc compared to placebo. No studies in children under 12 years have been done with doses higher than 10 mg.

Trials in pediatric and adult subjects with AR and mild asthma showed improvement in AR symptoms without a change in asthma symptoms. This supports safety of cetirizine in the mild asthma patient population. In clinical trials for efficacy to support the drug's initial approval, the 10 mg dose showed better effect over the 5 mg dose, and no difference over a 20 mg dose in children and adults > 12 years old.

4.4.3 Pharmacokinetics

Table 4 provides the results of the submitted bioequivalence trial. See **Section 5.3** for a discussion and analysis of the trial and results. Also see the clinical pharmacology review.

Table 4: Table of Pharmacokinetic Data

	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

From Applicant's submission Mod 2, Vol 1, p 293

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

A single bioequivalence trial, summarized in **Table 5**, was performed to support the application**.**

Table 5: Clinical Trial Summary

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE and Food-Effect	CETALY 1003	Module 5, Section 5.3.1.2	BE of ODT with and without water vs. tablet Food-Effect of ODT	Open-label, crossover	A: 10 mg ODT, oral, with water, fasted B: 10 mg ODT, oral, without water, fasted C: 10 mg ZYRTEC tablet, oral, with water, fasted D: 10 mg REACTINE tablet, oral, with water, fasted E: 10 mg ODT, oral, fed	28*	Healthy Subjects	Single dose	Complete; Full

Source: Applicant's submission

5.2 Review Strategy

Since the applicant is relying on the approved NDA 19-835/S-022 (Zyrtec® tablets 10 mg) to support efficacy of the proposed formulation, **Section 6** is not the focus of this review. FDA has previously determined that cetirizine is safe and effective for its intended indications in an OTC setting. This review will evaluate the safety of the bioequivalence trial (see **Section 7**), as well as safety data accumulated by the applicant since January 16, 2007. This date is the cutoff for the four-month safety update following approval of NDA 19-835/S-022. I will comprehensively review the postmarketing safety data from the following sources in **Section 8**.

The accumulated safety data include

- Company commercial marketing safety data for the period since the four-month safety update for NDA 19-835/S-022 from January 17, 2007 – November 15, 2009.

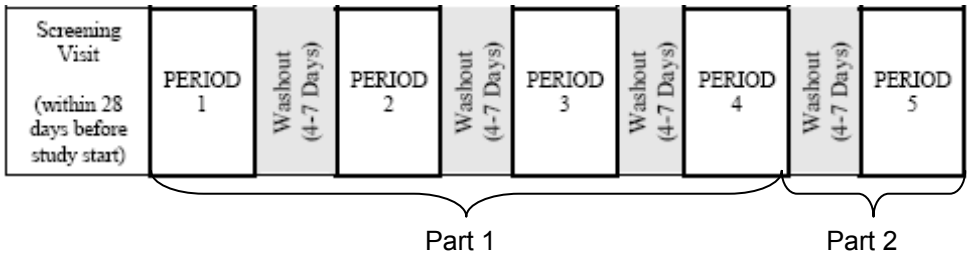
- Adverse Event Reporting System (AERS) data from January 1, 2007 - December 31, 2008.
- WHO Collaborating Centre for International Drug Monitoring, Uppsala (WHO-UMC) data from January 1, 2007 - May 20, 2009.
- Association of Poison Control Centers (AAPCC) data from January 1, 2007 to June 15, 2009.
- Drug Abuse Warning Network (DAWN) data from January 1, 2007 to June 22, 2009.
- Published literature safety data from clinical trials for the period from January 1, 2007 – November 18, 2009.

The applicant relies on the data of their single bioequivalence trial, submitted in this application described in **Section 5.3**. No review is necessary from a specific subject matter review division.

5.3 Discussion of Individual Studies/Clinical Trials

The bioequivalence trial was a randomized, open-label, single-dose crossover in healthy male and female adults (18-59 years). Twenty eight (28) subjects were enrolled and randomized to a sequence of treatment arms. Twenty seven (27) subjects completed the trial. The trial was conducted at a single center in healthy U.S. adults 20-52 years old using the highest approved dose strength (10 mg). 75% of subjects were male, 43% were black and 29% white. The mean age was 35 years and the mean BMI (kg/m^2) was 26. Enrollment ran for 30 days with each period of Parts 1 (fasting) and 2 (fed) separated by 4-7 day washout periods. **Figure 1:** Trial Design - CETALY1003 shows the overall trial design. Target enrollment was 28 subjects with two reserves.

Figure 1: Trial Design - CETALY1003



Subjects in Part 1 received the following treatment (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: A single 10 mg dose of the currently marketed U.S. cetirizine tablet (ZYRTEC®) with 240 mL water

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

All subjects participated in Part 2 and received the following treatment (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 meal with 240 mL water

Screening entailed meeting established criteria, providing a medical history, physical examination, ECG, and clinical laboratory tests within 28 days of the first dose. Period 1 included the first of the randomized Treatments A-D. Concomitant medications were recorded. Dropouts were not to be replaced unless the number of subjects completing Part 1 was less than 24, or less than 18 for Part 2. Twenty seven (27) of 28 subjects completed the trial that included all 5 dosing periods. Subjects underwent a 10-hour fast prior to each dosing period in Part 1, followed by blood sampling over the next 32 hours in each period for both parts (1 and 2). Blood samples were collected pre-dose, 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. A total of 355 mL of blood per male subject and 370 mL per female subject were collected. After dosing, subjects continued to fast for four hours. At two hours postdose, they were provided four ounces of water for hydration.

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 4**). The majority of cetirizine exposure was captured during the sampling interval, reflected by the low percent of AUC_{inf} extrapolated. Results of comparisons of Treatments A versus C and B versus C to evaluate the bioavailability of cetirizine ODT administered with or without water showed no difference in the fasted state (**Table 6**).

Table 6: Statistical Comparison of BE Parameters for Total Plasma Cetirizine

		Treatment			
		LS Means			
Treatment Comparison (Test vs Reference)	Parameter	Test	Reference	% Mean 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_{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: Applicant's submission Module 2, Vol. 1, p. 294, Table 2

See **Table 7** for a comparison of the mean C_{max} and T_{max} of three formulations in the fed and fasted parts of respective clinical trials. There is no significant food effect on overall cetirizine exposure (AUC). There is no direction in the current OTC or prescription labels to adjust the dosing based on food effect for any formulation. The applicant concludes that, "[f]or a once-daily dosing product, th[e] delay in absorption and a lower peak plasma concentration is not considered clinically relevant. Therefore, similar to previous R_x and current OTC labels that do not restrict Zyrtec® dosing relevant to food, no changes are proposed for the OTC Zyrtec® ODT label in this regard."[4]

Table 7: Differences in C_{max} and T_{max} for Various Formulations of Cetirizine

Cetirizine formulation	C_{max} difference (% fed/fasted)	T_{max} difference (fed minus fasted; hr)
Tablet	77*	1.7*
Proposed ODT	62	2.9
Chewable tablet	63*	2.8*

* historical data; Source: Table 4 above and approved Zyrtec® prescription label

Reviewer comments: The 90% confidence interval for the log-transformed LS means ratios for the rate (C_{max}), but not the extent ($AUC_{0\text{-}inf}$) of cetirizine absorption falls outside

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*the equivalence limits of 80-125 percent in comparison of the fed and fasted (E vs. A) treatment arms (see **Table 6** and the Clinical Pharmacology Review). Also, the T_{max} is delayed by nearly three hours for the cetirizine ODT following food intake versus fasting. Historically, findings have been similar for approved formulations. This reviewer and the clinical pharmacology review team agree that the changes in C_{max} and T_{max} following food intake do not significantly affect the overall efficacy of cetirizine for once-daily use.*

See **Section 9.2** for further information on pharmacokinetics in special populations and drug-drug interactions. No new data on exposure-response relationships were included in this application.

6 Review of Efficacy

The applicant supported efficacy by relying on data in support of NDA 19-835 and by demonstrating bioequivalence of the ODT formulation to an approved Zyrtec® product. The applicant originally performed, reviewed and analyzed 25 clinical studies, which establish the efficacy of 5 mg and 10 mg per day doses of cetirizine in the treatment of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), and chronic idiopathic urticaria (CIU) (see Table A-1 in the Appendix of Dr. Lolita Lopez' September 4, 2007 review for a listing of studies). All studies were conducted in the U.S., with the exception of study A160, a European trial conducted in children 2 to 6 years of age.

7 Review of Safety

The safety of cetirizine for this application is supported by the safety data accrued in the bioequivalence trial, and the postmarketing data (**Section 8**) that has accrued since the four-month safety update following approval of NDA 19-835/S-022. Data from the CDER OTC Switch Review Team regarding the safety of cetirizine in an OTC setting is also included in **Section 8**.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

There were no separate safety trials performed for this application.

7.1.2 Categorization of Adverse Events

For the CETALY 1003 trial, all observed or volunteered AEs were recorded and classified by severity (mild, moderate or severe). The regulatory definition of serious AEs indicates any event that results in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, results in persistent or

significant disability/incapacity, or results in congenital anomaly/birth defect. Frequency counts were made for all AE data, which were coded with MedDRA version 12.0 and tabulated. AEs that changed in severity or frequency were counted separately.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not indicated, because only one trial was performed.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Because cetirizine has been available for many years in several different formulations, the overall extent and duration of exposure of patients and consumers to the drug is more than adequate. Support for safety is well established. Drug exposure in the CETALY1003 trial was adequate.

The target population on the label for the proposed product will not differ from that of other approved cetirizine products at the same dosage strength. Cetirizine has a long time and extent of use in the OTC marketplace, and a safety profile that supports such use.

7.2.2 Explorations for Dose Response

Not indicated.

7.2.3 Special Animal and/or In Vitro Testing

Not indicated.

7.2.4 Routine Clinical Testing

Predose assessments included CBC, basic metabolic panel, urinalysis, HIV antibodies, Hepatitis B surface antigen, Hepatitis C antibody, serum pregnancy test and urine toxicology screen. Serum pregnancy tests and urine screens were repeated at check-in during all five periods of Parts 1 and 2 of the trial. Results were recorded for each subject on their CRF.

A complete physical exam was performed at screening and exit from the trial. Blood pressure and pulse rate were recorded at screening, check-in, pre-dose, 24 hours after dose for all periods, and at exit from the trial. Respiratory rate and temperature were

recorded at points during period 5. A complete ECG was performed at screening. **Table 8** shows the schedule of evaluations.

Table 8: Schedule of Evaluations for CETALY1003

Study Procedures	Screening Visit	PART 1				PART 2		
		Periods 1, 2, 3, and 4				Period 5		
	≥ Day -28[1]	Check-in Day -1	Day 1	Day 2	Washout (4-7 Days)	Check-In Day -1	Day 1	Day 2
Informed Consent for Study Participation	X							
Demography	X							
Medical and Surgical History	X							
Physical Examination	X							X
12-Lead Electrocardiogram	X							
Hematology	X							
Biochemistry	X							
Urinalysis	X							
HIV Antibodies	X							
Hepatitis B Surface Antigen	X							
Hepatitis C Antibody	X							
Serum Pregnancy Test	X[2]	X[2]				X[2]		
Drugs of Abuse Urine Screen	X[2]	X[2]				X[2]		
Randomization		X[2,7]						
Treatment Administration			X[2]				X[2]	
Pharmacokinetic Blood Sample Collection			X[3]	X[3]			X[3]	X[3]
Dietary Restrictions		X[2]	X[2]	X[2]	X	X[2,4]	X[2,4]	X[2]
Vital Signs [2, 5]	X	X	X	X		X	X	X
Prior or Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Event Monitoring [6]			X	X	X	X	X	X

[1] Screening visit was within 28 days of study start.
[2] See Appendix A of the protocol (Appendix 16.1.1), Detailed Schedule of Events for all Periods.
[3] PK blood samples (4 mL) were collected during each period at predose (0), 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. There was a 4 to 7 day washout interval between each study period.
[4] After an overnight fast of approximately 10 hours starting on Day -1, dose was administered on Day 1 approximately 30 minutes after start of a high-fat breakfast.
[5] Vital signs (heart rate and blood pressure) were assessed at Day-1 at check-in; Day 1 at -0.5 hours predose; Day 2 at 24 hours postdose for all periods. An additional assessment at 32 hours postdose was taken for Period 5.
[6] Adverse event monitoring started after first administered dose until end-of-study.
[7] Randomization occurred in Period 1 only, on either Day -1 or 1.

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Reviewer's comments: The schedule was adequate for safety monitoring during the trial.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not indicated.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

See **Section 2.4** for safety information on other first and second generation antihistamines.

Reviewer's comments: The methods and safety assessments were adequate for this small BE trial. No additional pre- or postmarketing safety assessments are necessary.

7.3 Major Safety Results

Fifteen subjects (53.5%) reported at least one AE of any severity during the entire trial. There were 32 total AEs reported, 26 in the test drug arms (Treatments A, B and E), and six (6) in the reference drug arms (Treatments C and D). All AEs were nonserious. Two to five subjects reported an AE for each treatment period in Part 1. Twelve subjects reported an AE following Treatment E in Part 2. All reported AEs, except somnolence and one report of dizziness, were considered by the investigator to be *remotely* or *unrelated* to the study drug product. One episode of chest pain (ECG that followed was normal) after Treatment E was considered moderate in severity, but *unrelated* to study drug, while all other AEs were mild. **Table 9** shows AEs by frequency, severity and relation to the study drug.

*Reviewer's comments: One to three subjects had episodes of somnolence during Treatments A-D, while 11 (41%) subjects reported somnolence after Treatment E, and one subject reported dizziness in Treatment B (See **Table 9**). These AEs are known to be frequently (> 2%) associated with cetirizine use, and this is indicated by the sponsor. Other AEs from the trial that have been previously reported with use of cetirizine are headache, nausea and abdominal pain (all more common in pediatric patients). AEs infrequently associated with cetirizine are rash and chest pain. Rash may be a sign of a mild hypersensitivity reaction, and could be reconsidered as possibly or probably related to the drug or some underlying allergy-related medical condition. Chest pain was reported three hours after dosing and could be reconsidered as remotely related to the drug. Headache has been more commonly reported in placebo arms of other cetirizine clinical trials, but may be possibly related to the drug. The other AEs are still likely remotely related or unrelated to the study drug.*

Table 9: AE Frequency by Treatment, Severity and Relation to Study Drug - Number of Subjects

Adverse Event*	Treatment	Number of Subjects with Adverse Events	Severity			Relationship		
			Mild	Moderate	Severe	Definite	Probable	Possible
Abdominal pain upper	B	1	1	0	0	0	0	0
Chest pain	E	1	0	1	0	0	0	0
Dizziness	B	1	1	0	0	0	0	1
Headache	A	1	1	0	0	0	0	0
Local swelling	B	1	1	0	0	0	0	0
Musculoskeletal chest pain	D	1	1	0	0	0	0	0
Nausea	A	1	1	0	0	0	0	0
Oral herpes	A	1	1	0	0	0	0	0
Pain in extremity	E	1	1	0	0	0	0	0
Rash	A	1	1	0	0	0	0	0
Rash papular	E	1	1	0	0	0	0	0
Somnolence	A	3	3	0	0	0	3	0
	B	1	1	0	0	0	1	0
	C	2	2	0	0	0	2	0
	D	2	2	0	0	0	2	0
	E	11	11	0	0	0	11	0
Tooth impacted	B	1	1	0	0	0	0	0
	A	5	5	0	0	0	3	0
	B	4	4	0	0	0	1	1
	C	2	2	0	0	0	2	0
	D	3	3	0	0	0	2	0
	E	12	12	1	0	0	11	0

Note: * Adverse events are classified according to MedDRA Version 12.0.
When a subject experienced the same AE at more than one level of severity during a treatment period, each AE was counted separately. When a subject experienced the same AE at more than one level of drug relationship during a treatment period, each AE was counted separately.
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
Source: Applicant's submission Module 5 Vol 1 Pg 113

7.3.1 Deaths

There were no deaths recorded during this trial.

7.3.2 Nonfatal Serious Adverse Events

There were no nonfatal serious AEs recorded during this trial.

7.3.3 Dropouts and/or Discontinuations

One subject was discontinued from the trial due to a positive alcohol screen before dosing at period 5 of part 2 of the trial. The subject's fasting BE data were included in the final analysis. The remaining 27 subjects completed the trial.

7.3.4 Significant Adverse Events

The most commonly reported AE was somnolence, reported by 14 (50%) subjects and categorized as nonserious in every case. The investigator considered all reports of

somnolence to be *probably* related to the drug. The applicant notes the greater reporting of somnolence in Treatment E versus Treatments A-D. Treatment E was given under fed conditions to all subjects in a single period compared to the other Treatments given in fasting conditions in a randomized, crossover design. All other AEs listed as Preferred Terms (PT) were reported by only one subject each, and included several System Organ Classes (SOC) with no apparent clustering.

Reviewer's comments: The reason for an increased frequency of somnolence in this BE trial, particularly Treatment E, compared to that reported in current labeling (41% versus 14%) is difficult to assess. It is possible that satiation after the high-fat breakfast meal, and inactivity during the regimented blood draw schedule contributed to this adverse event.

7.3.5 Submission Specific Primary Safety Concerns

There is background described in the ADVERSE REACTIONS section of the prescription label supporting the somnolence reports in the BE trial. The original NDA 19-835 included clinical trials with more than 6000 subjects 12 years of age and older, a duration of treatment ranging from one week to 6 months, and a mean exposure of 30 days. Most AEs were mild to moderate in these samples with no difference in the incidence of withdrawal or dropout compared to the placebo groups. The incidence of somnolence, the most frequent AE in the test group, was dose-related occurring in 14% of subjects receiving up to 10 mg per day. Compare this rate with 6% of subjects reporting somnolence in the placebo group. In pediatric trials (6-11 year olds), 1300 subjects received doses up to 10 mg per day over 2 to 12 weeks. Most AEs were also mild to moderate with the incidence of withdrawal or dropout not significantly different from the placebo groups. The incidence of somnolence ranked 5th (1.9%) and 3rd (4.2%) in frequency for those subjects taking 5 mg or 10 mg, respectively, and appeared dose-related and higher than in the placebo groups.

Reviewer's comments: Cetirizine is a metabolite of the first generation sedating antihistamine, hydroxyzine. Although it is of the same class as loratadine and fexofenadine, considered by the general public to be "non-drowsy," cetirizine does cause drowsiness, or somnolence. A labeling warning is already in place for other cetirizine formulations regarding avoidance of concomitant use of sedating drugs or alcohol and participation in activities requiring "mental alertness," such as driving. These warnings are similar to those allowed for OTC monograph antihistamines. These labeling warnings should remain if the proposed product is approved.

7.4 Supportive Safety Results

There were no clinically significant screening or testing results that would impact approval or OTC use of this drug product.

7.4.1 Common Adverse Events

Somnolence was the most frequently reported AE and is addressed elsewhere.

7.4.2 Laboratory Findings

There were no issues reported. There were no clinically significant findings that would impact approval or use of the drug product.

7.4.3 Vital Signs/ Physical Examination

There were no issues reported. All mean vital sign parameters remained within normal limits without significant mean changes from baseline. There were no significant physical examination findings that would impact the safe use of cetirizine.

7.4.4 Electrocardiograms (ECGs)

Three subjects had minor screening ECG abnormalities (two with incomplete bundle branch block, and one with a P wave inversion in V1 and V2) that were not considered clinically significant by the investigator. All three subjects were entered into and completed the trial without any significant events. The subject who complained of chest pain during the trial was one of the subjects with incomplete bundle branch block. The pain resolved without intervention, and a follow up ECG was normal.

7.4.5 Special Safety Studies/Clinical Trials

No special studies were performed.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

The applicant relies on NDAs 19-835, 20-346 and 21-621 for further safety data as regards intrinsic and extrinsic factors, drug-demographic, drug-disease and drug-drug interactions related to cetirizine.

7.5.1 Dose Dependency for Adverse Events

Not applicable. The subjects in the BE trial received only a single dose of 10 mg of cetirizine.

7.5.2 Time Dependency for Adverse Events

AEs were collected continuously throughout the trial while subjects were in-house. For subjects who reported somnolence, 8/11 reported during Treatment E within 60 minutes of T_{max} (4 hrs postdose); however, 0/7 reported within the same timeframe during any other Treatment Period. After review of the time of onset of other reported AEs (Appendix 16.2.7.1, Module 5, Vol. 3, Pg. 170), only papular rash, chest pain and headache were reported on the same day as dosing in the respective period, and there was no proximity to T_{max}. See **Section 7.3** for further review of these AEs.

*Reviewer's comments: See comments under **Section 7.4**.*

7.5.5 Drug-Drug Interactions

See **Section 9.2.** No clinically significant drug interactions have been found.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No carcinogenicity studies were performed for this application. According to the prescription insert, 2-year carcinogenicity studies in mice showed an increased incidence of benign liver tumors at six times the maximum recommended human adult dose. The clinical significance of this finding with long-term use of cetirizine is unknown.

7.6.2 Human Reproduction and Pregnancy Data

No trials were performed for this application. Cetirizine is a Pregnancy Category B drug. Cetirizine was not teratogenic in animals at oral doses up to 220 times the maximum oral adult dose. There are no adequate, well-controlled trials in pregnant women. The prescription insert states that it should only be used in pregnancy if clearly indicated. Pregnant women should ask a health professional before use. Lactating women should not take this product since cetirizine is reported to be expressed in human breast milk, and the drug has caused poor weight gain in the pups of lactating mice at doses up to 40 times the maximum human adult dose.

7.6.3 Pediatrics and Assessment of Effects on Growth

Cetirizine is available for prescription use in children as young as 6 months of age. It is approved, in appropriate formulations, for OTC use in children 2 years of age and older. The applicant submitted a request for a partial waiver from pediatric trials, as this new formulation triggers PREA.

The applicant requests a partial waiver of trials in children 6 months to 5 years old. They are seeking approval as "appropriately labeled" for children 6 years and older.

- Birth to 6 months: The disease does not appear to exist in a substantial portion of this population.
- 6 months to 23 months: The FDA previously determined that dosing in this age group should remain by prescription only, regardless of formulation. According to the applicant, additional research with the proposed formulation would not provide information to support a meaningful therapeutic benefit over existing formulations.
- 2 to 5 years: Again, the applicant states that additional research with this new formulation would not provide information to support a meaningful therapeutic benefit over existing formulations. Also, they state that the proposed formulation would not likely be used in a substantial number of children in this age group.
- 6 to 17 years: Trials have previously been completed with other formulations for children over 12 years, and efficacy data are extrapolated to children 6 – 12 years of age. The applicant feels that no additional meaningful information would be gathered over data already available for this age group.

Previously, this applicant performed pediatric PK trials for patients down to 6 months old for the indication of relief of itching from hives and for patients down to 2 years old for the "relief from symptoms of AR" indication. Safety and efficacy in pediatric patients under 6 months have not been established because it is believed that AR and hives do not exist in this population. Efficacy in children from 6 months to <12 years of age is extrapolated from adult trials where the conditions (AR and CIU) and the natural history, pathophysiology and drug effects are likely similar between the two populations. More specifically, efficacy is extrapolated down to 6 months old for perennial AR and down to 2 years old for seasonal AR because these diseases are thought to occur down to these ages. The applicant has performed adequate safety and efficacy trials for children between 12 and <18 years old.

Reviewer's comments: This reviewer finds the applicant's reasoning sound for all age groups. The applicant's main premise for their proposed formulation is to provide an alternative, convenient option for dosing. This reviewer believes that the proposed formulation does not represent a meaningful therapeutic benefit over existing therapies.

Because this new formulation triggered PREA, the Pediatric Review Committee (PeRC) evaluated the application. The final determination was to waive clinical trials in children from birth to <6 years of age. PeRC agreed with the opinion of the applicant and reviewer that AR does not exist in children under 6 months, that cetirizine should remain by prescription only for children 6 to 23 months, and that there is no meaningful benefit of this proposed formulation over existing formulations for children 2 to <6 years of age. PeRC also concluded that the label for the proposed target population of adults and children over 6 years of age is appropriate. The sponsor will not be required to perform any additional pediatric trials.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No assessments were indicated for this application.

8 Postmarket Experience

Cetirizine has been marketed since 1995 with a good safety profile in the U.S. An extensive safety database of postmarketing experience exists. Over (b) (4) (5 mg, 10 mg and 5 mL) were sold/dispensed worldwide from January 2007 – January 2009. In the U.S., over (b) (4) prescription and OTC doses were distributed[5]. It is difficult to estimate the number of consumers who may have used cetirizine products since there is no limit on the duration of use. Some may use the products only a few times, whereas others may use them daily for years. As will be further discussed below, reports that included convulsions, arrhythmias, thrombocytopenia and somnolence are of special interest following the switch to OTC marketing. The applicant provided reports of safety data from several sources:

- Data from submitted bioequivalence trial CETALY1003 – See **Section 7**
  - Number of subjects exposed = 28
- Applicant's database (January 17, 2007 to January 16, 2009)
  - The start date is the day after the applicant's 4 month safety update submission following approval of cetirizine OTC switch on November 16, 2007.
- FDA AERS database (January 1, 2007 to December 31, 2008)
- WHO-UMC database (January 1, 2007 to May 20, 2009)
- Published literature data from clinical trials (January 1, 2007 to June 22, 2009)
  - Number of subjects exposed = 2431
- Association of Poison Control Centers (AAPCC) data from January 1, 2007 to June 15, 2009.
- Drug Abuse Warning Network (DAWN) data from January 1, 2007 to June 22, 2009.

Interpretation of spontaneously reported AEs have several limitations:

- Reports are submitted voluntarily and the magnitude of underreporting is unknown.
- The reporting systems yield reporting rates and not incidences.
- Clinical information is often limited in the reports, and causality can not often be determined.
- Hypothesis testing can not be performed.

There may be several reasons why AEs are reported or not. A causal relationship between the use of cetirizine and any particular AE or clustering of AEs is difficult to determine. An event may occur due to a subject's underlying disease, past medical

[5] Applicant's submission; Table 2.7.4, Module 2, Vol. 1, Pg. 166

history, concomitant medications or may be only coincidental in its temporal relationship to use of the drug.

Summaries and analyses of safety data from prior clinical trials performed by the applicant can be found in Dr. Lolita Lopez' review (September 4, 2007). Although the proposed product is not labeled for children under 6 years, for consistency with safety reporting, the sponsor included all AEs from birth through adulthood, and they will be analyzed here.

Applicant's database

The applicant received 4778 case reports involving single-ingredient cetirizine for the specified two-year time period. A total of 4105 (85.9%) were reported as non-serious, 621 (13%) as nonfatal-serious, and 52 (1.1%) as deaths. Consumers submitted the majority (73.8%) of the reports. The mean age was 39 years (SD 25.82). With regard to overall case outcomes: 59% were reported as "unknown," 19% reported as "recovered" and 17% reported as "not recovered." 8109 adverse events were reported (6250 (77.1%)-nonserious; 1859 (22.9%)-serious) (**Table 10**). For serious reports, the most commonly reported adverse events (≥0.5%) include[6]:

- Drug exposure during pregnancy 40; 2.1%
- Convulsion 36; 2%
- Hypersensitivity 33; 1.7%
- Somnolence 32; 1.7%
- Death 32; 1.7%

Reviewer's comments: Eleven cases (31%) of "convulsion"- (PTs were "convulsion," "grand mal convulsion" and "petit mal epilepsy") occurred in children 6-12 years of age among the 36 total nonfatal serious reports submitted from the applicant's database. All of the reports were reviewed, and most did not contain enough clinical information to make any assessment of causality. A few of the subjects had pre-existing seizures or seizure disorders. Others were subsequently diagnosed with seizure disorders while off of cetirizine. "Convulsions" as rare, but serious, known AEs have been addressed previously (see Dr. Lopez' clinical review September 4, 2007 pp. 37-38), and will be further discussed below in the subsection "Other Safety Topics."

Of the cases reported as nonfatal serious or death (n=673):

- 45 cases (6.7%) in children < 6 years; Most frequent PTs were "wrong drug administered" (n=7), "hallucination" (n=6), "pyrexia" (n=4) and "abnormal behavior" (n=4)
- 36 cases (5.3%) in children 6-12 years; Most frequent PTs were "convulsion" (n=11), somnolence (n=3), malaise (n=3) and hypersensitivity (n=3)

[6] The % come from the total number of serious reports (n/1859).

- 20 cases (3%) in adolescents 12-17 years; Most frequent PTs were “overdose” (n=3), “loss of consciousness” (n=3) and “hallucination” (n=3)
- 268 cases (40%) in adults 18-65 years; Most frequent PTs were “hypersensitivity” (n=17), “somnolence” (n=17), “convulsion” (n=16), “dizziness” (n=15) and “drug ineffective” (n=14)
- 90 cases (13.3%) in adults > 65 years; Most frequent PTs were “wrong drug administered” (n=9), “somnolence” (n=7) and “drug ineffective” (n=5)
- 214 cases (32%) in “age unknown”; Most frequent PTs were “drug exposure during pregnancy” (n=34), “death” (n=27), “abortion spontaneous” (n=19), “disability” (n=13) and “hypertension” (n=9)

Table 10: Summary of AEs by SOC, MedDRA Preferred Term, and Seriousness with Frequency >0.5%- Company Database

System Organ Class MedDRA Preferred Term[a]	Nonserious Events	Death or Other Serious Events
Number of Adverse Events	6250	1859
Injury, poisoning and procedural complications	1479	154
Wrong drug administered	510	17
Overdose	410	16
Drug exposure during pregnancy	221	40
Incorrect dose administered	83	-
Accidental exposure	65	-
Accidental overdose	61	-
Medication error	34	-
Road traffic accident	-	14
Fall	-	11
General disorders and administration site conditions	1675	216
Death	-	32
Drug ineffective	949	23
Fatigue	132	12
Therapeutic Response Decreased	130	-
Feeling Abnormal	59	16
Malaise	57	19
Condition aggravated	46	8
Oedema peripheral		12
Pain		11
Drug interaction		11
Nervous system disorders	944	264
Somnolence	556	32
Headache	107	11
Dizziness	88	23
Convulsion	-	36
Balance disorder	-	10
Loss of consciousness	-	10
Gastrointestinal disorders	410	99
Nausea	49	12
Diarrhoea	48	-
Vomiting	42	12
Dry mouth	35	11
Abdominal pain upper	35	-
Psychiatric disorders	314	156
Insomnia	93	-
Hallucination		17
Depression		15

Table 10 Continued:

System Organ Class MedDRA Preferred Term[a]	Nonserious Events	Death or Other Serious Events
Skin and subcutaneous tissue disorders	404	100
Rash	101	11
Pruritus	68	14
Urticaria	63	13
Respiratory, thoracic and mediastinal disorders	279	105
Epistaxis	33	-
Cough	32	-
Dyspnoea	31	13
Asthma	-	15
Immune system disorders	70	54
Hypersensitivity	65	33
Cardiac disorders	41	61
Palpitations	32	-
Eye disorders	-	66
Vision blurred	-	10
Metabolism and nutrition disorders	-	28
Diabetes Mellitus	-	15
Pregnancy, Puerperium and Perinatal conditions	-	44
Abortion spontaneous	-	24
Social circumstances	-	35
Disability	-	25
Surgical and medical procedures	-	71
Surgery	-	16
Vascular disorders	-	47
Hypertension	-	22

a: A patient may be reported in more than one system organ class category.
Source: Applicant's submission Table 2.5-5; Mod 2 Vol 1

Reviewer's comments: Based on the number of dosage units distributed over the same two year time period, the report frequency of individual serious AEs is extremely low. The serious AEs are generally similar to those reported in clinical trials and included in the prescription label. Reports of arrhythmias and thrombocytopenia were very rare. The most frequently reported non-serious AEs are generally consistent with the current labeling for cetirizine. A causal relationship, following administration of cetirizine, has

*not been established with many of the less frequent serious and non-serious AEs listed in both **Table 11**, and in the prescribing information. Dr. Lopez' 2007 review also summarized the applicant's safety data from 1995 through May 2006. Overall, there were no major safety concerns at the time of OTC switch, and no new safety signals since that time.*

Deaths

There were 52 reported deaths during the two-year time period. One death (2%) was reported in a child less than 6 years. This death was a report of sudden infant death syndrome in a 6 month old, born prematurely, who had received a dose of Zyrtec® syrup of unknown strength or duration for an unknown indication. One death (2%) was reported in a child from 6 -<12 years – an eight year old who suffered what was described as a cardiac event following prolonged QT. No deaths were reported in children 12-17 years of age. Ten deaths (19%) were reported in adults 18-65 years. There were four (7.7%) reports for adults > 65 years, and 36 (69%) reports with age "unknown." No details were provided regarding the adult deaths other than the applicant's assessment that the cause of death was unknown in 19 (37%) reports, and unexplained in seven (13%) reports. The only AE terms reported more than once with the reports of death were "drug exposure during pregnancy" (4; 7.7%), "cytogenetic abnormality" (2; 3.8%), "dysmorphism" (2; 3.8%) and "abortion, spontaneous" (2; 3.8%). The applicant does not provide details of these reported deaths.

Reviewer's comments: This reviewer evaluated all 52 MedWatch forms included in the applicant's submission (Appendix D, Module 5, Vol. 7, Pg.329). There were no significant safety signals identified in the reports of death. The 8 year old who died from arrhythmia while taking Zyrtec® had an unknown medical history, and it was unknown if she was taking concomitant medications. Although most of the adult deaths appeared unrelated to cetirizine use, had unknown causes or were confounded, two cases were identified for their relationship to cetirizine use.

- *A 23 year old male (2007034919) began taking cetirizine at bedtime and clemastine twice daily for allergy relief. Two weeks after starting these medications, he reportedly went out for drinks with friends. On his way home, he climbed a fence and fell eight stories to his death. It is possible that the combination of alcohol with these antihistamines could have contributed to a sedated state and to his death. A warning against concomitant use of alcohol with antihistamines is included in the OTC label.*
- *A 36 year old female (2007046364) had several miscarriages while taking cetirizine. She had a miscarriage prior to starting the medication, and a few of them were linked to lethal chromosomal abnormalities. There was no information on frequency and duration of use of cetirizine during her early pregnancies. Cetirizine is a Category B drug, and the label advises pregnant consumers to consult their doctors before use.*

FDA – AERS Database

The applicant submitted safety data from the AERS database for a two-year time period. Their search included single-ingredient cetirizine as the primary or secondary suspect drug. The applicant identified serious adverse events based on the FDA regulatory definition (21 CFR 310.305(b)). In total, 814 reports of AEs were included in the database. There were 72 (8.8%) nonserious reports, 702 (86.2%) serious nonfatal reports, and 40 (4.9%) deaths. Different and multiple outcomes could be counted for each report. There were 610 (74.9%) expedited 15-day reports submitted. The mean age was 37 years. The majority of reports were made by health professionals (27%), followed by foreign reports (21%) and consumers (14%). Some reports had multiple sources. There were 2977 AE terms (**Table 11**) associated with these reports. The SOCs that included the most frequently reported serious AEs were: nervous system disorders, psychiatric disorders, and general disorders and administration site conditions. The most commonly reported serious AEs, for all age groups, were[7]

- convulsion (n=59; 2.1%)
- drug exposure during pregnancy (n=56; 2%)
- somnolence (n=42; 1.5%)
- pruritis (n=39; 1.4%)
- dizziness (n=36; 1.3%)
- drug ineffective (n=32; 1.2%)
- abnormal behavior (n=31; 1.1%)
- hypersensitivity (n=31; 1.1%)
- depression (n=30; 1.1%)

[7] The % is from the total number of serious AEs (n/2754).

Table 11: Most Frequent (≥ 0.5%) Adverse Event Terms by System Organ Class, MedDRA Preferred Term, and Seriousness for Cetirizine Ordered by Most Frequent Event - FDA AERS Database

System Organ Class MedDRA Preferred Term	Nonserious Events	Other Serious Events or Deaths
Number of AEs	223	2754
Nervous system disorders	12	428
Convulsion	0	59
Somnolence	3	42
Dizziness	1	36
Headache	1	21
Loss of consciousness	0	19
Crying	5	12
Tremor	0	16
Dysgeusia	0	14
Psychiatric disorders	32	366
Abnormal behaviour	6	31
Depression	3	30
Aggression	3	21
Suicidal ideation	2	22
Suicide attempt	0	22
Insomnia	4	16
Hallucination	0	18
Anger	4	10
Drug dependence	2	6
General disorders and administration site conditions	48	336
Drug ineffective	7	32
Fatigue	2	26
Malaise	2	21
Feeling abnormal	3	19
Condition aggravated	1	18
Drug withdrawal syndrome	5	14
Drug interaction	1	16
Oedema peripheral	1	16
Product quality issue	8	9
Chills	3	6
Drug effect decreased	3	4

Table 11 Continued:

System Organ Class MedDRA Preferred Term	Nonserious Events	Other Serious Events or Deaths
General disorders and administration site conditions (Continued)		
Therapeutic response unexpected with drug substitution	2	2
Hunger	2	1
Injury, poisoning and procedural complications	47	228
Drug exposure during pregnancy	1	56
Maternal drugs affecting foetus	0	29
Medication error	16	7
Fall	1	19
Drug dispensing error	12	7
Overdose	1	17
Wrong drug administered	5	12
Circumstance or information capable of leading to medication error	3	0
Intercepted drug dispensing error	3	0
Skin and subcutaneous tissue disorders	30	218
Pruritus	13	39
Urticaria	4	29
Pruritus generalised	3	19
Rash	1	18
Erythema	4	6
Generalised erythema	2	0
Investigations	11	176
Weight decreased	2	11
Gastrointestinal disorders	14	147
Nausea	2	17
Dry mouth	2	16
Vomiting	2	13
Abdominal pain	3	6
Respiratory, thoracic and mediastinal disorders	9	116
Rhinorrhoea	3	11
Nasal congestion	2	5

Table 11 Continued:

System Organ Class MedDRA Preferred Term	Nonserious Events	Other Serious Events or Deaths
Respiratory, thoracic and mediastinal disorders (Continued)		
Sneezing	2	4
Eye disorders	8	84
Eye pruritus	2	7
Accommodation disorder	2	1
Lacrimation increased	2	0
Mydriasis	2	0
Cardiac disorders	1	86
Cardiac arrest	0	14
Pregnancy, puerperium and perinatal conditions	0	84
Abortion spontaneous	0	26
Premature baby	0	20
Immune system disorders	2	56
Hypersensitivity	2	31
Vascular disorders	3	48
Flushing	2	5

Source: Applicant's submission Table 2.5-7; Mod 2 Vol 1

Of the AEs reported as nonfatal serious or death (n=2754):

- 187 AEs (6.7%) in children < 6 years; the most frequent PTs were "abnormal behavior" (n=7), "pyrexia" (n=7), "rhinorrhea" (n=7) and "cough" (n=6)
- 125 AEs (4.5%) in children 6-12 years; the most frequent PTs were "dystonia" (n=7), "hypersensitivity" (n=6), "drug dispensing error" (n=4) and "paraesthesia oral" (n=3)
- 63 AEs (2.3%) in adolescents 12-17 years; the most frequent PTs were "abnormal behavior" (n=3), "headache" (n=3) and "hallucination" (n=3)
- 1033 AEs (37.5%) in adults 18-65 years; the most frequent PTs were "convulsion" (n=39), "dizziness" (n=20), "urticaria" (n=18), "fatigue" (n=17) and "depression" (n=16)
- 213 AEs (7.7%) in adults > 65 years; the most frequent PTs were "somnolence" (n=6), "cardiac arrest" (n=6), "suicide attempt" (n=6) and "bradypnoea" (n=6)
- 1133 AEs (41.1%) in "age unknown"; the most frequent PTs were "drug exposure during pregnancy" (n=42), "maternal drugs affecting foetus" (n=27), "abortion spontaneous" (n=21), "drug ineffective" (n=18) and "premature baby" (n=16)

Reviewer's comments: The reporting frequency of these AEs is extremely low. Many of these are likely duplicates of those included in the applicant's database.

Deaths

Of the 40 reported deaths, one occurred in a child under 12 years (the eight year old described in the applicant's database). Fifteen deaths were reported in adults 18-65 years, three were reported in adults > 65 years and 21 were reported with age "unknown." The most frequent System Organ Classes (SOC) with reported deaths were "Injury, Poisoning and Procedural Complications" followed by "General Disorders and Administrative Site Conditions," "Pregnancy, Puerperium and Perinatal Conditions," and "Nervous System Disorders." AEs reported more than four times in reports with death as an outcome were "death" (n=13), "fall" (n=5), "overdose" (n=5), and "convulsion" (n=5). No narratives were provided regarding the adult deaths. The applicant did not provide information on any temporal relationship between the use of cetirizine and death. Most likely, all or most of the reports included here were reviewed above as part of the applicant's database. The applicant found the data collected from the AERS database supportive of cetirizine's excellent safety profile.

Reviewer's comments: There were no new AEs identified that occurred at a significant frequency in the reports of deaths. There were no significant trends or patterns identified. The reported AEs are similar to those reported from both clinical trials and the applicant's database. Based on the number of dosage units distributed, the number of deaths and AEs reported are extremely low. This reviewer performed a search of the AERS database for reports with death as an outcome and did not identify any information that would require labeling changes or other action toward the current cetirizine OTC marketing status.

WHO-UMC database

The applicant submitted reports (January 1, 2007 to May 20, 2009) obtained from the WHO Collaborating Centre for International Drug Monitoring, Uppsala. These reports are received from national authorities in countries, including the U.S., participating in the program. The data are not homogenous with respect to origin. The reports included information where cetirizine as a single-ingredient unspecified dose was the suspect drug. The database included 883 reports worldwide. Multiplicity of reports is common because the reports are often submitted to more than one regulatory authority. The mean age of the reported population was 37.2 years (SD 23.8 years). There were 292 (33.1%) nonserious reports, 562 (63.6%) nonfatal serious reports, and 29 (3.3%) deaths. The number of reports with outcome considered "recovered" was 260 (29.4%). Unknown and missing outcome data made up another 67.5%. The majority of reports were from consumers (22.3%) and physicians (21.4%). The reporting source was missing in 22.3% of cases.

Table 12 lists the most frequently reported AE terms by SOC and PT. AEs reported more than 0.5% of the time are listed (n=2260 for events with serious outcomes; n=657 for events with non-serious outcomes). The most common SOCs for serious reports

were "psychiatric disorders," "body as a whole – general disorders," "secondary terms" and "central and peripheral nervous system disorders." The most common AEs reported in serious reports were[8]

- Pruritis (n=59; 2.6%)
- Somnolence (n=57; 2.5%)
- Dizziness (n=46; 2%)
- Medicine ineffective (n=40; 1.7%)
- Urticaria (n=38; 1.7%)
- Paraesthesia (n=33; 1.5%)
- Grand mal convulsion (n=32; 1.4%)
- Medication error (n=32; 1.4%)

For non-serious reports, the most common AEs were medication error (n=57), medicine ineffective (n=42), somnolence (n=26), pruritis (n=22), headache (n=16), urticaria (n=15) and rash (n=14).

Of the AEs reported as nonfatal serious or death (n=2260):

- 186 AEs (6.7%) in children < 6 years; the most frequent PTs were "aggressive reaction" (n=8), "crying abnormal" (n=8), and "paraesthesia" (n=7)
- 130 AEs (4.5%) in children 6-12 years; the most frequent PTs were "anxiety" (n=7), and "paraesthesia" (n=6)
- 61 AEs (2.3%) in adolescents 12-17 years; the most frequent PT was "suicide attempt" (n=4)
- 755 AEs (37.5%) in adults 18-65 years; the most frequent PTs were "pruritis" (n=34), "dizziness" (n=25), "urticaria" (n=22), "somnolence" (n=22) and "medicine ineffective" (n=18)
- 159 AEs (7.7%) in adults > 65 years; no frequent PTs used
- 969 AEs (41.1%) in "age unknown;" the most frequent PTs were "somnolence" (n=24), "medicine ineffective" (n=17), "pruritis" (n=16), and "allergic reaction" (n=15)

Reviewer's comments: The reporting frequency of these AEs is extremely low. Many of these are likely duplicates of those included in the applicant's database and AERS.

[8] The % is from the total number of serious AEs (n/2260).

Table 12: Most Frequent AE Terms by SOC, WHOART Term, and Seriousness for Cetirizine Ordered by Most Frequent Event - WHO-UMC

System Organ Class WHOART Preferred Term	Nonserious Events	Death or Other Serious Events
Number of AEs	657	2260
Psychiatric Disorders	104	373
Somnolence	26	57
Aggressive Reaction	11	29
Suicide Attempt	3	29
Nervousness	6	22
Insomnia	8	18
Depression	6	17
Depersonalization	3	19
Anxiety	1	20
Hallucination	3	18
Agitation	3	15
Emotional Lability	4	14
Amnesia	4	10
Sleep Disorder	1	12
Anorexia	5	6
Body As A Whole - General Disorders	121	332
Medicine Ineffective	42	40
Fatigue	11	23
Allergic Reaction	3	28
Malaise	9	18
Withdrawal Syndrome	7	14
Pain	0	20
Crying Abnormal	6	12
Therapeutic Response Increased	2	14
Anaphylactic Reaction	2	12
Allergy	1	12
Condition Aggravated	0	13
Therapeutic Response Decreased	4	7
Oedema Mouth	5	1
Medicine Ineffective Unexpected	5	0
Secondary Terms	102	325
Term Under Assessment for WHOART	5	112
Term Not Accepted In WHOART	7	97

Table 12 Continued:

System Organ Class WHOART Term	Nonserious Events	Death or Other Serious Events
Secondary Terms Continued	57	32
Medication Error	13	11
Incorrect Drug Administered	7	11
Drug Quality Problem	1	15
Fall Intercepted Medication Error	5	0
Central and Peripheral Nervous System Disorders	62	258
Dizziness	11	46
Paraesthesia	10	33
Headache	16	18
Convulsions Grand Mal	1	31
Coma	1	14
Muscle Contractions Involuntary	4	11
Ataxia	1	12
Hypoaesthesia	5	3
Skin and Appendages Disorders	71	195
Pruritis	22	59
Urticaria	15	38
Rash	14	30
Rash Erythematous	4	13
Gastrointestinal Disorders	60	114
Abdominal Pain	12	21
Mouth Dry	8	19
Nausea	6	15
Vomiting	12	9
Diarrhoea	6	5
Respiratory System Disorders	27	121
Rhinitis	9	17
Dyspnoea	6	15
Asthma	3	16
Sinusitis	0	17

Table 12 Continued:

System Organ Class WHOART Term	Nonserious Events	Death or Other Serious Events
Metabolic and Nutritional Disorders	12	84
Weight Increase	2	17
Weight Decrease	3	13
Vision Disorders	17	47
Vision Abnormal	4	14
Conjunctivitis	5	6
Musculoskeletal System Disorders	11	49
Arthritis	0	14
Myalgia	6	6
Heart Rate and Rhythm Disorders	16	41
Palpitation	9	11
Foetal Disorders	3	47
Drug Exposure in Pregnancy	3	18
Abortion	0	14
Cardiovascular Disorders, General	9	29
Hypertension	5	17

Source: Adapted from Applicant's submission Table 2.5-9; Mod 2 Vol 1

Deaths

A total of 29 deaths were reported across all ages. Of these, 22 were reported from the U.S. One death in a 6.5 month old and one death in an eight year old were described above. There was one death reported in a 14 year old, 12 deaths in adults 18-65 years, four deaths in adults > 65 years and 10 deaths in persons with age unknown. The death of the 14 year old was described as a reaction including coma, convulsions, pain, drug and hypersensitivity syndrome with a cetirizine treatment duration of five days. No other information was provided. Deaths were reported most frequently in the SOC "Body as a Whole – General Disorders," followed by "Secondary Terms," "Foetal Disorders" and "Central and Peripheral Nervous System Disorders." AEs reported more than twice were "death" (n=11), "medication error" (n=4), "abortion" (n=3) and "convulsions grand mal" (n=3). The applicant determined that the data provided support for the excellent safety profile of cetirizine.

Reviewer's comments: See comments in the FDA-AERS database section above. This database did not reveal any new or unexpected safety signals.

Overdose, Abuse, Misuse and Dependence

Information submitted for single-ingredient cetirizine was collected from the applicant's database, the FDA-AERS database and the WHO-UMC database in addition to the following:

- American Association of Poison Control Centers (AAPCC) (January 1, 2007 to June 15, 2009)
    - Data on overdose, abuse, misuse and dependence
- Drug Abuse Warning Network (DAWN) (January 1, 2007 to June 22, 2009)
    - Data on overdose, abuse, misuse and dependence

The applicant's database included 503 reports of overdose. There were two deaths (literature reports of multidrug ingestions), 29 nonfatal serious reports and 472 nonserious reports.

The FDA-AERS database included 52 reports with eight deaths (all multidrug ingestions), 43 nonfatal serious reports, and one nonserious report. The WHO database included 45 reports with three deaths (all multidrug ingestions), 38 nonfatal serious reports and four nonserious reports. For serious reports, the most common PTs were overdose, accidental overdose, intentional overdose, suicide attempt, coma, drug toxicity and therapeutic response increased.

The AAPCC tabulates information on all cases reported to participating poison control centers across the U.S. The majority of cases reported in the AAPCC database regarding human exposure to cetirizine were in children less than six years (60.1% of over 25,000 reports), with the large majority of cases in all age groups being unintentional (92.2%). 79.5% of cases were of single substance exposures. There was one reported death (40 year old male, suspected suicide with multidrug ingestion). The most frequently reported terms were drowsiness/lethargy, tachycardia, agitated/irritable and vomiting. Two cases in the professional label for Zyrtec®, and animal data documenting the minimal lethal oral doses, indicate few serious medical consequences of overdose. One adult and one child (18 months) ingested up to 180 mg of Zyrtec® with resulting somnolence, restlessness and irritability, but no signs of abnormal blood tests or other acute or chronic medical ailment. Exposures do not necessarily represent a poisoning or overdose. The recommendation following overdose is supportive care since there is no antidote. Dialysis is not an effective means of removing cetirizine from the blood.

Regarding abuse, misuse and dependence, the applicant includes 771 reports from their database. There was one death (multidrug ingestion), 34 nonfatal serious reports, and 736 nonserious reports. From the AERS database, 94 reports with 4 deaths (3

were multidrug ingestions), 63 nonfatal serious events, and 27 serious events were included. From the WHO database, 106 reports with four deaths (appear to be the same case with multiple reports), 57 nonfatal serious events, and 45 nonserious events were included. The most common PTs from serious reports included "wrong drug administered," "withdrawal syndrome," "drug withdrawal syndrome," "drug dependence," and "somnolence." Six reports were filed in children under 6 years, and one each in children 6-11 years and children 12-17 years (no deaths). The DAWN included 622 reports mentioning cetirizine. The majority of cases were in adults 18-64 years. No deaths, but 121 hospitalizations were reported for a variety of diagnoses including "adverse reaction," "overmedication," "suicide attempt" and "accidental ingestion." There was no published literature describing abuse, misuse or dependence related to cetirizine. The professional label states the same, and the applicant finds no indication of abuse or dependence potential for cetirizine.

Withdrawal and Rebound

There are postmarketing reports of pruritis, urticaria and other "withdrawal syndrome" events following stoppage of cetirizine treatment. There were 42 reports submitted by the applicant. Of these, 28 were nonfatal serious and 14 were nonserious. There may be duplicate information due to multiple filings of the same report. 79% were female subjects. The most frequently reported dose was the 10 mg tablet. 40/42 (95%) involved ingestion of only cetirizine. The line listings were reviewed. There is no indication that the current labeling should be changed.

Reviewer's comments: I agree with the applicant that there is no indication that abuse or misuse of cetirizine occurs to a significant degree. Following submission of the original NDA, the "Abuse, Misuse and Dependence" reports from the WHO database were found to be deficient of 44 cases. A programming error was the cause of the mistake. The corrections were included in an amendment submitted by the applicant on March 2, 2010. On March 24, 2010, the applicant reported another programming error resulting in incorrect data from the AAPCC database. The AAPCC database was corrected, in a minor amendment, to reflect eight additional reports, and a reclassification of over 430 cases from the 12-17 age group to the 6- <12 age group. The main "Postmarketing Experience" section were not affected. The reports are included in the summary above, and do not affect the overall conclusions.

Other Safety Topics

An extensive review of safety information was completed by FDA in 2001 following submission of a Citizen Petition (1998) requesting that cetirizine, loratadine and fexofenadine be switched to OTC marketing status. For cetirizine, the three clinical areas that raised the most concern were convulsions/seizures, cardiac arrhythmias and thrombocytopenia. There were some indications of a causal relationship between these AEs and use of cetirizine, however the data were incomplete and inconclusive.

Somnolence/ drowsiness is also an area of interest for these 2nd generation anti-histamines, particularly, cetirizine. Dr. Lopez addressed these safety topics in her September 4, 2007 review.

Including all submitted safety data (company database, FDA-AERS and WHO-UMC), the total number of reports was 6475. There were 154 (2.4%) serious cases reported with AEs related to convulsions/seizures. The applicant provided age stratification for some reports.

- 2 cases in children < 6 years of age
- 16 cases in children 6-11 years
- 2 cases in children 12-17 years
- 23 cases in adults 18-65 years
- 2 cases in adults >65 years
- 8 cases in age "unknown"

Reviewer's comments: All of the cases are not included in the list. The applicant did not include age stratification information from the WHO-UMC database because this information was unavailable. Some reports may be repeated.

Death was reported in only one case, but this 23 year old male also overdosed on nefopam, which is associated with seizures.

There were 39 (0.6%) reports with AEs related to arrhythmias, including "prolonged QT interval." Thirty one (31) cases were labeled serious and eight were labeled nonserious. The applicant provided age stratification for some reports.

- 2 cases in children 12-17 years of age
- 17 cases in adults 18-65 years
- 3 cases in adults >65 years
- 8 cases in age "unknown"

A single death was reported in the case of the eight year old female with prolonged QT described above.

There were 28 (0.4%) reports with AEs related to thrombocytopenia.

- 5 cases in adults 18-65 years of age
- 3 cases in adults >65 years

There were 1006 (16%) cases reported with the AEs somnolence or drowsiness. This frequency of reports is consistent with the prescription label and general frequency of somnolence reported in clinical trials.

The terms "convulsion" and "thrombocytopenia" are included in the prescription package insert. The term "arrhythmia" is not included, but "tachycardia" is in the insert (See

Section 2.4). Although serious, none of these terms are included in the OTC labeling due to their extremely rare occurrence.

Reviewer's comments: Convulsions are included in the postmarketing experience section of the Zyrtec® prescription label as occurring very rarely. Although related terms were included as AEs in 2% of all reports assessed in this review, this reviewer believes that it is not appropriate to presume an increased frequency of convulsions with cetirizine use. Many of the consumers referred to in the reports had underlying epileptic conditions, subsequent seizure disorder diagnoses and concomitant medications that may put them at risk for seizures. Other reports contained too little clinical information to address causality. Also, new onset convulsions may prompt individuals to focus on potential inciting factors, such as medications, to explain the etiology thereby leading to an increased MedWatch reporting frequency for these serious events. There are no conclusive data indicating an increased risk of convulsions with cetirizine use.

The Executive Summary of the CDER OTC Switch Review Team who performed a safety review of cetirizine is found at http://www.fda.gov/ohrms/dockets/ac/01/briefing/3737b_03_risk.html (accessed June 21, 2010). The most commonly reported events from the reviewed databases and literature were somnolence, fatigue and dry mouth. Psychiatric disorders, not otherwise specified, were reported at a rate twice that of placebo in adult clinical trials. Nearly 40% of AE reports in the FDA-AERS database up to March 2001 included one or more nervous system or psychiatric terms. Ultimately, the Team identified convulsions, arrhythmia and thrombocytopenia as possible safety signals, but determined that there was not enough evidence to preclude switching cetirizine to OTC status.

There are no unresolved safety issues for cetirizine currently under evaluation by the FDA's Office of Surveillance and Epidemiology. Prior safety reviews of cetirizine included risk assessments for nervous system and psychiatric events (DDRE review, March 28, 2001), for suicidal ideation (DDRE review, January 13, 2004), and for medication errors with prescription confusion between Zyrtec®, Zyprexa® and Zantac® (Division of Medication Errors and Prevention Analysis (DMEPA), June 13, 2006).

Reviewer's comments: In the 2001 DDRE assessment, the safety evaluator felt that the data were limited in making a claim of causality between cetirizine and seizures or other psychiatric disorders. However, there were similar numbers of reports of nervous system and psychiatric disorder AEs associated with cetirizine and the other 2nd generation anti-histamines (loratadine, fexofenadine). A possible link between these agents and seizures was posited. Dr. Lopez (clinical review, September 4, 2007) included AERS crude counts of postmarketing reports of convulsion/seizure for cetirizine and loratadine as a comparison. The counts were similar. Line listings and AERS reports that included convulsion-associated PTs were reviewed, and no concerns were raised about the appropriateness of OTC marketing of cetirizine.

In the 2004 review, the safety evaluator analyzed 34 AERS reports of suicide-related and intentional overdose events. Although the data were sparse, she suggested that cetirizine may be associated with suicide-related events in some patients, as the prescription insert includes "depression" in the adverse event section. Suicide-related information is included in the current prescription labeling.

Safety Update

As per 21 CFR 314.50(d)(5)(vi)(b)(1), the applicant submitted a 4-month safety update received on March 8, 2010. The data include information on adverse events, overdose and abuse, misuse and dependence from the company database and published literature. There were no new clinical trials completed during this time. The data will be summarized and analyzed here, separate from the data in the original submission.

Overall, 2632 case reports with 4329 AEs were included in the company database for the time period January 17, 2009 to November 15, 2009. There were a total of 144 serious cases including three deaths (0.1%). Three articles in the published literature reported clinical trials with cetirizine over the time period June 24, 2009 to November 18, 2009. Among the trials reported, 789 subjects were involved in clinical trials with no reported serious AEs or deaths.

Applicant Database – Adverse Events

All cases were included if cetirizine was listed as the suspect or suspect-interacting drug. The population that comprised the database was 61% female with an average age of 41 years. There were 2488 nonserious reports, 141 serious reports and three deaths. The majority (58.9%) of outcomes were unknown, while 20% were listed as recovered, 19.6% as nonrecovered and 1% each as recovering or not applicable. Consumers were the report source for 90% of the cases. The most commonly reported AEs ($\geq$0.5%) in the serious reports[9] (n=455) included wrong drug administered (n=14, 3%), somnolence (n=11, 2.4%), dizziness (n=10, 2.2%) and headache (n=10, 2.2%). See **Table 13** for a list of all AEs stratified by age.

The applicant also searched the special safety topics of convulsions, arrhythmias and thrombocytopenia for cases during the reporting period. There were three reports of convulsion across all age groups. Two cases included subjects with known history of seizures, another had a normal EEG. There was one report of arrhythmia complicated by use of multiple medications. There were three cases of thrombocytopenia. One subject had a history of HIV infection, another had decreased platelets only after stopping cetirizine.

[9] Expressed as % (n/455)

Table 13: Summary of All AE Reports by Age and Seriousness – Company Database (January 17, 2009 through November 15, 2009)

Category	Nonserious Events n	Death or Other Serious Events n
Total number of events	3874	455
<6 years a	344	29
6 to <12 years b	230	45
12-17 years c	151	21
18-65 years d	1246	184
>65 years e	974	71
Age unknown	929	105

Source: Applicant's 120-day safety update submission p. 30

The most frequent serious AEs reported[10] in children < 6 years included wrong drug administered (n=2, 6.8%) and asthma (n=2), with all other AEs listed only once. In children 6-11 years, the most frequent serious events[11] were aggression (n=3, 6.7%), product quality issue (n=2, 4.4%), urticaria (n=2), asthma (n=2) and off-label use (n=2). In children 12-17 years, the most frequent serious event[12] was hypersensitivity (n=2, 9.5%). Somnolence (n=8, 5.3%) was listed as a frequent event in nonserious reports. In adults 18-65 years, the most frequent serious events[13] were somnolence (n=7, 3.8%), pruritis (n=6, 3.3%), pyrexia (n=5, 2.7%) and dizziness (n=5), with somnolence (n=135, 10.8%) also listed as one of the most frequent events in the nonserious reports. In adults over 65 years, the most frequent serious events[14] were wrong drug administered (n=10, 14.1%), dizziness (n=4, 5.6%) and blood pressure increased (n=3, 4.2%). Somnolence (n=67, 6.9%) was listed as a most common event in the nonserious reports. In persons with unknown age, the most frequent serious events[15] were exposure during pregnancy (n=8, 7.6%), drug ineffective (n=3, 2.8%) and headache (n=3). Somnolence (n=112, 12%) was listed as a common event in nonserious reports.

Reviewer's comments: Asthma, urticaria, hypersensitivity, and pruritis were listed as serious AEs; however, these symptoms are also commonly reported in persons with allergic rhinitis and idiopathic urticaria for which cetirizine is prescribed. Somnolence was more commonly reported as a serious and nonserious event in children and adults over the age of 12 years, and those with unknown age. The frequency does not appear

10 Expressed as % (n/29)
11 Expressed as % (n/45)
12 Expressed as % (n/21)
13 Expressed as % (n/184)
14 Expressed as % (n/71)
15 Expressed as % (n/105)

to be different from that reported in databases and the scientific literature, and warnings are already in place in the proposed OTC label for this formulation and other cetirizine products. There was no significant clustering of the remaining AEs. The data presented here do not warrant changes to the proposed label.

Where not indicated, somnolence was uncommonly reported. However, overall there were 479 cases (18% of all reports) of somnolence or drowsiness. This is already included in the current and proposed OTC labels.

Overdose, Abuse, Misuse and Dependence

Overall, there were 420 reports of cetirizine overdose. Ten (10) reports were categorized nonfatal serious, and two reports were fatal. Both fatal cases were multidrug ingestions in the 18-65 age group and are included in the "Deaths" subsection below. Of the 10 nonfatal serious reports, one each occurred in the 6-<12 age group, >65 age group and the age unknown group. Two cases were reported in the 12-17 age group and five cases reported in the 18-65 age group. There were 32 total AEs listed for the 12 serious cases. The most commonly reported AEs in these cases were "overdose" (n=6), "intentional overdose" (n=4), "dizziness" (n=3) and "suicide attempt" (n=2). The 10 mg dosage strength was specified in four cases, and six cases involved multiple other drugs. The most commonly reported AEs in the nonserious cases (n=610) were "overdose" (n=351), "accidental overdose" (n=57), "drug ineffective" (n=42) and "somnolence" (n=21).

Overall, there were 585 reports of abuse, misuse and dependence with 21 nonfatal serious reports and no deaths. The majority (n=10) of serious reports occurred in the >65 age group. Three cases were reported in children < 6. The others were more evenly distributed. There were 79 total AEs listed for the 21 serious reports. The most commonly reported AEs was "wrong drug administered" (n=14). The remainder of AEs were only reported once or twice without significant clustering. The 10 mg dosage strength was specified in 11 cases, and 14 cases involved multiple other drugs. The most commonly reported AEs in the nonserious cases (n=1243) were "wrong drug administered" (n=482), "drug ineffective" (n=116), "somnolence" (n=70), "overdose" (n=43), "accidental exposure" (n=36), and "off label use" (n=27). There were no newly reported cases in the literature.

Deaths

Two of the three deaths were detailed in reports of overdose. A 45 year old male with a history of depression, recreational drug use and suicidality experienced drug intoxication and respiratory depression while taking multiple medications including hydroxyzine and cetirizine. A 53 year old female accidentally overdosed on a combination of gamma hydroxybutyrate (Xyrem® - narcolepsy), tramadol (analgesic) and carisoprodol (Soma® - sleep aid). The third case reported "apparent death" as the

preferred term to describe a 58 year old female who self-reported requiring cardiopulmonary resuscitation after "dying" following ingestion of multiple medications for various medical ailments. The inclusion of multiple medications, including those with known abuse potential, confounds the association of cetirizine in the two actual deaths.

Reviewer's comments: Overall, there are no significant safety issues identified that would necessitate labeling changes. Most of the serious and frequent AEs are already included in the label. There was no consistent clustering of unlabeled AEs. Other serious AEs do not contain enough clinical data to make determinations of causality. Additionally, it does not appear that somnolence associated with cetirizine use has led to any increase in vehicle or machinery accidents. The labeling precaution recommending care when driving or using machinery should remain if the proposed product is approved.

9 Appendices

9.1 Literature Review/References

The applicant performed a comprehensive literature review to obtain cetirizine safety data from three online databases (MEDLINE®, EMBASE® and Derwent Drug File) for the time period from January 2007 through June 22, 2009. Additionally, Dr. Lolita Lopez provided synopses of surveyed medical literature by this applicant from 1995 through July 2006 (clinical review; September 4, 2007). The applicant's current search used "cetirizine" combined with "clinical trial or controlled clinical trial or meta-analysis or systematic review or double blind or single blind." The search was limited to humans. Eleven articles from the literature were identified. Summary tables of the articles that evaluated clinical safety and efficacy data in the treatment of labeled indications were prepared with reference to other related published articles. The results and summaries were reviewed for safety issues since the efficacy of cetirizine is well known.

Seven articles detail placebo-controlled trials with 10 mg cetirizine in over 2000 subjects. One article was an open-label trial (10 mg) in 50 subjects, and three articles describe active-control trials, also with a 10 mg dose, in over 300 subjects. No deaths were reported. Four non-related serious AEs were reported in one placebo-controlled trial. The applicant concludes that the published literature supports the continued safety of cetirizine for OTC marketing.

Reviewer's comments: I performed a follow up literature search using the applicant's criteria in addition to the terms "adverse events or effects," "safety," and "case report/series" for the time period from January 2007 to the present to update this review of safety data to capture other pertinent articles. My summaries of two additional papers from Kuna et al. and Lee et al. are below. The results and conclusions do not

differ from those referred by the applicant. A paper by Takenaka et al. was submitted by the applicant with the 120-day safety update and is also included here.

The applicant's summaries of 12 identified pertinent studies (full references are listed at the end of this section):

Enomoto et al [Enomoto 2007] reported the results of a randomized, double-blind, placebo-controlled, single-dose, crossover trial. Cetirizine 10 mg was compared to placebo in 20 subjects with known cedar pollinosis. Subjects received study medication 30 min after beginning exposure to pollen. There were no significant differences between cetirizine and placebo in terms of subjective somnolence or objective psychomotor performance.

Philip et al [Philip 2007] reported the results of a randomized, double-blind, placebo-controlled, parallel, multicenter, multidose, six-week trial. Cetirizine 10 mg once daily was compared to montelukast 10 mg once daily and placebo in 1365 subjects with a documented clinical history of perennial allergic rhinitis for at least two years. Both cetirizine and montelukast were well tolerated and no serious drug-related adverse events were reported in either group. Four cetirizine-treated subjects discontinued due to clinical adverse events compared to 29 montelukast-treated subjects and 24 placebo-treated subjects. No cetirizine-treated subjects discontinued due to a laboratory adverse event compared to two montelukast-treated subjects and three placebo-treated subjects.

Sologuren et al [Sologuren 2007] reported the results of a randomized, double-blind, placebo-controlled, single-dose, crossover trial. Cetirizine 10 mg was compared to bilastine 2.5, 5, 10, 20, and 50 mg and placebo in 21 healthy male volunteers. Each study medication was administered to 12 subjects. Thirteen of the subjects reported 30 adverse events, all mild in intensity. No clinically significant trends in ECG, vital signs, or physical examination findings were observed.

Fantin et al [Fantin 2008] reported the results of a randomized, double-blind, placebo-controlled, parallel, multicenter, multiple-dose, 12-week trial. Cetirizine 10 mg once daily was compared to rupatadine 10 mg once daily and placebo in 543 subjects 12 years or older with perennial allergic rhinitis. Five cetirizine-treated subjects discontinued due to an adverse event compared to two rupatadine-treated subjects and four placebo-treated subjects. No significant difference was observed in the percentage of subjects reporting adverse events who were treated with cetirizine (23%), rupatadine (23%), or placebo (21%). The most frequently reported adverse events were headache (29% to 36%), somnolence (4.3% to 10%), and nasopharyngitis (6% to 10%) with no significant difference among the treatment groups. Four not related serious adverse events included a suicide attempt occurring before one subject was randomized, two episodes of metrorrhagia in one cetirizine-treated subject and a blighted ovum in one placebo-treated subject.

Takahashi et al [Takahashi 2008] reported the results of a randomized, double-blind, placebo-controlled, crossover, multiple dose trial. The effect of cetirizine 10 mg once daily was compared to olopatadine 5 mg twice daily, fexofenadine 60 mg twice daily, and placebo on histamine-induced flare and wheal response in 10 healthy volunteers. No significant differences were noted in subjective drowsiness and objective cognitive function between cetirizine, olopatadine, fexofenadine, and placebo.

Badorrek et al [Badorrek 2009] reported the results of a randomized, double-blind, placebo-controlled, single-dose, crossover trial. The effect of cetirizine 10 mg, pseudoephedrine 120 mg, and the combination of cetirizine 10 mg and pseudoephedrine 120 mg was compared to placebo in 49 subjects with intermittent allergic rhinitis. Overall, 49 adverse events were reported by 49 subjects. The most frequently reported adverse event was headache (15/49) with no difference between subjects treated with active treatments and placebo. No serious adverse events were reported. Three subjects discontinued the study due to upper respiratory infections. Adverse events considered probably or possibly related to study treatment included headache, hot flush, feeling asthenic/sleepy, dizziness, xerostomia, feeling of heart beat, abdominal cramps, diarrhea, and sensitivity to light.

Ratz et al [Ratz 2009] reported the results of a randomized, double-blind, double-dummy, placebo-controlled, single-dose, crossover trial. Cetirizine 10 mg, loratadine 10 mg, azelastine 137 µg/spray, and placebo were compared in 70 subjects with seasonal allergic rhinitis to ragweed. Reported adverse events were similar between all treatments.

Garg et al [Garg 2007] reported the results of an open-label, crossover, six-week trial. The effect of cetirizine 10 mg once daily was compared to levocetirizine 5 mg once daily in subjects with chronic idiopathic urticaria. Subjects were treated sequentially, first with cetirizine for six weeks. Subjects that showed complete symptomatic control with cetirizine were then treated with levocetirizine for six weeks. Forty-five subjects achieved complete symptomatic control with cetirizine. Of the 45 subjects treated with levocetirizine, 30 completed the six-week study period for both drugs. Three (10%) subjects reported occasional headache and fatigue when treated with levocetirizine.

Shohrati et al [Shohrati 2007] reported the results of a randomized, double-blind, active-controlled, parallel, single-center, four-week trial. The effect of cetirizine 10 mg/day was compared to doxepine 10 mg/day and hydroxyzine 25 mg/d in 75 male subjects with chronic pruritus due to exposure to sulfur mustard. Six cetirizine-treated subjects reported sedation compared to 14 doxepine-treated subjects and 18 hydroxyzine-treated subjects. Dizziness was reported by two subjects in each treatment group. No significant differences among treatments were observed in sedation or dizziness. There were no differences in complications among groups.

Harahap et al [Harahap 2008] reported the results of a randomized, open-label, active-controlled, single-dose, crossover trial. The bioavailability of two cetirizine 10 mg tablet formulations were compared in 18 healthy male volunteers. Both cetirizine formulations were well tolerated and no serious clinical adverse events were reported.

Lou et al [Lou 2009] reported the results of a randomized, double-blind, double-dummy, active-controlled, seven-day trial. The effect of cetirizine was compared to the combination of cetirizine and pseudoephedrine in 210 subjects with seasonal or perennial allergic rhinitis. The incidence of adverse events was not significantly different between treatments. No serious adverse events were reported.

Takenaka et al [Takenaka 2009] reported the results of an open-label trial evaluating the administration of cetirizine 10 mg once daily in 26 subjects with urticaria who had not previously received oral or injectable steroids within the previous two weeks. Severe sleepiness was reported by 19.2% of subjects. Three subjects with no improvement in symptoms were dissatisfied with treatment, regardless of sleepiness (one subject reported sleepiness and two subjects did not report it).

Reviewer's comments: The most commonly reported adverse events were somnolence/drowsiness, fatigue and headache. This is consistent with the applicant's original clinical trials adverse events database, and U.S. and foreign safety databases for cetirizine, with headache being more common in pediatric age groups. Sedation and drowsiness were reported at a higher frequency for cetirizine compared to other second generation antihistamines. Most observed adverse events are well known to be associated with cetirizine. Those that had not been previously reported had limited clinical information or no conclusive evidence of causality. My further review of the current published literature resulted in two clinical trials summarized below (Kuna and Lee).

***Kuna et al** [Kuna 2009] compared efficacy and safety of once-daily bilastine 20 mg with cetirizine 10 mg and placebo for symptoms of SAR in a 14-day, multicenter, randomized, double-blind trial. 683 subjects, 12-70 years old with at least a two year history of documented SAR were enrolled. 37 withdrew from the trial before completion for various reasons. Four withdrew (3 in placebo group, 1 in bilastine group) for adverse events. The most common AEs overall were headache, somnolence, fatigue and dyspnea. More subjects in the cetirizine group experienced somnolence and fatigue (7.5% vs. 1.8% and 4.8% vs. 0.4%, respectively) than those in the bilastine group. No serious AEs or deaths were reported.*

Investigators used an efficacy index to determine their "clinical global impression" (CGI) of each patient. This included the subject's degree of therapeutic effect and the intensity of adverse events on a 16-point scale, with one representing vast improvement and no AEs, and 16 representing unchanged or worsening symptoms with AEs outweighing the therapeutic effect. The mean CGIs at the end of the trial were 5.0, 4.7

and 7.2 for bilastine, cetirizine and placebo, respectively ($p < 0.001$ for bilastine/cetirizine vs. placebo).

***Lee et al** [Lee 2009] compared efficacy and safety of cetirizine, levocetirizine and placebo in treating children (6-12 years old) with symptoms of PAR. Eighty children with moderate to severe PAR for at least one year were enrolled in a 12-week randomized, double-blind, placebo-controlled trial. The subjects were evaluated every 4 weeks with vital signs and physical exams. Somnolence and fatigue were reported in two subjects. There were no serious AEs or deaths. No subjects withdrew due to AEs.*

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9.2 Labeling Recommendations

A reviewer in the Division of Nonprescription Regulation Development (DNRD) will review the proposed label and principal display panel (PDP) in detail.

The applicant submitted a label with a table comparing the proposed “Drug Facts” with current, approved OTC cetirizine labels (approved November 25, 2008 under NDA 19-835/S-025). The proposed “relief of symptoms of AR” indication is the same as that for other approved OTC formulations. The label for this ODT formulation is consistent with the labels for other OTC formulations. The applicant includes all of the important warnings from the OTC labels. The only differences between the labels relate to storage information (i.e. “avoid high humidity”) and inactive ingredients, both reflective of this new formulation.

The tradename, Zyrtec®, is well known to consumers since the product line’s inception. Because of the new formulation, the terms (b) (4) and “Melts in Your Mouth” were originally proposed for the PDP. Reviewers from DNRD and the Division of Medication Error Prevention and Analysis (DMEPA) in the Office of Surveillance and Epidemiology

have further addressed the appropriateness of these terms, the labeling, and the proposed trade name.

The overall recommendations were to remove the term (b) (4) because it could be misleading as a comparative claim with an unknown basis for comparison. On June 10, 2010, the applicant submitted revised labeling with " (b) (4) still in place and the term "Melts in Your Mouth" revised to "Melts in Your Mouth (b) (4) On June 31, 2010, the applicant resubmitted revised labeling with (b) (4) replaced by (b) (4) Negotiations have not reached an agreement at the time this review was finalized. Further, DMEPA performed an AERS search for medication errors relevant to Zyrtec® labeling. Sixteen (16) cases were identified, but determined not to be the result of inadequate labeling.

Dosing Regimen and Administration

Cetirizine is available in several formulations and dose strengths. The tablets and chewable tablets are approved for OTC indications of relief from AR and itching from hives down to 6 years old. The syrup formulation is approved for allergic rhinitis down to 2 years old. The proposed regimen is essentially the same as the current, approved regimen for Zyrtec® 10 mg tablets. Although there is no 5 mg ODT dosage strength, the label appropriately directs consumers to dose adjustments for children, the elderly and those with liver or kidney disease (see **Table 14**).

Table 14: Comparison of Regimens for Current and Proposed 10 mg OTC Dosing

Target pop.	6yrs – adult	Over 65yrs	Birth – 6yrs	Liver/Kidney disease
Current	10 mg once daily*	Ask Doctor	Ask Doctor	Ask Doctor
Proposed	10 mg once daily*	Ask Doctor	Ask Doctor	Ask Doctor

Adapted from Applicant's submission Module 1.5.1
* Labeling states that another 5 mg product may be appropriate for less severe symptoms.

Drug-Drug Interactions

There are no new drug-drug interactions, and no interactions that preclude use or warrant additional warnings on the label. Currently, consumers are advised that concurrent use of cetirizine with alcohol or other central nervous system (CNS) depressants should be avoided because additional reduction and impairment of alertness may occur. The proposed label contains the same warnings. Consumers are also warned not to use cetirizine if they have a history of allergy to any of the inactive ingredients, or to products containing hydroxyzine, because cetirizine is a metabolite. Additionally, the results of PK trials described in the prescription label show that there were no clinically significant drug interactions. A small decrease (16%) in clearance of cetirizine was caused by a 400 mg daily dose of theophylline. Larger theophylline doses may have a greater effect.

Special Populations

No new information regarding special populations was submitted with this application. The following information is included in the prescription label for cetirizine.

Pediatrics
The cetirizine package insert includes PK information for the 7 year old to adult target population. When pediatric patients aged 7 to 12 years received a single, 5-mg oral cetirizine capsule, the mean C_{max} was 275 ng/mL. Based on cross-study comparisons, the weight-normalized, apparent total body clearance was 33% greater and the elimination half-life was 33% shorter in this pediatric population than in adults.

The safety of daily doses of 5 mg or 10 mg has been established in placebo-controlled RCTs in children over age 6 years. Over 600 subjects receiving doses for up to 12 weeks have been studied. The AUC and C_{max} in subjects from 6-11 years of age who received a single 10 mg dose was between that observed in adults who received either a single 10 mg dose or a single 20 mg dose.

Pregnancy
This application has no new information regarding pregnant women. Cetirizine is currently listed as Pregnancy Category B. There was no teratogenic effect in animal studies up to 220x the maximum recommended daily oral dose for adults on a mg/m^2 basis. There are no adequate and well-controlled trials in pregnant women. Because animal studies are not always predictive of human response, Zyrtec® should be used during pregnancy only if clearly needed. The proposed OTC label directs pregnant women to ask their doctor before use.

Nursing Mothers
Cetirizine has been reported to be excreted in human breast milk. Because many drugs are excreted in human milk, use of Zyrtec® in nursing mothers is not recommended. The proposed label has this recommendation.

Geriatric Use
The cetirizine prescription label states that the elimination half-life of a single, 10 mg oral dose was prolonged by 50%, and apparent total body clearance decreased by 40% in 16 geriatric patients with a mean age of 77 years compared to a similar number of adults with a mean age of 53 years. The decrease in clearance was presumed to be due to decreased renal function. Because there is substantial renal clearance of cetirizine, and the elderly are more likely to have renal insufficiency, the proposed label states that consumers over 65 should ask their doctor before use. This is consistent with the current approved label.

Renal and Hepatic Impairment
Consumers with renal or hepatic impairment are recommended to ask their doctors before use. The prescription label instructs those persons over 12 years of age with creatinine clearance 11-31 mL/min (includes Stage IV and V chronic kidney disease), on hemodialysis or with hepatic impairment to start with a 5 mg dose. Similarly, children 6-11 years old with the same impairments are instructed to start at the lower recommended dose.

Reviewer's comments: Five (5) mg is not a proposed dosage strength for this application. Therefore, the recommendation to ask a doctor is supported.

The pharmacokinetics of cetirizine were similar in tested normal adult subjects and those with mild renal impairment (creatinine clearance 42-77 mL/min) following multiple, oral 10 mg daily doses for seven days. Moderately to severely impaired subjects (creatinine clearance 11-31 mL/min) had a 3-fold increase in half-life and a 70% decrease in clearance compared to normal subjects. Hemodialysis patients given a single, 10 mg dose had the same changes in half-life and clearance compared to normals. Less than 10% of the dose was removed during a single dialysis session.

Sixteen patients with chronic liver diseases (hepatocellular, cholestatic and biliary cirrhosis) given a single oral dose of 10-20 mg had a 50% increase in half-life and a 40% decrease in clearance compared to normals.

Gender and Race
An effect on gender has not been adequately studied. No race-related differences in kinetics have been observed.

9.3 Advisory Committee Meeting

No new Advisory Committee Meeting addressed this application. A Nonprescription drug products and Pulmonary-Allergy drug products Joint Advisory Committee Meeting was held on May 11, 2001 and supported the use of second generation antihistamines, including cetirizine, in an OTC setting.

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/

RYAN M RAFFAELLI
07/07/2010

LESLEYANNE A FURLONG
07/07/2010

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22-578 **Applicant: McNeil Consumer Healthcare** **Stamp Date: 11/9/09**

Drug Name: Cetirizine **NDA/BLA Type: 505(b)(1) – Standard Review**

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Paper submission
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?			X	
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Reference is made to NDA 19-835
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?			X	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?			X	Reference made to NDA 19-835
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	Reference made to NDA 19-835
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements?			X	
17.	Has the applicant submitted a rationale for assuming the			X	

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	applicability of foreign data to U.S. population/practice of medicine in the submission?				
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			Post-marketing use of same dose in different formulation.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?		X		No datasets submitted
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			Post-marketing data
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	No deaths or serious AEs resulting in dropout
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			Post-marketing data
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S.			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	population?				
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?		X		
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?		X		
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?		X		
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___YES_____

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

- The sponsor's waiver request for pediatric studies in children from birth to 5 years will be evaluated by the Pediatric Review Committee (PeRC) near the end of the review cycle as per the Pediatric Research Equity Act (PREA). Our clinical review and the PeRC evaluation will determine FDA's response to the request for a waiver. At this point in our review, we are considering whether lower dosages (i.e. 2.5 mg or 5 mg) of the ODT may provide a meaningful therapeutic benefit to children from 2-5 years as an alternative dosing option.

- Electronic clinical datasets should be submitted by the sponsor in order to further analyze the results and safety data of the bioequivalence trial. The datasets may be submitted in a compatible SAS transport file (version 5). Please refer the sponsor to the appropriate draft guidance for details on the electronic submission. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072362.pdf. This point can be communicated in an Information Request.

Ryan Raffaelli, M.D. — January 6, 2010
Reviewing Medical Officer — Date

Lesley Furlong, M.D. — January 6, 2010
Clinical Team Leader — Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

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/

RYAN M RAFFAELLI
01/06/2010

LESLEYANNE A FURLONG
01/06/2010