

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-429

MEDICAL REVIEW(S)

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Clinical Review

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical safety standpoint, Banner's proposed cetirizine softgel capsules 5 and 10 mg indicated for the indication of temporary relief of symptoms of runny nose, itchy, watery eyes, sneezing, and itching of the nose or throat due to hay fever or other upper respiratory allergies, and relief of itching due to hives in adults and children 6 years of age and older has an acceptable safety profile for OTC marketing. Therefore, this reviewer recommends approval of this application as long as the sponsor incorporates the reviewing team's labeling recommendations. Final approvability depends on the adequacy of the bioequivalence studies.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No special risk management activities are recommended for this NDA.

1.2.2 Required Phase 4 Commitments

No required phase 4 commitments are recommended.

1.2.3 Other Phase 4 Requests

No other phase 4 requests are recommended.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Banner Pharmacaps, Inc. (BPI) is seeking approval to market their proposed products, cetirizine hydrochloride (HCl) 5 and 10 mg softgel capsules for over-the-counter (OTC) use. The indications will be similar to the already approved OTC indications for cetirizine HCl which are: temporary relief of symptoms of runny nose, itchy, watery eyes, sneezing, and itching of the nose or throat due to hay fever or other upper respiratory allergies, and relief of itching due to hives. However, the proposed age indication will be limited to adults, and children 6 years of age and older.

In support of this NDA, the sponsor conducted two bioavailability studies, 20-219-SA under fasting conditions and 20-220-SA under fed conditions, comparing the pharmacokinetics (PK) of a single dose of the proposed cetirizine HCl 10 mg softgel capsule (also referred to as capsule)

and the currently marketed Zyrtec® 10 mg tablet, the reference listed drug (RLD), in healthy subjects. The sponsor is requesting a waiver of the bioequivalence (BE) requirement for the 5 mg tablet because this dosage strength is proportional to the proposed 10 mg strength in their active ingredient (drug substance) and excipients. This cetirizine soft capsule formulation has not been marketed anywhere else.

This NDA is submitted under a 505(b)(2) application and relies on the Agency's previous finding of safety and efficacy for cetirizine HCl tablets. Reference is made to NDA 19-835 (Zyrtec® tablets) marketed by Pfizer, Inc./McNeil to obtain information on study reports related to pharmacology/toxicology, statistical, clinical, and other studies. Additional information submitted were the sponsor's bioavailability studies, safety update for cetirizine, literature review and postmarketing information.

1.3.2 Efficacy

There were no efficacy trials conducted for this application except for PK evaluation. Efficacy is based on prior approval for the RLD and supported by the sponsor's PK data from the single-dose relative bioavailability studies assessing the sponsor's cetirizine HCl 10 mg capsule and Zyrtec® 10 mg tablet (RLD). Study 20-219-SA was a single-center, randomized, single-dose, 2-sequence, crossover bioavailability study that compared BPI's cetirizine capsule and Zyrtec® (Pfizer) 10 mg tablets under fasting conditions in healthy adult male and female subjects. Study 20-220-SA was also a single-dose bioavailability study with a study design similar to Study 20-219-SA but was conducted under fed conditions. The 90% confidence interval of the relative geometric mean of the test (cetirizine 10 mg capsule) to the reference (Zyrtec® 10 mg tablets) formulation for C_{max}, AUC_{0-t} and AUC_∞ were within FDA's requirements for bioequivalence limits of 80-125% (see section 5.1, Table 3).

Efficacy of this NDA will be reviewed by the Division of Pulmonary and Allergy Products (DPAP) and the relative bioavailability studies will be reviewed by the Office of Clinical Pharmacology (OCP).

1.3.3 Safety

The sponsor primarily relies on the safety information from the reference listed drug Zyrtec® tablets and safety data from the sponsor's bioavailability studies 20-219-SA and 20-220-SA. In addition, an integrated review of safety that included safety information from the following postmarketing databases was provided:

- A report summarizing adverse event reporting to the FDA Adverse Event Reporting System (AERS) (June 1, 2007 to July 31, 2008)
- American Association of Poison Control Centers' (AAPCC) National Poison Data System (NPDS) database (June 1, 2007 to July 31, 2008)
- A report of the Drug Abuse Warning Reports (DAWN) (June 6, 2007 to July 31, 2008)
- A report summarizing adverse event reporting to the World Health Organization's (WHO) International Drug Monitoring Program (June 1, 2007 to July 31, 2008)

- A review of medical literature relevant to the safety of cetirizine (June 1, 2007 to July 31, 2008)

In the bioavailability studies conducted by the sponsor, a total of 47 subjects were exposed to both the proposed cetirizine HCl capsule and Zyrtec® tablet formulations, 10 mg. There were neither deaths nor serious adverse events (SAEs) reported from these studies, and no subject was withdrawn due to an adverse event (AE) from the treatment. In the combined PK studies, the most common AEs experienced for both treatments were headache (6/48, 12.5%); somnolence (2/48, 4%); and nausea (2/48, 4%). In the fasting study (20-219-SA, N=24), a total of 6 (25%) subjects experienced a total of 9 AEs: 3 (13%) subjects reported at least one AE after administration of BPIs cetirizine capsule and 3 (13%) subjects after administration of Zyrtec® tablet. One subject was dropped from the study due to non-compliance (i.e., positive urine drug screen). In the food effect study (20-220-SA, N=24), 6 (25%) subjects experienced a total of 8 AEs: 5 (21%) subjects reported at least one AE after administration of BPIs cetirizine capsule and 3 (13%) subjects after administration of Zyrtec® tablet. The most common and possibly treatment related AEs were headache and somnolence.

In controlled (15) and uncontrolled (10) clinical efficacy trials conducted in the United States and Canada for the marketing of prescription cetirizine which included more than 6,000 patients aged 12 years and older (more than 3,900 patients received cetirizine at doses of 5 to 20 mg per day), most adverse reactions reported during therapy with cetirizine were mild or moderate. The duration of treatment ranged from 1 week to 6 months, with a mean exposure of 30 days. The most common AEs were: somnolence 13.7%, fatigue 5.9%, dry mouth 5%, pharyngitis 2% and dizziness 1.2%. Treatment-related AEs include fatigue, dry mouth and somnolence; the latter was dose related (6% in placebo, 11% at 5 mg and 14% at 10 mg). The most commonly reported SAEs from the clinical efficacy trials (N=216) were asthma (36, 9.2%); vomiting (14, 3.6%); pyrexia (14, 3.6%) and bronchitis (11, 2.8%).¹ Pediatric studies were also conducted in more than 1,300 pediatric patients aged 6 to 11 y/o, more than 900 patients were treated with cetirizine at doses of 1.25 to 10 mg per day (controlled and uncontrolled clinical trials) with a duration of treatment ranging from 2 to 12 weeks. The most common AEs in this age group were headache, pharyngitis, abdominal pain, coughing, somnolence, diarrhea, epistaxis, bronchospasm, nausea and vomiting. Among these, treatment-related AEs were abdominal pain, and somnolence; the latter was dose-related (1.3% in placebo, 1.9% at 5 mg, 4.2% at 10 mg). The majority of adverse reactions reported were mild or moderate.²

The postmarketing safety databases NPDS AAPCC, FDA AERS, WHO, and DAWN submitted with the Safety Update during the reporting period June 1, 2007 to July 31, 2008 did not reveal any specific trend or signal detected with the use single-ingredient cetirizine. NPDS reported 253 human exposures involving cetirizine; of these, 49 cases had (a total of 88) identifiable specific clinical effects (CEs). The most frequently reported CEs were: drowsiness/lethargy (24, 27%); tachycardia (7, 8%); agitated/ irritable (6, 7%); dizziness/vertigo (4, 5%); ataxia (3, 3%); dyspnea (3, 3%); hallucinations/delusions (3, 3%); vomiting (3, 3%); and abdominal pain

¹ See cetirizine prescribing information.

² See cetirizine prescribing information

(2, 2%). Most of the exposures resulted in no effect or minor effects. In the FDA AERS database, there were a total of 233 cases with 902 associated AE terms during the reporting period. Overall, the most frequently reported AEs were: convulsion (24, 2.7%); hypersensitivity (14, 1.6%); somnolence (12, 1.3%); drug exposure during pregnancy (12, 1.3%); depression (11, 1.2%); drug ineffective (11, 1.2%); pruritus (11, 1.2%); abnormal behavior (10, 1.1%); feeling abnormal (10, 1.1%), dizziness (9, 1%), and fatigue (9, 1%). In the WHO database, there were 274 cases reported involving 854 AEs. The most common AEs reported were: dizziness (24, 2.8%); drug ineffective (24, 2.8%), somnolence (22, 2.6%), drug dispensing error (21, 2.4%) medication error (21, 2.4%), fatigue (17, 1.9%), urticaria (15, 1.7%), convulsion (14, 1.6%), pruritus (14, 1.6%), and wrong drug administered (14, 1.6%). The DAWN data did not reveal any signal that lansoprazole is being abused or misused. A review the medical literature did not reveal any new significant safety concerns with the use of cetirizine.

The types of adverse events that were noted in the postmarketing safety databases and the medical literature are generally similar to those previously reported with the use of cetirizine both during clinical trials and from postmarketing experience. There is also no conclusive evidence of a causal relationship between the use of cetirizine and any previously unidentified serious or life-threatening adverse event from postmarketing databases. This is largely due to a lack of more specific clinical information to properly evaluate an event such as unknown to time to onset, extent of exposure, dechallenge and/or rechallenge information. In addition, reports regarding the same case may sometimes be received from several different sources at different times as seen in some of the reported cases.

Cetirizine hydrochloride has been marketed with a well-characterized safety profile in the United States since its approval for prescription use in 1995. An extensive safety database exists for cetirizine postmarketing experience. In November 2007, the Rx-to-OTC switch of cetirizine hydrochloride (Zyrtec®) was approved, and the safety of cetirizine for OTC use was reviewed in detail.

The combination of postmarketing information from safety databases, previous clinical trials, literature review, and adverse events information from the relative bioavailability studies conducted by the sponsor do not raise any new safety concern for the OTC use of cetirizine capsules at the recommended dose.

1.3.4 Dosing Regimen and Administration

The sponsor's proposed dosing and indications are similar to those of the currently approved cetirizine (Zyrtec®) tablets for OTC use except for a narrower age indication. The approved indications for cetirizine OTC are for the temporary relief of allergic rhinitis symptoms in adults and children ≥ 2 years of age, and relief of itching due to hives (hives relief) in adults and children ≥ 6 years of age. In this submission, the sponsor is seeking for both approved indications of allergic rhinitis and hives relief in adults and children ≥ 6 years of age. The proposed dosing regimen is 5 or 10 mg ~~capsule~~ capsule once a day depending on symptom severity. **b(4)**

1.3.5 Drug-Drug Interactions

There are no new drug-drug interactions evaluated with this submission. Patients are advised that concurrent use of cetirizine with alcohol or other central nervous system (CNS) depressants should be avoided because additional reduction in alertness and additional impairment of CNS performance may occur.

The prescription label for cetirizine states that there was no clinically significant drug interactions found with theophylline at a low dose, azithromycin, pseudoephedrine, ketoconazole, or erythromycin. There was a small decrease in the clearance of cetirizine caused by a 400-mg dose of theophylline.

There are no new drug interaction warning listed in the proposed OTC label. There is no new significant information regarding drug interaction that warrants additional warning in the proposed OTC label for this submission. The OTC label warns consumers not to use the product if there is allergic reaction to the product or any of its ingredients or to an antihistamine containing hydroxyzine (cetirizine is a metabolite of hydroxyzine). It also warns patients that when using cetirizine: drowsiness may occur; alcohol, sedatives and tranquilizers may increase drowsiness; and to avoid alcoholic drinks when using the product. In addition, the proposed label warns patients to ask a doctor or pharmacist if taking tranquilizers or sedatives.

1.3.6 Special Populations

Since this NDA only contains PK studies conducted in healthy subjects, there are no new significant data regarding other patient population (such as hepatic and renal failure patients), and the effects of gender, race or age on safety. There is also no new information provided that would warrant any changes regarding special population other than those already included in the currently approved cetirizine OTC label.

Cetirizine is currently listed as Pregnancy Category B. The proposed OTC label includes appropriate warnings to certain consumers including asking a doctor if pregnant women or if with renal or kidney problems. The label also states that the product is not recommended in breastfeeding mothers.

Pediatrics

Pediatric patients were not evaluated in this NDA. Cetirizine is approved for OTC use for the treatment of allergic rhinitis symptoms in adults and children ≥ 2 years of age; it remains available for prescription use in children 6 months old to <2 years of age. Cetirizine is also approved for OTC use for hives relief in adults and children ≥ 6 years of age; it remains available for prescription use children < 6 years of age. The safety and effectiveness of cetirizine in pediatric patients under the age of 6 months have not been established.

This submission triggers the Pediatric Research Equity Act (PREA) because it is a new dosage formulation. This cetirizine softgel capsule formulation will only be labeled in adults and children ≥ 6 years old. For children < 6 years of age, the label directs a consumer to ask a

doctor. The doctor/healthcare professional is assumed to direct the consumer to a formulation that is more appropriate for this age group, such as the syrup or chewable tablet.

The sponsor is requesting a waiver for pediatric studies below 6 years of age, and states that the proposed softgel capsule formulation does not represent a meaningful therapeutic benefit over existing therapies, and it is not likely to be used in a substantial number of children below 6 years of age. This reviewer agrees with the sponsor that no additional studies below 6 years of age are needed, and recommends granting a waiver for this age group. The efficacy of this capsule formulation in children ≥ 6 years of age is extrapolated based on PK data from the single-dose relative bioavailability studies assessing the proposed cetirizine capsule 10 mg and the currently marketed Zyrtec® tablet 10 mg (RLD).

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Cetirizine hydrochloride is a second generation antihistamine and a human metabolite of hydroxyzine in which its principal effects are mediated via selective inhibition of peripheral H-1 receptors. It was initially approved for prescription use on December 8, 1995 for the relief of symptoms associated with allergic rhinitis (seasonal and perennial) and treatment of chronic idiopathic urticaria (CIU) in adults & children ages ≥ 12 years, and later (September 1996) in children ages ≥ 6 years. In May 1998, an expansion of labeling use in children as young as two years old was approved; in October 2002, it was approved for the indication of perennial allergic rhinitis (PAR) and CIU in children as young as 6 months old. Cetirizine is currently available in the following formulations: tablets (5 and 10 mg), chewable tablets (5 and 10 mg), and syrup (1 mg/1 mL). In November 2007, cetirizine was switched from prescription to nonprescription or over-the-counter (OTC) use.

The currently approved OTC indications for cetirizine are:

- 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 adults and children ≥ 2 years of age
- relief of itching due to hives in adults and children ≥ 6 years of age

The indications for cetirizine in the younger population remain prescription for the following indications and age groups (syrup formulation only):

- relief of symptoms associated with *perennial allergic rhinitis (PAR)* in children 6 months to < 2 years of age
- treatment of the uncomplicated skin manifestations of *chronic idiopathic urticaria (CIU)* in adults and children 6 months to < 6 years of age

In this submission, Banner Pharmacaps, Inc. is seeking for the approval of cetirizine HCl 5 and 10 mg capsules for OTC use in adults and children ≥ 6 years of age. The proposed indications are similar to those of the currently approved cetirizine tablets (Zyrtec®) for OTC use. The proposed capsule formulation has not been marketed elsewhere.

2.2 Currently Available Treatment for Indications

There are other currently available medical treatments for the relief of allergic rhinitis symptoms and relief of itching due to hives. These are the first and second generation H₁-antagonist antihistamines marketed either prescription or OTC. The second-generation antihistamines currently available for OTC use are loratadine and cetirizine. Loratadine is marketed under brand names such as Claritin® (10 mg tablet, 10 mg reditabs, 1mg/mL syrup, 5 mg chewables)

and Alavert® (10 mg tablet or 10 mg quick dissolving tablet) or as a generic loratadine product. Cetirizine is marketed under the brand name Zyrtec® or as a generic cetirizine product. The following are currently marketed formulations of cetirizine: tablets (5 and 10 mg), chewable tablets (5 and 10 mg), and syrup (1mg/mL). A cetirizine/pseudoephedrine combination product (Zyrtec-D®) is also marketed for OTC use. Fexofenadine (Allegra®) and levocetirizine (Xyzal®) are other second generation antihistamines with the same indications but are currently available for prescription use only.

The first generation antihistamine products available for OTC use for the relief of allergic rhinitis symptoms are drugs in which the active ingredients are included in the list of OTC monograph drugs or approved under an NDA. The following active ingredients are included in the list of OTC monograph drugs:³ brompheniramine (e.g. Dimetapp Cold® & Allergy Elixir®, Robitussin Allergy & Cough Liquid®), chlorcyclizine, chlorpheniramine (Singlet®), dexbrompheniramine, diphenhydramine (Benadryl Allergy®, Nytol®, Sominex®), doxylamine (Vicks NyQuil®, Alka-Seltzer Plus Night-Time Cold Medicine®), phenindamine, pyrilamine, thonzylamine and triprolidine (Actifed®). Some of these active ingredients are also marketed via the NDA approval process if the formulation is other than that specified in the monograph (e.g., extended-release) or if marketed in combination with a non-monograph ingredient.

2.3 Availability of Proposed Active Ingredient in the United States

Cetirizine was originally approved as a single-ingredient prescription-only drug in the United States in 1995, and a cetirizine/pseudoephedrine combination product in 2001; both single-ingredient and combination cetirizine products have been switched to OTC status in November 2007. Generic cetirizine products were approved for OTC marketing in December 2007. Cetirizine (single-ingredient) products for OTC use have a narrower age indication in children: relief of allergic rhinitis (AR) symptoms in children ≥ 2 years of age, and relief of uncomplicated hives in children ≥ 6 years of age. Cetirizine remains available as a prescription product in younger age group for these indications.

2.4 Important Issues with Pharmacologically Related Products

Antihistamines are known for their sedative effects. Second generation antihistamines (cetirizine, fexofenadine and loratadine) cause a much lesser degree of somnolence compared to the first generation antihistamines. However, cetirizine may cause a higher incidence of somnolence even at recommended doses when compared to fexofenadine and loratadine although to a much lesser degree than older first generation antihistamines.

Terfenadine (withdrawn in 1998) and astemizole (discontinued 1999) are two non-sedating second generation antihistamines with similar structures that have been removed from the market due to the associated risk of causing cardiac arrhythmia, Torsades de Pointes secondary to QT prolongation at high serum concentrations. The metabolism of each drug may decrease (hence increase serum concentration) when given concomitantly with certain drugs such as antifungals

(e.g. ketoconazole and fluconazole), macrolides (erythromycin), antivirals and those with the potential to inhibit hepatic microsomal enzymes, particularly isozyme CYP3A4.

There have been no reports of the Torsades de Pointes with cetirizine as the single suspect drug.

2.5 Presubmission Regulatory Activity

On July 19, 2007, FDA received an original IND 78,232 submission from the sponsor with a proposal to conduct two bioavailability (fasting and fed) studies comparing a single-dose of their proposed cetirizine 10 mg softgel capsule and the currently marketed cetirizine (Zyrtec®) tablets, 10 mg. This IND was submitted to the Division of Pulmonary Products (DPAP) because cetirizine (Zyrtec®) was marketed as a prescription product at that time.

On August 1, 2008, the Agency received this 505(b)(2) application from the sponsor. To support this NDA, two completed bioavailability (pharmacokinetics) studies comparing their cetirizine HCl softgel-capsules to Zyrtec® tablets, 10 mg, in both fasted and fed states were submitted. The sponsor requested a waiver of the bioequivalence requirement for the 5 mg tablet because this dosage strength is proportional to the proposed 10 mg strength in their active ingredient (drug substance) and excipients. Reference is made to NDA 19-835 (Zyrtec® tablets) marketed by Pfizer, Inc./McNeil to obtain information on study reports related to pharmacology/toxicology, statistical, clinical, and other studies.

2.6 Other Relevant Background Information

The request for the OTC switch of second generation antihistamines was first generated when the California Blue Cross submitted a Citizen's Petition requesting OTC status for loratadine, fexofenadine and cetirizine in 1998. A CDER OTC Switch Review Team was formed which comprised of reviewers from the Division of Pulmonary and Allergy Drug Products and the Division of Drug Risk Evaluation I and conducted a review of worldwide safety information to determine whether there were any safety concerns that would prevent the use of these class of drugs in an OTC setting. The Citizen Petition, along with the safety of these medications for OTC use, was the topic of discussions in a Joint Nonprescription and Pulmonary Advisory Committee meeting held on May 11, 2001 (<http://www.fda.gov/ohrms/dockets/ac/cder01.htm>). The Advisory Committee determined that these medications, including cetirizine, have a safety profile acceptable for OTC marketing.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The proposed cetirizine hydrochloride 5 and 10 mg tablets are immediate release soft gelatin capsules containing cetirizine hydrochloride. These are ~~soft gelatin capsules~~ soft gelatin capsules

b(4)

Microbiology review was not necessary for this application. See Chemistry review for details.

b(4)

3.2 Animal Pharmacology/Toxicology

There are no new non-clinical studies conducted by the sponsor for this 505(b)(2) application. Due to the extensive marketing experience for cetirizine, the sponsor was not required to conduct any nonclinical toxicology studies. The sponsor refers to the Agency's previous non-clinical pharmacology and toxicology findings for cetirizine (NDA ~~22-429~~, Zyrtec® tablets) and submitted a summary of published nonclinical research on cetirizine from the literature since its initial approval. The following information is reflected in the prescription label for cetirizine under the PRECAUTIONS section; Carcinogenesis, Mutagenesis and Impairment of Fertility:

b(4)

In a 2-year carcinogenicity study in rats, cetirizine was not carcinogenic at dietary doses up to 20 mg/kg (approximately 15 times the maximum recommended daily oral [MRDO] dose in adults on a mg/m² basis, or approximately 7 times the MRDO dose in infants on a mg/m² basis). In a 2-year carcinogenicity study in mice, cetirizine caused an increased incidence of benign liver tumors in males at a dietary dose of 16 mg/kg (approximately 6 times the MRDO dose in adults on a mg/m² basis, or approximately 3 times the MRDO dose in infants on a mg/m² basis). No increase in the incidence of liver tumors was observed in mice at a dietary dose of 4 mg/kg (approximately 2 times the MRDO dose in adults on a mg/m² basis, or approximately equivalent to the MRDO dose in infants on a mg/m² basis). The clinical significance of these findings during long-term use of cetirizine is not known. Cetirizine was not mutagenic in the Ames test, and not clastogenic in the human lymphocyte assay, the mouse lymphoma assay, and in vivo micronucleus test in rats. In a fertility and general reproductive performance study in mice, cetirizine did not impair fertility at an oral dose of 64 mg/kg (approximately 25 times the MRDO dose in adults on a mg/m² basis).

In preclinical studies, the acute minimal lethal oral doses were 237 mg/kg in mice (approximately 95 times the MRDO dose in adults on a mg/m² basis, or approximately 40 times the MRDO dose in infants on a mg/m² basis) and 562 mg/kg in rats (approximately 460 times the MRDO dose in adults on a mg/m² basis, or approximately 190 times the MRDO dose in infants on a mg/m² basis). In rodents, the target of acute toxicity was the central nervous system, and the target of multiple-dose toxicity was the liver.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

There were no new clinical efficacy studies conducted by the sponsor to support this application.

The clinical data utilized in this review were the safety data from sponsor's bioavailability studies comparing the 10 mg cetirizine HCl capsules to Zyrtec® tablets (Pfizer/McNeil), the prescription and OTC label of Zyrtec®, and the sponsor's integrated review of postmarketing safety data for cetirizine for the past year. Reference is made to NDA 19-835 (Zyrtec® tablets) marketed by Pfizer/McNeil to obtain information on study reports related to pharmacology/toxicology, statistical, clinical, and other studies. Additional safety information submitted (on October 29, 2008 and updated on March 25, 2009) was from the following sources:

- o AERS database (June 1, 2007 to July 31, 2008)
- o American Association of Poison Control Centers' (AAPCC) National Poison Data System (NPDS) database (June 1, 2007 to July 31, 2008)
- o WHO Vigibase (June 1, 2007 to July 31, 2008)
- o DAWN database (June 6, 2007 to July 31, 2008)
- o Medical literature review (June 1, 2007 to July 31, 2008)

4.2 Tables of Clinical Studies

Table 1: Banner's Bioavailability Studies (20-219-SA and 20-220-SA)

Type of Trial	Name of Trial	Objective	Trial Design	Treatment	Subjects Completed
PK	20-219-SA	Compare Bioavailability of Cetirizine 10 mg Softgel caps in Healthy Volunteers under Fasted conditions	Open label, Randomized, Crossover, 7-day Washout Period in 24 Healthy Subjects	Oral Single-dose Cetirizine 10 mg softgel caps, vs. Zyrtec® 10 mg tablets	N=23
PK	20-220-SA	Compare Bioavailability of Cetirizine 10 mg Softgel caps in Healthy Volunteers under Fed conditions	Open label, Randomized, Crossover, 7-day Washout Period in 24 Healthy Subjects	Oral Single-dose Cetirizine 10 mg softgel caps, vs. Zyrtec® 10 mg tablet	N=24

Reviewer's table

4.3 Review Strategy

This review will evaluate cetirizine safety data only. The bioavailability studies (one fasting and one fed) submitted by the sponsor comparing the PK profile of one 10 mg dose of cetirizine capsule (BPI) to one Zyrtec® 10 mg tablet (Pfizer/McNeil) were mainly utilized in the review of this NDA. The efficacy review for this application will be evaluated by the Division of Pulmonary and Allergy Products (DPAP). The Office of Clinical Pharmacology will review the adequacy of submitted relative bioavailability studies in detail. A reviewer from the Division of Nonprescription Regulation Development (DNRD) will be reviewing the proposed OTC label in detail.

4.4 Data Quality and Integrity

An inspection by the Division of Scientific Investigations (DSI) was requested for studies 20-219-SA and 20-220-SA. According to the DSI inspection memorandum by dated March 11, 2009, an aberrant internal standard response was identified in runs 6 and 7 in study 1001659 (20-219-SA). DSI recommended that the data generated in runs 6 and 7 (for subjects 217, 218, 219, 220, 221, 222, 223, and 224) be excluded from the BE determination. The rest of the study data was determined to be acceptable for review (see DSI and Biopharm review entered in DFS).

4.5 Compliance with Good Clinical Practices

The sponsor signed a statement that the research trials (Protocols 20-219-SA and 20-220-SA) were conducted in compliance with 21 CFR Part 56 Institutional Review Board and 21 CFR Part 50 Protection of Human Subjects (including Subpart B Informed Consent of Human Subjects).

4.6 Financial Disclosures

An FDA form 3454 was submitted certifying that as a sponsor of the submitted studies, it has not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). There were no financial disclosures that would cast doubt on the findings of the studies.

5 CLINICAL PHARMACOLOGY

There is no new clinical pharmacology information submitted with this application. The sponsor conducted PK studies to assess the bioavailability of Banner's cetirizine capsules when compared to Pfizer's Zyrtec® tablets (RLD), 10 mg, in healthy adult subjects under fasting (20-219-SA) and fed (20-219-SA) conditions. The sponsor requested a waiver of the bioequivalence requirement for cetirizine HCl capsule 5 mg because this dosage strength is proportional to the proposed 10 mg strength in their active ingredient (drug substance) and excipients. The sponsor reports that both drug products are manufactured by the same process and differ only in strengths. See Clinical Pharmacology review for details.

5.1 Pharmacokinetics

Cetirizine is an oral antihistamine and a human metabolite of hydroxyzine. Its principal effects are mediated via selective inhibition of peripheral H-1 receptors. Below is the PK information in adults and children ≥ 6 years of age, detailed information can be found in the prescription label for cetirizine:

Cetirizine was rapidly absorbed with a time to maximum concentration (T_{max}) of approximately 1 hour following oral administration in adults. When healthy volunteers were administered cetirizine 10 mg tablets once daily for 10 days, a mean peak plasma concentration (C_{max}) of 311 ng/mL was observed. No accumulation was observed. Cetirizine PK was linear for oral doses ranging from 5 to 60 mg. Food had no effect on the extent of exposure (AUC) of the cetirizine tablet or chewable tablet, but T_{max} was delayed by 1.7 hours and 2.8 hours respectively, and C_{max} was decreased by 23% and 37%, respectively in the presence of food. The mean plasma protein binding of cetirizine is 93%. The mean elimination half-life in 146 healthy volunteers across multiple PK studies was 8.3 hours and the apparent total body clearance for cetirizine was approximately 53 mL/min.

In pediatric patients 7 to 12 y/o who 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 population than in adults.

In geriatric patients, following a single 10-mg oral dose, the elimination half-life was prolonged by 50% and the apparent total body clearance was 40% lower in 16 subjects (mean age=77 years) compared to 14 subjects (mean age=53 years). The decrease in cetirizine clearance in these elderly volunteers may be related to decreased renal function.

The PK of cetirizine was similar in patients with mild impairment and normal volunteers. Moderately impaired patients had a 3-fold increase in half-life and a 70% decrease in clearance compared to normal volunteers. Patients on hemodialysis (n=5) given a single, 10-mg dose of cetirizine had a 3-fold increase in half-life and a 70% decrease in clearance compared to normal volunteers. Less than 10% of the administered dose was removed during the single dialysis session. Dosing adjustment is necessary in patients with moderate or severe renal impairment and in patients on dialysis.

Sixteen patients with chronic liver diseases given 10 or 20 mg of cetirizine as a single, oral dose had a 50% increase in half-life along with a corresponding 40% decrease in clearance compared to 16 healthy subjects. Dosing adjustment may be necessary in patients with hepatic impairment.

Sponsor's Bioavailability Studies

The two bioavailability studies (20-219-SA and 20-220-SA) conducted by the sponsor have similar study designs, treatment administration and clinical procedures except that one was conducted under fasting and the other under fed conditions.

Study 20-219-SA (Fasting)

This was an open-label, single-dose, 2-treatment, 2-period, randomized, crossover study that compared cetirizine 10 mg capsule (BPI) and Zyrtec® (Pfizer/McNeil) tablets under fasting conditions in 24 healthy adult male and female subjects. See Table A-1 in the Appendix section for demographic profile of subjects who completed the study. Subjects were scheduled to

receive a single-dose of each two treatment in two assigned dosing periods separated by a 7-day washout period.

Subjects received each of the treatment below following an overnight fast of at least 10 hours:

- Treatment A (Test): Banner’s cetirizine 10 mg softgel capsule
- Treatment B (Reference): Zyrtec® 10 mg tablet

Table 2: Table of Procedures 220-219 SA

Procedure	Screening	Each study period	Discharge (48 hrs)
Informed consent	X		
Medical and medication histories	X		
ECG	X		X
Vital signs ¹	X	X	X
Physical examination	X		X
Biochemistry, hematology, urinalysis	X		X
Serology	X		
Urine drug screen	X	X	
Pregnancy test (female subjects)	X	X	X
Drug administration ²		X	
Blood sample collection for pharmacokinetic analysis ³		X	
Adverse events ⁴		X	X

¹ BP and pulse measured at approximately 2, 4, 24, and 36 hours after each drug administration

²The mouths of subjects will be inspected to ensure that the capsules are swallowed intact

³ Blood samples collected out to 48 hours after drug administration

⁴ Subjects are instructed to tell personnel of any adverse events that occur

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Each dose was administered with 240 mL of water. Identical standard meals were served at approximately 4 and 10 hours after drug administration and at appropriate times thereafter during the in-house confinement. Subjects were confined to the clinical research site the evening prior to dose administration until approximately 36 hours postdose. Vital signs (pulse, blood pressure, respiratory rate and temperature) were measured at screening, prior to and after each dose administration, and at discharge. Blood pressure and pulse rate were evaluated at approximately 2, 4, 24 and 36 hours after each dose for each study period. Adverse events were monitored and documented from confinement until study discharge, and were followed to resolution. Blood samples were collected prior to and at several time points after drug administration to measure PK parameters. The total blood volume collected did not exceed 264 ml including lab screening and study discharge lab exams.

Twenty-three of the 24 subjects completed the study. One subject was dropped from the study due to non-compliance, i.e., positive urine drug screen at Period 2 check-in. Bioavailability of the two formulations of cetirizine was essentially equivalent under fasting conditions. The PK parameters derived from the cetirizine plasma concentrations versus time profiles and the comparative bioavailability data are presented in Table 3. The 90% confidence interval of the relative geometric mean of the test (cetirizine 10 mg capsule) to the reference (Zyrtec® 10 mg

tablets) formulation for C_{max} , AUC_{0-t} and AUC_{∞} were within FDA's requirements for bioequivalence limits of 80-125%.

There were a total of nine adverse events reported by six subjects over the course of the study which were all considered mild in severity; no serious adverse events were reported. Study exit clinical laboratory, ECG, and physical examination evaluations were completed with no significant clinical findings. Adverse events reported in this study will be discussed in Section 7 of this review.

Study 20-220-SA (Food Effect)

This was an open-label, single-dose, 2-treatment, 2-period, randomized, crossover study that compared cetirizine 10 mg softgel capsule (BPI) and Zyrtec® (Pfizer/McNeil) tablets under fed conditions in 24 healthy adult male and female subjects. See Table A-2 in the Appendix section for demographic profile of subjects. Subjects were scheduled to receive a single-dose of each two treatment in two assigned dosing periods. Each dose administration was separated by a 7-day washout period.

Subjects fasted overnight for at least 10 hours the evening prior to dosing and then consumed a high-fat, high-calorie standard breakfast just prior to receiving either:

- Treatment A (Test): Cetirizine 10 mg softgel capsule
- Treatment B (Reference): Zyrtec® 10 mg tablet

The schedule of procedures was similar to that of the fasting study (20-220-SA) except that patients were fed with a standard high fat meal before each drug administration in this study. Each dose was administered with 240 mL of water. Identical standard meals were served at approximately 4 and 10 hours after drug administration and at appropriate times thereafter during the in-house confinement for each study period. Vital signs (pulse, blood pressure, respiratory rate and temperature) were measured at screening, prior to and after each dose administration, and at discharge. Blood pressure and pulse rate were evaluated at approximately 2, 4, 24 and 36 hours after each dose for each study period. Adverse events were monitored and documented from confinement until study discharge, and were followed to resolution. Blood samples were collected prior to and at several time points after drug administration to measure PK parameters.

All 24 subjects enrolled completed the study. Bioavailability of the two formulations of cetirizine was essentially equivalent under fed conditions. The PK parameters derived from the cetirizine plasma concentrations versus time profiles and the comparative bioavailability data are presented in Table 3. The 90% confidence interval of the relative geometric mean of the Test (cetirizine 10 mg softgel capsule) to the reference (Zyrtec® 10 mg tablets) formulation for C_{max} , AUC_{0-t} and AUC_{∞} were within FDA's requirements for bioequivalence limits of 80-125%.

There were a total of eight adverse events reported by six subjects over the course of the study which were all considered mild to moderate in severity; no serious adverse events were reported. Study exit clinical laboratory, ECG, and physical examination evaluations were completed with

no significant clinical findings. Adverse events reported in this study will be discussed in Section 7 of this review.

**Table 3: Statistical Summary of the Comparative Bioavailability Data
 (Studies 20-219-SA and 20-220-SA)**

Drug: Cetirizine Dose (1 x 10 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study (20-219-SA)				
Parameter	Test	Reference	Ratio	90% C.I.
AUC _{0-t}	2631.9062	2585.3569	101.80	96.06 107.89
AUC _∞	2681.7712	2635.7309	101.75	96.05 107.78
C _{max}	347.7594	339.9893	102.29	95.81 109.20
Fed Bioequivalence Study (20-220-SA)				
Parameter	Test	Reference	Ratio	90% C.I.
AUC _{0-t}	2655.9442	2678.1237	99.17	96.28 102.15
AUC _∞	2713.6279	2733.6557	99.27	96.37 102.25
C _{max}	279.7276	276.0859	101.32	92.90 110.50
Comparison Report DCN 1002614 (20-219-SA/20-220-SA)				
Parameter	Test	Reference	Ratio	90% C.I.
AUC _{0-t}	2655.9442	2624.6599	101.19	89.15 114.86
AUC _∞	2713.6279	2674.3707	101.47	89.41 115.16
C _{max}	279.7276	346.9882	80.62	71.93 90.35

Test: cetirizine softgel capsule 10 mg Reference: Zyrtec tablet 10 mg
 From Sponsor's submission, Module 2, Table 3

See Clinical Pharmacology review for detailed analysis of the PK studies.

5.2 Pharmacodynamics

There are no new pharmacodynamic data submitted with this NDA.

5.3 Exposure-Response Relationships

There is no new exposure-response relationship information submitted with this NDA.

6 INTEGRATED REVIEW OF EFFICACY

There were no new efficacy trials conducted for this application, the sponsor relies on the Agency's efficacy findings for cetirizine. Efficacy of this product is extrapolated based on PK data from the single dose bioavailability studies 20-219-SA and 20-220-SA assessing the proposed cetirizine capsules and currently marketed Zyrtec®, 10 mg tablets, conducted by the sponsor. The adequacy of the relative bioavailability studies will be reviewed by the Office of

Clinical Pharmacology (OCP), and the efficacy will be addressed by the Division of Pulmonary and Allergy Products.

7 INTEGRATED REVIEW OF SAFETY

The safety of cetirizine HCl for OTC use for the indication of relief of allergic rhinitis symptoms and hives relief has been reviewed in detail at the time of the Rx-to-OTC switch of the different cetirizine (Zyrtec®) formulations approved on November 16, 2007.

Safety data reviewed for this NDA include safety information from the reference listed drug Zyrtec® tablets (NDA 19-835) and safety data from the sponsor's fasting and fed bioavailability studies (20-219-SA and 20-220-SA). In addition, the sponsor provided an integrated review of safety that included safety information from postmarketing databases (listed below). The clinical data utilized in the review of cetirizine safety include information from the following:

- A report summarizing adverse event reporting to the FDA Adverse Event Reporting System (AERS) (June 1, 2007 to July 31, 2008)
- American Association of Poison Control Centers' (AAPCC) National Poison Data System (NPDS) database (June 1, 2007 to July 31, 2008)
- A report of the Drug Abuse Warning Reports (DAWN) (June 6, 2007 to July 31, 2008)
- A report summarizing adverse event reporting to the World Health Organization's (WHO) International Drug Monitoring Program (June 1, 2007 to July 31, 2008)
- A review of medical literature (June 1, 2007 to July 31, 2008)
- Prescription and OTC labels for cetirizine in the United States
- Proposed cetirizine 5 and 10 mg OTC labels

7.1 Methods and Findings

All of the subjects in the two PK studies (20-219-SA and 20-220-SA) conducted by the sponsor were healthy adults. Neither trial was conducted specifically to assess safety issues with the sponsor's cetirizine product; however, safety data from these studies were evaluated. In both trials, safety assessments consisted of monitoring of adverse events, ECG, physical examination, clinical laboratory parameters (including hematology, blood chemistry and urinalysis) and urine drug screen. For female volunteers, pregnancy tests were also performed at screening, each study period and discharge. The total volume of blood collected per subject (238 mL from a total of 34 blood draws) is considered to be acceptable.

Safety analysis included those who entered the study and received at least one dose of each treatment. There were 24 subjects enrolled in each PK study (total of 48) and who received at least one dose of cetirizine.

7.1.1 Deaths

There were no deaths in the two bioavailability studies conducted by the sponsor.

7.1.2 Other Serious Adverse Events

There were no serious adverse events reported in the two bioavailability studies conducted.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

One subject (#201) from Study 20-219-SA was dropped from the study due to non-compliance, i.e., positive urine drug screen at Period 2 check-in (test product).

7.1.3.2 Adverse events associated with dropouts

There were no subjects who dropped out due to an adverse event.

7.1.3.3 Other significant adverse events

There were no other significant adverse events reported.

7.1.4 Other Search Strategies

This section is not applicable.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Subjects were monitored for any adverse events (AEs) from the beginning of confinement until study discharge.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

AEs were described in terms of severity, seriousness and relationship to treatment. The sponsor stated that it did not use any dictionary to code the AEs; the clinical investigator assigned a diagnosis after reviewing the AE source information during the clinical trial. The adverse event categorization and preferred terms used in the study is acceptable for the PK studies conducted that involved a small number of subjects (N=24 for each study).

7.1.5.3 Incidence of common adverse events

Historically, the most commonly reported adverse events from clinical efficacy trials conducted with cetirizine in patients aged 12 years and older are the following:⁴

⁴ Cetirizine (Zyrtec) prescription label, Table 1 (www.PDR.net accessed on 12-31-08).

- somnolence
- fatigue
- dry mouth
- pharyngitis
- dizziness

Somnolence, fatigue and dry mouth are treatment-related adverse reactions. In clinical efficacy studies, the incidence of somnolence associated with cetirizine use was dose related; 6% in placebo, 11% at 5 mg and 14% at 10 mg.

In children 6 to 11 years of age, the most commonly reported adverse events from cetirizine (5 or 10 mg dose) placebo-controlled trials conducted in the U.S. which occurred at a frequency of $\geq 2\%$ were the following:

- | | |
|------------------|----------------|
| • headache | • pharyngitis |
| • abdominal pain | • coughing |
| • somnolence | • diarrhea |
| • epistaxis | • bronchospasm |
| • nausea | • vomiting |

Of the above adverse events, abdominal pain was considered treatment-related and somnolence appeared to be dose-related, 1.3% in placebo, 1.9% at 5 mg and 4.2% at 10 mg. The above list can be found in the prescription label for cetirizine.

In the combined PK studies conducted for this application, the most common adverse events experienced for both treatments were headache (6/48; 12.5%), somnolence (2/48; 4%) and nausea (2/48; 4%). In study 20-219-SA, the most common AE reported was headache 4/24 (17%) subjects: 3/23 (13%) from BPIs cetirizine capsule and 1/24, (4%) from Zyrtec® tablet. See Table 4 below. In study 20-220-SA, the most common AEs for both treatments were headache (2/24; 8%) and somnolence (2/24; 8%), each AE experienced by one subject from each treatment group. See Table 5 below.

7.1.5.4 Common adverse event tables

Tables 4 and 5 list the number and percentage of subjects with adverse events by treatment group from the two PK studies.

Table 4: Incidence of Adverse events in Fasting Study 20-219-SA

Parameter	Treatment	
	A (Banner cetirizine softgel capsule)	B (Zyrtec®) tablet
No. of subjects exposed	23	24
No. of subjects reporting at least 1 AE	3	3
Total no. of withdrawals	1	0
Total no. of AEs reported	3	6
AEs at least possibly drug related	2	6
Adverse Event	No. of subjects reporting AEs	No. of subjects reporting AEs
Headache	3 (13%)	1 (4%)
Abdominal wall pain	0	1 (4%)
Abnormal taste	0	1 (4%)
Dizziness	0	1 (4%)
Flushing	0	1 (4%)
Nausea	0	1 (4%)

Sponsor's table ISS

In study 220-219-SA, all reported AEs were considered, at least possibly related to drug administration except for an episode of headache reported by a subject after treatment A. See Tables A-3 and A-4 in the Appendix section for a detailed listing of AEs.

Table 5: Incidence of Adverse events in Fed Study 20-220-SA

Parameter	Treatment	
	A (cetirizine softgel capsule)	(Zyrtec®) tablet
No. of subjects exposed	24	24
No. of subjects reporting at least 1 AE	3	3
Total no. of withdrawals	0	0
Total no. of AEs reported	5	3
AEs at least possibly drug related	2	4
Adverse Event	No. of subjects reporting AEs	No. of subjects reporting AEs
Headache	1 (4%)	1 (4%)
Somnolence	1 (4%)	1 (4%)
Broken tooth	0	1 (4%)
Left arm pain with venipuncture	1 (4%)	0
Nausea	1 (4%)	0
Polyuria	1 (4%)	0

Sponsor's table ISS

In study 20-220-SA, somnolence, polyuria and headache (after treatment B) were all considered at least possibly related to cetirizine; while broken tooth, left arm pain, nausea and headache (after treatment A) were either unlikely or not related to drug administration. See Tables A-5 and A-6 in the Appendix section for a detailed listing of AEs.

7.1.5.5 Identifying common and drug-related adverse events

The common AEs considered possibly related to treatment for both studies were headache and somnolence; these AEs have been reported during clinical trials with cetirizine use.

7.1.5.6 Additional analyses and explorations

There were no additional analyses and explorations performed by the sponsor.

7.1.6 Less Common Adverse Events

There were no significant less common AEs in the bioavailability studies conducted.

In clinical efficacy trials conducted using cetirizine, there were AEs observed infrequently (<2%) in almost 4,000 adults and children 12 years and older, or in 659 pediatric patients aged 6 to 11 years in U.S. trials. This list can be found in the prescribing information for cetirizine; causality with the use of cetirizine has not been established.

7.1.7 Laboratory Findings

Clinical laboratory tests (chemistry, hematology and urinalysis) were performed at screening and at the end of the study. Serology tests (Hepatitis B, Hepatitis C and HIV) were performed on all subjects at screening. Urine drug screens were done at screening and at check-in for each study period. Urine pregnancy tests were done at screening, check-in for each study period and at discharge. There were no subjects who had treatment-emergent clinically significant changes for any laboratory test found.

It is stated in the prescription label for cetirizine that during clinical efficacy trials, occasional instances of transient, reversible hepatic transaminase elevations have occurred. Hepatitis with significant transaminase elevation and elevated bilirubin in association with the use of cetirizine has been reported.

7.1.8 Vital Signs

Vital signs (pulse, blood pressure, respiratory rate and temperature) were measured at screening, prior to and after each dose administration, and at discharge. Blood pressure and pulse rate were additionally evaluated at approximately 2, 4, 24 and 36 hours after each dose for each study period. Physical examination was performed at screening and at discharge. No clinically significant abnormalities were noted during vital signs measurement and on physical examination.

7.1.9 Electrocardiograms (ECGs)

ECGs were performed during screening and at discharge. The sponsor stated that no clinically significant abnormalities were noted for safety parameters (including ECG) during the study conduct.

7.1.10 Immunogenicity

There was no immunogenic evaluation conducted in this submission; no known immunogenicity issues are related to cetirizine.

7.1.11 Human Carcinogenicity

No new animal or toxicology studies were submitted with this NDA. References have been made to its toxicological profile of the reference drug, Zyrtec® tablets (NDA 19-835). There are no known human carcinogenicity issues related to cetirizine.

7.1.12 Special Safety Studies

There was no special safety studies conducted for this application.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no sufficient information to indicate that abuse or dependency occurs with cetirizine.

The abuse potential for cetirizine has been evaluated during the Rx-to-OTC switch of cetirizine under NDA 19-835/S-022. To evaluate drug abuse or dependency with cetirizine in this application, the sponsor searched the Drug Abuse Warning Network (DAWN) database from June 6, 2007 to July 31, 2008. There were 301 cases (30% males and 70% females) involving the active ingredient cetirizine HCl and the product Zyrtec® in this database. The report types for these cases were: adverse reactions 65% (197), accidental exposure 9% (28), overmedication 13% (40), suicide attempt 9% (26), and other 3% (10). No cases were reported in the categories of malicious poisoning or seeking detox. There were no deaths during the reporting period.

The distribution of cases by age was: 16% in children <6y/o, 1% in children 6 to <12 y/o, 10% in adolescents aged 12 to 17 y/o, 64% in adults 18 to 64 y/o and 12% in geriatrics patients ≥ 65 y/o. In children <6y/o, accidental ingestion was higher than for any other age group while suicide attempt was most common in patients 12 to 20 y/o. No clustering of any individual report type is noted in any adult age category. Overall, majority (71%, 214) of the cases were discharged home.

Medical Officer Comments: The DAWN data do not reveal any signal that cetirizine is being abused or misused.

7.1.14 Human Reproduction and Pregnancy Data

The following information on pregnancy and nursing mothers are reflected in the prescribing information for cetirizine:

Cetirizine is currently classified as Pregnancy Category B. There are no adequate and well-controlled studies in pregnant women. In preclinical studies involving a fertility and general reproductive performance study in mice, cetirizine did not impair fertility at an oral dose of 64 mg/kg (approximately 25x the maximum recommended daily oral dose in adults on a mg/m² basis). In mice, rats, and rabbits, cetirizine was not teratogenic at oral doses up to 96, 225 and 135 mg/kg, respectively (approximately 40, 180 and 220x the maximum recommended daily oral dose in adults on a mg/m² basis). Because animal reproduction studies are not always predictive of human response, cetirizine should be used during pregnancy only if clearly needed.

In mice, cetirizine caused retarded pup weight gain during lactation at an oral dose in dams of 96 mg/kg (approximately 40 times the maximum recommended daily oral dose in adults on a mg/m² basis). Studies in beagle dogs indicated that approximately 3% of the dose was excreted in milk. Cetirizine has been reported to be excreted in human breast milk. Because many drugs are excreted in human milk, use of cetirizine in nursing mothers is not recommended.

There were no reported pregnancy or deaths related to drug exposure during pregnancy in the PK studies conducted by the sponsor.

Deaths related to drug exposure during pregnancy (AERS)

The following are reports from AERS on deaths involving pregnancy.

There were 6 cases of spontaneous abortions, one case of induced abortion, and one case of unknown etiology.

- Case # 6355578 was a drug exposure during pregnancy in a 28 y/o female who took cetirizine 5 mg for one day. The timing of the exposure and the abortion were not reported. Co-suspect medication included clemastine fumarate.
- Cases # 6437370, 6441528, and 657113 were drug exposures during pregnancy, the reported age of the patient in all cases was 39 years. The onset date of exposure (October 6, 2003) during pregnancy was the same in two of the cases. Cosuspect medications were topiramate and paroxetine HCl. The dose of cetirizine, the timing of exposure during pregnancy and the abortion were not provided. As two of these cases have the same age of patient, concomitant medications, and date of onset, it is suspected two or more may involve the same patient.
- Case # 6563343 was involving a 29 y/o female. The dose of cetirizine and the timing of exposure during pregnancy were not provided. Cosuspect medications included fluticasone propionate, ibuprofen hydrochloride, cimetidine, and methylprednisolone.

Clinical Review

Lolita A. Lopez, M.D.

NDA 22-429

Cetirizine HCl Soft Gelatin Capsules, 5 & 10 mg

- Case # 6563327 was a case of induced abortion involving a 31 y/o female. The dose of cetirizine and the timing of exposure during pregnancy were not provided. Cosuspect medications included fluticasone propionate.
- Case # 6470247 a case of unintended pregnancy and spontaneous abortion in a patient of unknown age. The dose of cetirizine and the timing of exposure during pregnancy were not provided.
- Case # 6511742 was a case of drug exposure during pregnancy and abortion in a patient of unknown age. The dose of cetirizine was 10 mg and the timing of exposure during pregnancy was not provided.

Medical Officer Comments: It should be noted that in all of the reported cases related to drug exposure during pregnancy, there was insufficient information provided. In all of the cases, the duration of exposure is unknown, and in 6 of the 8 cases, the patient was taking concomitant medications. The information provided does not preclude the OTC use of cetirizine nor warrant any changes in the current label. The proposed OTC label appropriately directs pregnant women to consult a health professional before using cetirizine. The label also states that the product is not recommended in breastfeeding mothers.

7.1.15 Assessment of Effect on Growth

No information was submitted regarding the effect of cetirizine on growth. The proposed OTC cetirizine capsules will not be indicated in children <6 years old. There is a cetirizine syrup marketed and is indicated for children as young as 6 months old under the supervision of a physician or healthcare provider.

7.1.16 Overdose Experience

There have been reports of overdosage reported with cetirizine. Somnolence was displayed by an adult patient who took 150 mg of cetirizine, no other clinical signs or abnormal blood chemistry or hematology results were reported. In an 18 month old who had an overdose of cetirizine (approximately 180 mg), restlessness and irritability were observed initially; this was followed by drowsiness. There is no known specific antidote for this drug and it is not effectively removed by dialysis.⁵

In the WHO Vigibase database (June 2007 to July 2008), there were 10 reports of cetirizine overdose; these included accidental overdoses, intentional overdoses, and suicide attempts. Nausea, dizziness, and somnolence were reported in patients after taking cetirizine doses ranging from 30 to 60 mg. A 33 y/o who ingested multiple substances including cetirizine experienced coma. The maximum reported overdose was in a patient who took 300 mg cetirizine with alcohol. In both of these cases, no further information was provided. *(Medical Officer Comments: It is also not clear from the reports if the patient who was in coma was the same patient who took 300 mg of cetirizine).* There was very limited information provided in all of the cases reported; the cases do not add to the understanding of the effects of cetirizine overdose.

⁵ This information is reflected in the prescription label for cetirizine.

Adverse Events from the National Poison Data System (NPDS) from the AAPCC

The NPDS is the data system into which all reports received by poison control centers across the United States are entered. (For a list of scenarios included in the NPDS data, see the Appendix section of this review.) The sponsor performed a search of the NPDS through the American Association of Poison Control Centers (AAPCC) for single-ingredient cetirizine exposures from June 1, 2007 to July 31, 2008.

There were 253 cases involving exposure to cetirizine HCl in this database. Of these cases, 60% (151) were children 0 to 12 y/o, 8% (23) were adolescents 13 to 18 y/o, 22% (55) were adults 19 to 64 y/o, 5% (12) were geriatric patients \geq 65 y/o and 4% (10) had no age data. Demographic information was not provided in 3 cases. Of the 253 cases, 49 cases had identifiable specific clinical effect (CE); 88 clinical effects were reported in these 49 cases. NPDS reported 253 human exposures involving cetirizine; of these, 49 cases had (a total of 88) identifiable specific clinical effects (CEs). The most frequently reported CEs were: drowsiness/lethargy (24, 27%); tachycardia (7, 8%); agitated/irritable (6, 7%); dizziness/vertigo (4, 5%); ataxia (3, 3%); dyspnea (3, 3%); hallucinations/delusions (3, 3%); vomiting (3, 3%); and abdominal pain (2, 2%).

There were 156 cases in this database involving overdose ranging from 10 mg to 560 mg of cetirizine. In the pediatric population, overdose (accidental) was most frequent among children < 5 y/o with doses ranging from 10 mg to 110 mg; most cases resulted in minor or no clinical effect. In patients aged 6 to 18 years, overdose ranged between 10 mg to 200 mg, and in adults (>19 y/o), overdose ranged from 100 mg to 560 mg; the effects reported were mostly minor or no clinical effect.

There was one case reporting a major effect in a 45 y/o male who acutely ingested unknown quantities of cetirizine, a selective serotonin reuptake inhibitor (SSRI), propoxyphene, an angiotensin-converting enzyme (ACE) inhibitor, a beta blocker, biguanide, and a histamine-2 receptor antagonist suicide attempt. Reported events for this case included bradycardia, drowsiness, lethargy, and hypotension.

There was one report of death. This was an adult who acutely ingested an unknown quantity of cetirizine and an antidepressant in an intentional suicide attempt which resulted in cardiac arrest leading to death. Critical information needed to review the case such as past medical history, dose, dose formulation, and duration of use was lacking to permit a complete analysis of the case.

Most (95%) of the cases involving exposure to cetirizine had either no effect or minor effects. Of the cases which resulted in moderate effect, most had signs or symptoms that were considered to be nonserious, and that are consistent with the known safety profile of cetirizine.

Medical Officer Comments: It appears from the AAPCC data provided that cetirizine does not represent a significant toxicologic risk.

7.1.17 Postmarketing Experience

Cetirizine has been marketed with a well-characterized safety profile in the United States since its approval for prescription use in 1995. An extensive safety database exists for cetirizine postmarketing experience. The safety of cetirizine from postmarketing experience has been evaluated in detail on November 16, 2007 in a Rx-to-OTC switch of cetirizine (Zyrtec®) formulations for the relief of allergic rhinitis symptoms and hives relief.

The following reports based on post-marketing experience with cetirizine were provided in this submission: FDA AERS databases, WHO Database, AAPCC NPDS database (discussed in section 7.1.16), Drug Warning (DAWN) database (discussed in section 7.1.13), and a review of the medical literature relevant to the safety of cetirizine. It should be noted that the sponsor submitted version 1 (October 29, 2008) and version 2 (March 25, 2009) of postmarketing safety information. The review of medical literature will be discussed in section 8.6.

Summary of Safety Data Derived from the FDA's AERS Database

A search of the FDA AERS database from June 1, 2007, and July 31, 2008 was conducted for cases in which cetirizine HCl 5 mg or 10 mg was a primary or secondary suspect medication; the most recent data available were for the quarter ending March 31, 2008. There were a total of 233 cases reported, 192 (82%) were serious cases (at least one event in each of these cases is a serious adverse event) and 22 (9%) were reports of death. Events in the AERS database were coded using the MedDRA coding dictionary, and data included here are coded at the preferred term (PT) level. Of the 233 cases, 34% (80) were in males, 58% (136) were in females, and gender was unknown in 7% (17). The age distribution of the patients in these cases included 16% (39) pediatric/adolescent patients aged 0 to 18 years, 40% (93) adult patients aged 19 to 64 years, 6% (14) elderly patients aged ≥ 65 years, and age was unknown for 37% (87) patients.

A total of 902 adverse events were reported for the 233 cases. Overall, the most frequently reported adverse events were: convulsion (24, 2.7%); hypersensitivity (14, 1.6%); somnolence (12, 1.3%); depression (11, 1.2%); drug ineffective (11, 1.2%); pruritus (11, 1.2%); abnormal behavior (10, 1.1%); feeling abnormal (10, 1.1%), dizziness (9, 1%), and fatigue (9, 1%). Drug exposure during pregnancy (12, 1.3%) is also among the most frequent events across all cases (these cases were discussed in section 7.1.14). The following psychiatric events were reported at a much higher frequency in pediatric/adolescent patients aged 0 to 18 years compared to adults: abnormal behavior (5 vs. 1), aggression (5 vs. 0), anger (4 vs. 0), crying (3 vs. 0), and oppositional defiant disorder (2 vs. 0). No unusual pattern of events or frequency of events was noted in patients reported to be in the geriatric age group (aged 65 years or older).

Medical Officer Comments: It was noted in this database that behavioral/psychiatric events were more commonly reported in children than adults. However, the number of cases for each event reported is too few and the clinical information provided was limited to draw a conclusion regarding these events. In addition, most of the behavioral events are generally known to occur more commonly in children than in adults. The following psychiatric events have been reported with the use of cetirizine in adults and/or children: abnormal thinking, agitation, amnesia,

anxiety, decreased libido, depersonalization, depression, emotional lability, euphoria, impaired concentration, insomnia, nervousness, paroniria, sleep disorder.

In addition to evaluating adverse events by preferred terms, it is always ideal to group and analyze AEs by system organ class; this was not done by the sponsor. However, since there were only a few number of cases reported, and there were no new safety issues identified from the reports, the method of reporting is acceptable. Also, various postmarketing safety databases were evaluated in detail for the Rx-to-OTC switch of cetirizine in November 2007 in which no new safety issues were identified.

Serious (Nonfatal) Adverse Events (AERS)

Of the 233 cases reported for cetirizine, 192 cases involving 402 unique AE preferred terms were classified as serious (at least one event in each of these cases is a serious adverse event [SAE]). Of the 192 serious cases, 18% (34) were patients aged 0 to 18 years, 36% (70) were adults aged 19 to 64 years, 7% (14) geriatric patients aged ≥ 65 years, and 39% (74) had unknown age. The most frequently reported adverse event term was convulsion (21); it was noted that a number of these cases involved patients of the same age and with the same concomitant medications that are likely to represent, in some cases, the same patient or case. Other AEs most frequently reported ($\geq 2\%$) include hypersensitivity (13); somnolence (12); depression (9); drug ineffective (9) pruritus (11); abnormal behavior (10); feeling abnormal (9); fatigue (9) and dizziness (8). Convulsions, somnolence, depression, pruritus, dizziness, fatigue and feeling abnormal have been reported with the use of cetirizine.⁶ Table A-7 in the Appendix section is a list of all nonfatal serious adverse events associated with cetirizine use. (*Medical Officer Comments: The sponsor did not provide the total number of SAEs (denominator) for the cases classified as serious. Therefore, the proportion of cases (in percentage) cannot be determined with the information provided.*)

To assess the relative reporting rates for cetirizine prescription product compared with OTC product, the receipt date, the date of onset, and/or the date(s) of therapy were reviewed. For cases received on or after January 24, 2008, the launch date for OTC Zyrtec®, an assumption was made that OTC product was used. Exceptions included cases where the date of onset was provided and preceded the Zyrtec® launch date, and/or the dates of therapy were provided and therapy stopped prior to the Zyrtec® launch date. This surrogate for product type is an approximation because prescription product will have still been in the hands of consumers for some time after OTC launch. Using this estimate, 18% (38/211) of serious cases were judged to involve cetirizine OTC product, and 82% (173/211) of cases were judged to involve cetirizine prescription product. Based on the search dates of June 1, 2007, through July 31, 2008, the reporting rates for prescription product compared with OTC product are considered to be similar.

Medical Officer Comments: It appears that only 2¼ months of cetirizine OTC marketing was captured for the reports involving the OTC product since its launch date on January 24, 2008 and the most recent data available were for the quarter ending March 31, 2008. It should be

⁶ Cetirizine prescription label.

noted that the majority (82%) of the cases reported for cetirizine overall were serious cases. This probably because most cases reported in the AERS system are those involving a serious AE. Therefore, it is not surprising that the types and the rates of adverse events for serious cases is very similar (if not the same) as the overall cetirizine cases.

Deaths from AERS Data

Among the 233 cases involving exposure to cetirizine from June 1, 2007 to March 31, 2008, 22 (9%) had a fatal outcome. Fatal outcomes were reported in 16 adult cases, 1 pediatric case, and 5 cases with patients of unknown age; no deaths were reported in geriatric patients ≥ 65 y/o. There were a total of 42 AEs (with 17 unique preferred terms) reported among the 22 fatal cases. The following is an adverse event listing for cetirizine fatal cases.

• Abortion spontaneous	6	• Abortion	1
• Death	6	• Abortion induced	1
• Drug exposure during pregnancy	6	• Drug toxicity	1
• Accidental exposure	4	• Electrocardiogram QT prolonged	1
• Convulsion	3	• Laryngeal edema	1
• Fall	3	• Laryngitis	1
• Overdose	3	• Respiratory failure	1
• Poisoning	2	• Unintended pregnancy	1
• Dyspnea	1		

Of the 22 cases of death, 8 were fetal deaths or cases involving pregnancy (discussed in section 7.1.14). The other 14 cases of death are summarized below:

- 1 case of electrocardiogram QT prolongation and death in an 8 y/o child (gender not provided). Cosuspect medications, dosing information, and time to onset were not provided.
- 3 cases with a fatal outcome of convulsion, fall, and overdose. Two of the cases were aged 23 years, and one had an unknown age. Cosuspect medication included nefopam and venlafaxine hydrochloride and co-codamol. It is suspected that two or more of these 3 reports may involve the same patient as these include the same events, concomitant medications, and same patient age in two cases.
- 7 cases with a fatal outcome in which the reported age for all patients was 62 years: 4 cases reported accidental exposure, of which, 2 reported poisoning and 1 reported drug toxicity; and 3 cases reported death as an event. All cases reported alprazolam, venlafaxine hydrochloride, and bupropion hydrochloride as co-suspect medications; 2 cases reported diazepam as an additional co-suspect medication. The maximum cetirizine dose ingested in these cases is unknown. The onset date of January 1, 2006, was provided for three cases. As these cases are similar, two or more of the cases may involve the same patient.
- 1 case of dyspnea, laryngeal edema, laryngitis, and respiratory failure with a fatal outcome in a 33 y/o patient. Concomitant medications, time to onset, and cetirizine dose were not provided.

- 2 cases reported as death had unknown age. No cetirizine dose information was provided; in one of the cases, cosuspect medications included Celebrex® and Glucotrol®.

Medical Officer Comments: It is to be noted causality cannot be determined in most of the death cases reported due to lack of more specific clinical information to properly evaluate an event. Limited details are known with respect to times to onset, extent of exposure, and clinical information. These reported deaths cannot be attributed to the use of cetirizine alone because of confounding factors such as concomitant use of other medications and/or underlying medical condition(s). In addition, reports regarding the same case may sometimes be received from several different sources at different times as seen in some of the reported cases.

The FDA/SRS database did not reveal any new serious, unusual or significant safety concerns associated with the use of cetirizine for a particular organ system or age group at the current recommended dose. In general, the types of adverse events from this database, such as drug ineffective, somnolence, pruritus, fatigue, dizziness and drug interaction, are similar to those previously reported with the use of cetirizine both during clinical trials and from postmarketing experience.

Summary of Safety Data Derived from the WHO's Vigibase Drug Safety Database

A search of the World Health Organization's (WHO) International Drug Monitoring Program Vigibase database was searched for all reactions reported from any country for the active moiety cetirizine between June 1, 2007 and July 31, 2008. There were 274 cases in which cetirizine HCl 5 mg or 10 mg was the primary or secondary suspect medication; 35% were males, 60% were females and 5% had unknown gender. The age distribution of the patients in these cases included 15% pediatric patients aged 0 to 18 years, 37% adults aged 19 to 64 years, 10% patients aged ≥ 65 years 38% unknown age. A total of 854 AEs were reported involving cetirizine; of these, 176 were unique preferred terms reported for cetirizine; the dose of cetirizine was unknown in the majority of cases. The most common AEs reported were: dizziness (24, 2.8%); drug ineffective (24, 2.8%), somnolence (22, 2.6%), drug dispensing error (21, 2.4%) medication error (21, 2.4%), fatigue (17, 1.9%), urticaria (15, 1.7%), convulsion (14, 1.6%), pruritus (14, 1.6%), and wrong drug administered (14, 1.6%).

Serious Adverse Events (WHO)

There were 217 serious cases (nonfatal) reported for cetirizine; 15% were pediatric patients aged 0 to 18 years, 36% were adults aged 19 to 65 years, 12% were adults aged ≥ 65 years, and age is unknown in 37% of the cases. A total of 475 AEs were reported for these serious cases. The most frequently reported AEs for these cases were: drug ineffective (4%, 20); dizziness (4%, 20); somnolence (3.7%, 18); urticaria (3%, 14); convulsion (2.7%; 13), pruritus (2.7%; 13), fatigue (2.5%, 12); asthma (2.5%, 12); pain (2.3%,11); fall (2.3%,11); anxiety (2.3%,11); and insomnia (2.3%,11). These AEs have been reported with the use of cetirizine.

Deaths (WHO)

Among the 274 cases involving exposure to cetirizine, 12 were death cases involving 37 AEs. Of these deaths, 6 involved fetal deaths wherein the extent of exposure to cetirizine was unknown; 1 case was reported as induced abortion and 5 cases were unspecified (3 of these had cosuspect medications reported). Important clinical information including prior reproductive history, presence or absence of congenital anomalies, timing and extent of exposure to cetirizine and other medications, and presence of other comorbid illnesses were not available to assess the fetal deaths. The following is a brief description provided for the 6 non-fetal death cases:

- 1 case of bullous dermatitis and pemphigoid was reported in an 83 y/o male. Cosuspect medication included Deroxat® (paroxetine).
- 1 case of coagulopathy, sick sinus syndrome, bradycardia, hyperkalemia, decreased blood pressure, gastritis, and pruritus in a 73 y/o male with a history of dementia of the Alzheimer's type. Treatment for the events consisted of hemodialysis. Cosuspect medications were famotidine and donepezil hydrochloride.
- 1 case of drug hypersensitivity, coma, convulsion, and pain in a 14 y/o male. Cosuspect medications for this event included diphenhydramine HCl and prednisone.
- 1 case of sudden infant death syndrome in a 6 months old infant. Cosuspect medications were not provided.
- 1 case of anaphylactic reaction in a male of unknown age. History included a documented hypersensitivity to the administered drug.
- 1 case of malignant neoplasm in a female of unknown age. Dates of cetirizine therapy, dose, cosuspect medications, and the patient's age were not reported.

Medical Officer Comments: The types of adverse events from the WHO database: dizziness, somnolence, fatigue, convulsion, insomnia, pruritus, pain and urticaria are similar to those previously reported adverse events with the use of cetirizine either during clinical trials or postmarketing. This database did not reveal any new clear safety signal with the use of cetirizine.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

In the bioavailability studies (20-219-SA and 20-220-SA) conducted by the sponsor in this application, a total of 48 subjects were exposed to cetirizine 10 mg formulations, the proposed softgel capsule and Zyrtec® tablet. In study 20-219-SA, 23 subjects received cetirizine softgel capsule and 24 received Zyrtec tablets; in study 20-220-SA, all 24 subjects received both capsule and tablet formulations.

For the marketing of prescription cetirizine (Zyrtec®), a total of 25 clinical trials (15 controlled/pivotal and 10 uncontrolled/supportive) were conducted in the United States and Canada. These trials included more than 6,000 patients aged 12 years and older; more than 3,900 patients

received cetirizine at doses of 5 to 20 mg per day. The duration of treatment ranged from 1 week to 6 months, with a mean exposure of 30 days. These trials also included more than 1,300 pediatric patients aged 6 to 11 y/o in which more than 900 patients were treated with cetirizine at doses of 1.25 to 10 mg per day for a duration of 2 to 12 weeks. In addition, these included placebo-controlled trials which were conducted in 168 pediatric patients aged 2 to 5 years who received cetirizine for up to 4 weeks duration, the majority of whom received single daily doses of 5 mg.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Postmarketing safety data is discussed in section 7.1.17 and safety data from published literature is discussed in section 8.6 of this review.

7.2.3 Adequacy of Overall Clinical Experience

Cetirizine has been proven safe and effective under prescription use at a daily dose up to 10 mg in the U.S. for over 10 years and for a longer period worldwide, and for OTC use in many countries. On November 16, 2007, the Rx-to-OTC switch of cetirizine (Zyrtec®) formulations was approved, and the safety of cetirizine from postmarketing experience was evaluated in detail. Cetirizine is approved for use at a higher dose for up to 20 mg in other countries (e.g. Canada). The safety profile of cetirizine is well-characterized and clinical experience is adequate from both prescription and OTC use. Therefore, the overall clinical and postmarketing experience appears adequate for the proposed cetirizine softgel capsule formulation for OTC use.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

There were no animal studies conducted by the sponsor for this NDA application. See Pharm/Tox review.

7.2.5 Adequacy of Routine Clinical Testing

This section is not applicable.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No new information on metabolic, clearance and interaction work-up was submitted with this NDA. The sponsor relies on the reference listed drug to characterize the pharmacological profile of cetirizine. The prescription label notes that the PK of cetirizine in patients with moderate renal impairment had a 3-fold increase in half-life and a 70% decrease in clearance compared to normal volunteers. In patients with chronic liver diseases, oral dose had a 50% increase in half-life along with a corresponding 40% decrease in clearance. Dose adjustment is necessary in patients with decreased renal function and hepatic impairment. See also section 5.1 for details on the metabolism of this drug.

Medical Officer Comments: In the proposed OTC label, patients with liver or kidney disease are directed to ask a doctor before use.

The prescription label also cautions patients that concurrent use of cetirizine with alcohol or other CNS depressants should be avoided because additional reductions in alertness and additional impairment of CNS performance may occur; this is because somnolence has been reported in patients taking cetirizine. There were no other clinically significant drug interactions found with the use of cetirizine.

The proposed OTC label warns patients that when using cetirizine: drowsiness may occur; alcohol, sedatives and tranquilizers may increase drowsiness; and to avoid alcoholic drinks when using the product. In addition, the proposed label warns patients to ask a doctor or pharmacist if taking tranquilizers or sedatives.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

There are no recommendations for further studies from a clinical safety perspective.

7.2.8 Assessment of Quality and Completeness of Data

A consult to the Division of Scientific Investigation was requested and the result of their evaluation is still pending at the time this review was written.

7.2.9 Additional Submissions, Including Safety Update

A safety update was submitted on October 29, 2008 that included summary and analysis of the following: FDA AERS databases, WHO Database, AAPCC NPDS database (discussed in section 7.1.16), Drug Warning (DAWN) database (discussed in section 7.1.13), and a review of the medical literature relevant to the safety of cetirizine. The report covered the period from June 1, 2007 to July 31, 2008.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Fatigue, dry mouth, abdominal pain and somnolence (the latter is dose-related) were drug-related adverse events experienced with the use of cetirizine in both clinical trials and postmarketing. These are also known to be among the most common adverse events experienced by patients taking any antihistamines, particularly first-generation antihistamines. Cetirizine has been marketed worldwide (including the United States) for over 10 years now and has been available for OTC use in many countries (including Canada and United Kingdom); in the United States, OTC marketing of cetirizine was approved on November 16, 2007.

Headache and somnolence were most common the drug-related adverse events from the two PK studies conducted by the sponsor. It should be noted that all of the subjects these PK studies (20-219-SA and 20-220-SA) were healthy adults, and neither trial was conducted specifically to assess safety issues with the proposed cetirizine product.

The safety profile of cetirizine is well-characterized; there should be no new unexpected safety issues if the proposed capsule formulation is marketed for OTC use in the United States.

7.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

Controlled and uncontrolled clinical studies were conducted using cetirizine for prescription use in the United States and Canada. These included more than 6,000 patients 12 years and older (3,900 patients received cetirizine) and 1,468 patients aged 2 years and older (1,068 patients received cetirizine). The most commonly adverse events in adults and patients aged 12 years and older (cetirizine=2,034, Placebo=1,612) receiving cetirizine in U.S. clinical trials were somnolence 13.7%, fatigue 5.9%, dry mouth 5%, pharyngitis 2% and dizziness 1.2%. Treatment related adverse events include fatigue, dry mouth and somnolence. Somnolence was dose related; 6% in placebo, 11% at 5 mg and 14% at 10 mg. In pediatric patients, aged 6 to 11 y/o, the most common adverse events were headache, pharyngitis, abdominal pain, coughing, somnolence, diarrhea, epistaxis, bronchospasm, nausea and vomiting. Among these, treatment related adverse events were abdominal pain, and somnolence; the latter was dose-related 1.3% in placebo, 1.9% at 5 mg, 4.2% at 10 mg.

Pharyngitis and somnolence were consistently reported among the clinical studies in both adults and children. Somnolence is considered to be a treatment related AE for both populations and is dose related; 1.9% to 11% at 5 mg, and 4.2% to 14% at 10 mg. Abdominal pain was a specific treatment-related adverse event in children less than 12 years old. In the two PK studies (20-219-SA and 20-220-SA) conducted in this application, the most common adverse events experienced for both treatments were headache, somnolence, and nausea.

7.4.2 Explorations for Predictive Factors

There were no explorations for predictive factors submitted with this application.

7.4.3 Causality Determination

This section is not applicable.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The sponsor's proposed dosing and indications are similar to those of the currently approved cetirizine (Zyrtec®) tablets for OTC use except for a narrower age indication. The approved indications for cetirizine OTC are for the temporary relief of allergic rhinitis symptoms in adults and children ≥ 2 years of age, and relief of itching due to hives/urticaria in adults and children ≥ 6 years of age. In this submission, the sponsor is seeking for both approved indications of allergic rhinitis and hives relief in adults and children ≥ 6 years of age. The proposed dosing regimen is 5 or 10 mg capsule once a day depending on symptom severity.

8.2 Drug-Drug Interactions

There are no new drug-drug interactions evaluated with this submission. Patients are advised that concurrent use of cetirizine with alcohol or other central nervous system (CNS) depressants should be avoided because additional reduction in alertness and additional impairment of CNS performance may occur. The proposed OTC labels include similar warnings.

The prescription information for cetirizine states that there were no clinically significant drug interactions found with theophylline at a low dose, azithromycin, pseudoephedrine, ketoconazole, or erythromycin. In a multiple dose study of theophylline (400 mg once daily for 3 days) and cetirizine (20 mg once daily for 3 days), a 16% decrease in the clearance of cetirizine was observed. The disposition of theophylline was not altered by concomitant cetirizine administration. It is possible that higher theophylline doses could have a greater effect.

There were four published studies included in the sponsor's submissions that describe interactions between use of cetirizine and other drugs⁷ including increased anticoagulant effect of acenocoumarol⁸, decreased exposure to ritonavir⁹ and increased level of oral pilsicainide¹⁰. However, the interactions described were confounded with complications of an underlying medical illness, intake of several other drugs or the information provided was limited to make a definitive conclusion.

There are no specific drug interaction warning listed in the proposed OTC label. There is no new significant information regarding drug interaction that warrants additional warning in the proposed OTC label for this submission.

⁷ Except for the drug ritonavir (an antiviral drug), these drugs are not marketed in the U.S.

⁸ Berod T. Case Report. *Ann of Pharmacother* Jan 1997; Vol. 31.

⁹ Peytavin G, Gautran C, Otoul C, et al. Evaluation of pharmacokinetic interaction between cetirizine and ritonavir, an HIV-1 protease inhibitor, in healthy male volunteers. *Eur J Clin Pharmacol* 2005; 61: 267-273.

¹⁰ Tsuruoka S, Ioka T, Wakaumi M, et al. Clinical pharmacology Grand Rounds. *Clin Pharmacol Ther* 2006; 79:389-96.

8.3 Special Populations

There were no new studies conducted by the sponsor regarding special populations with this application. There was also no new information provided that would warrant any changes to the proposed OTC label. The following information is listed in the cetirizine prescription label.

Pregnancy

This application has no new information regarding pregnant women. Cetirizine is currently listed as Pregnancy Category B. In mice, rats, and rabbits, cetirizine was not teratogenic at oral doses up to 96, 225, and 135 mg/kg, respectively (approximately 40, 180 and 220x the maximum recommended daily oral dose in adults on a mg/m² basis). There no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, cetirizine should be used during pregnancy only if clearly needed.

One study reported in the medical literature¹¹ followed 120 women who were exposed to either hydroxyzine or cetirizine during pregnancy. Of these, 53 were exposed to hydroxyzine during organogenesis and 39 to cetirizine. There were no significant differences found between the hydroxyzine or cetirizine groups and the control groups in the pregnancy outcome: rate of live births, spontaneous or therapeutic abortion, or stillbirth. There was also no difference in the rates of major or minor anomalies, mean birth weight, mode of delivery, gestational age, or presence of neonatal distress.

The proposed OTC label directs pregnant women to ask a health professional before using the product.

Nursing Mothers

Cetirizine has been reported to be excreted in human breast milk. Because many drugs are excreted in human milk, use of cetirizine in nursing mothers is not recommended. The OTC label is consistent to the prescription label and states that use of this product in nursing mothers is not recommended.

Geriatrics

The cetirizine prescription label states that following a single, 10-mg oral dose, the elimination half-life was prolonged by 50% and the apparent total body clearance was 40% lower in 16 geriatric subjects with a mean age of 77 years compared to 14 adult subjects with a mean age of 53 years. The decrease in cetirizine clearance in these elderly volunteers may be related to decrease renal function.

The prescription label recommends a dosage adjustment of 5 mg once daily for geriatric patients 77 years of age and older. Similarly, the proposed OTC label for the cetirizine 5 mg capsule directs consumers aged 65 years to take 1 capsule once a day while the cetirizine 10 mg label

¹¹ Einarson A, Bailey B, Jung G, Spizzirri D, et al. Prospective controlled study of hydroxyzine and cetirizine in pregnancy. *Ann Allergy Asthma Immunol* 1997; 78:183-6.

directs this age group to ask a doctor. It is then expected that the doctor will direct consumers aged 65 years to use the 5 mg capsule.

Renal Impairment

Dosage adjustment is recommended in patients with moderate or severe renal impairment and in patients on dialysis. In patients 12 years of age and older with decreased renal function (creatinine clearance 11-31 mL/min), patients on hemodialysis (creatinine clearance less than 7 mL/min), and in hepatically impaired patients, a dose of 5 mg once daily is recommended. Similarly, pediatric patients aged 6 to 11 years with impaired renal or hepatic function should use the lower recommended dose (i.e., 5 mg once daily).

The PK of cetirizine was similar in patients with mild renal impairment and normal volunteers. Moderately impaired patients had a 3-fold increase in half-life and a 70% decrease in clearance compared to normal volunteers. Patients on hemodialysis (n=5) given a single, 10-mg dose of cetirizine had a 3-fold increase in half-life and a 70% decrease in clearance compared to normal volunteers. Less than 10% of the administered dose was removed during the single dialysis session.

The proposed OTC label appropriately directs consumers with kidney disease to ask a doctor before use.

Hepatic Impairment

Dosage adjustment is recommended in patients with hepatic impairment. Sixteen patients with chronic liver diseases (hepatocellular, cholestatic, and biliary cirrhosis), given 10 or 20 mg of cetirizine as a single, oral dose had a 50% increase in half-life along with a corresponding 40% decrease in clearance compared to 16 healthy subjects.

The OTC label directs consumers with liver disease to ask a doctor before use.

Gender and Race

The effect of gender on cetirizine pharmacokinetics has not been adequately studied. No race-related differences in the kinetics of cetirizine have been observed.

Pediatrics

See section 7.4 below.

8.4 Pediatrics

Cetirizine is approved for OTC use for the treatment of allergic rhinitis symptoms in adults and children ≥ 2 years of age; it remains available for prescription use in children 6 months old to <2 years of age for the indication of perennial allergic rhinitis. Cetirizine is also approved for OTC use for the relief of itching due to hives in adults and children ≥ 6 years of age; it remains available for prescription use in children 6 months to <6 years of age (it is not an OTC approved population for this indication). The safety and effectiveness of cetirizine in pediatric patients under the age of 6 months have not been established.

In general, the effectiveness of cetirizine for the treatment of allergic rhinitis and chronic idiopathic urticaria in pediatric patients aged 6 months to 11 years is based on an extrapolation of the demonstrated efficacy of cetirizine in adults with these conditions and the likelihood that the disease course, pathophysiology and the drug's effect are substantially similar between these two populations. Efficacy is extrapolated down to 6 months of age for perennial allergic rhinitis and down to 2 years of age for seasonal allergic rhinitis because these diseases are thought to occur down to these ages in children.

Pediatric patients were not evaluated in this NDA. The sponsor is seeking to label this softgel capsule formulation in children 6 year of age and older. The efficacy of this capsule formulation in children ≥ 6 years of age is extrapolated based on PK data from the single-dose relative bioavailability studies assessing the proposed cetirizine capsule 10 mg and the currently marketed Zyrtec® tablet 10 mg (RLD) conducted in adults. Safety data collected during the PK studies and postmarketing surveillance did not reveal new or unexpected safety signals that warrant any further studies in the pediatric population.

PREA

This submission triggers the Pediatric Research Equity Act (PREA) because it is a new dosage formulation. This cetirizine softgel capsule formulation will only be labeled in adults and children ≥ 6 years old. The proposed product does not provide dosing for children < 6 years of age and directs a consumer to ask a doctor for this age group. The doctor/healthcare professional is assumed to direct the consumer to a formulation that is more appropriate for this age group, such as the syrup or chewable tablet. The sponsor is requesting a waiver for pediatric studies below 6 years of age, and states that the proposed softgel capsule formulation does not represent a meaningful therapeutic benefit over existing therapies, and it is not likely to be used in a substantial number of children below 6 years of age.

This reviewer agrees with the sponsor that no additional studies below 6 years of age are needed and recommends granting a waiver for this age group based on the following reasons:

Allergic Rhinitis:

- For children less than 2 years of age, it is the Agency's decision not to label cetirizine below this age based on the knowledge that children generally need to be exposed to allergens for at least two seasons before they develop (seasonal) allergic rhinitis. In addition, there is a concern that parents may not be able to properly diagnose (perennial) allergic rhinitis condition in this age group in an OTC environment. Cetirizine is available by prescription and labeled down to the age of 6 months to treat (perennial) allergic rhinitis.
- For children 2 to < 6 years of age, the proposed product would not offer any additional meaningful therapeutic benefit over existing therapies because there are other age appropriate cetirizine formulations (such as the syrup and chewable tablets) approved for the same indication in this age group.

Hives Relief

- It is the Agency's decision not to label cetirizine in children below 6 years of age due to the concerns about the ability of parents/caregivers to diagnose hives in children < 6 years old without the supervision of a physician. This was based on discussions at the joint Nonprescription and Pulmonary-Allergy Drugs Advisory Committee meeting dated May 11, 2001 (<http://www.fda.gov/ohrms/dockets/ac/cder01.htm>) in which 6 years of age was chosen as the minimum age for the nonprescription hives indication for second generation antihistamines (fexofenadine HCl, loratadine and cetirizine HCl). Age appropriate cetirizine (syrup) formulation is available by prescription and labeled down to the age of 6 months for the indication of hives relief/chronic idiopathic urticaria.

8.5 Advisory Committee Meeting

There is no Advisory Committee Meeting for this current submission; however, the Rx-to-OTC switch of the second generation antihistamines, including cetirizine had been the topic of discussions in a Joint Nonprescription and Pulmonary Advisory Committee meeting held on May 11, 2001 (<http://www.fda.gov/ohrms/dockets/ac/cder01.htm>).

8.6 Literature Review

A review of the medical literature for articles published from June 1, 2007 through July 31, 2008 to identify all published reports of adverse event reporting for cetirizine hydrochloride in adults and in children was conducted. CINAHL, EMBASE, Medline, International Pharmaceutical Abstracts (IPA), ADIS Newsletter-Reactions, Pharm-Line, and ToxFile were utilized by the sponsor. The search revealed eight articles that contained adverse event information with identifiable patient information. Five of the articles provided an analysis of adverse events that occurred for individual patients, and three articles provided an analysis of adverse events that occurred for patient's who were participating as part of a clinical study. Safety information relating to the prescription drug, levocetirizine (the active enantiomer of the racemic mixture) was also reviewed but will not be discussed in detail in this NDA review.

The literature search revealed the following cases: 7 reports of arthralgia (ADR News: Jan 2008), 2 reports of urticaria (Chang 2007, ADR News: Jan 2008), a fixed drug eruption (Cravo 2007), and a case of stuttering in a 3 y/o child (ADR News: Oct 2007). None of the cases described events that were serious, although one patient with hypersensitivity reaction was treated with epinephrine following a positive rechallenge. No significant new safety signal has been identified in the review of these cases. No significant new safety signal was identified through review of clinical studies reported in the literature.

Two clinical studies (Shohrati 2007, Kameyoshi 2007) involving the use of cetirizine 10 to 20 mg describe expected events of somnolence, sedation, and dizziness. One clinical study (Edlinger) described symptoms associated with depression in patients with chronic idiopathic urticaria.

A review of literature cases did not contain any reports of overdose for cetirizine hydrochloride.

Medical Officer Comments: A review of safety information on cetirizine found in the medical literature from June 1, 2007 through July 31, 2008 did not reveal any new significant safety concerns. The adverse events reported such as arthralgia, somnolence, urticaria, and skin eruptions previously reported with the use of cetirizine either from clinical trials or postmarketing. Stuttering have not been previously reported; however, due to the limited information provided in the article, there is no conclusive evidence of a causal relationship with the event and cetirizine use. A review of the published literature on cetirizine did not reveal any new serious or significant safety concerns that would preclude the OTC use of the proposed cetirizine product.

8.7 Postmarketing Risk Management Plan

There is no postmarketing risk management plan recommended for this NDA.

8.8 Other Relevant Materials

There are no other relevant materials submitted for the review.

9 OVERALL ASSESSMENT

9.1 Conclusions

It is known that allergic rhinitis and hives are OTC indications that consumers can self-diagnose and treat. Cetirizine has been recently approved for OTC use for the following indications: relief of allergic rhinitis symptoms in adults and children ≥ 2 years of age, and relief of itching due to hives in adults and children ≥ 6 years of age. A similar second generation antihistamine, loratadine, has been marketed OTC for the same indications and age group since December 2002.

A single dose of the sponsor's (BPI) cetirizine 10 mg ~~capsule~~ capsule is considered to be bioequivalent to a single dose of the reference product, Zyrtec® 10 mg tablet under fasted and fed conditions. Both treatments were well-tolerated with few adverse events reported from the bioavailability studies which were consistent with the already known adverse events for cetirizine. There were no deaths nor serious adverse events reported from these studies conducted by the sponsor. The sponsor is requesting a waiver of the bioequivalence requirement for cetirizine HCl ~~capsules~~ capsules 5 mg because this dosage strength is proportional to the proposed 10 mg strength in their active ingredient (drug substance) and excipients.

b(4)

b(4)

The adverse event data from the bioavailability studies conducted by the sponsor, postmarketing safety databases, and review of the medical literature did not identify any new safety concerns for the OTC use of cetirizine. The safety profile of cetirizine from clinical experience is well-

characterized as a prescription drug in the United States, and as OTC drug in foreign countries and so far, no serious unexpected adverse events have been reported with any of its formulations. The Rx-to-OTC switch of cetirizine in the United States was approved on November 16, 2007; although the OTC marketing of cetirizine has only been for over a year, no safety concerns has so far been raised since its product launch.

The OTC labels submitted to this NDA on the proposed cetirizine capsules are consistent with the currently approved cetirizine OTC label.

9.2 Recommendation on Regulatory Action

From a clinical safety standpoint, Banner's proposed cetirizine capsules 5 and 10 mg indicated for the indication of temporary relief of symptoms of runny nose, itchy, watery eyes, sneezing, and itching of the nose or throat due to hay fever or other upper respiratory allergies, and relief of itching due to hives in adults and children 6 years of age and older has an acceptable safety profile for OTC marketing. Therefore, this reviewer recommends approval of this application as long as the sponsor incorporates the reviewing team's labeling recommendations for this product.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No special risk management activities are recommended for this NDA.

9.3.2 Required Phase 4 Commitments

No required phase 4 commitments are recommended.

9.3.3 Other Phase 4 Requests

No other phase 4 requests are recommended.

9.4 Labeling Review

On February 19, 2009, the sponsor of this application (BPI) submitted an amendment to this NDA requesting to use the proprietary name _____ for their proposed cetirizine 5 and 10 mg capsule products. _____

_____ BPI plans to amend this submission with the proposed final printed labeling as soon as it becomes available.

b(4)

A member of the Interdisciplinary Scientist (IDS) group in the Division of Nonprescription Regulation Development (DNRD) will be reviewing the proposed label in detail. Figures 1-4

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illustrate the sponsor's proposed Drug Facts label (submitted on September 25, 2008). The proposed labels are acceptable from a clinical safety perspective. The following are this reviewer's additional comments to the proposed label:

- Under Questions or comments? If you have questions of a medical nature, please contact your pharmacist, doctor or health care professional is not acceptable. The sponsor needs to provide a 1-800 number for patients to call especially for issues pertaining to the product itself.
- The proposed labels for the hives relief indication should remove the text ~~_____~~ because this text is not applicable to the hives relief indication.

b(4)

6 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

10 APPENDICES

Table A-1: Demographic Profile of Subjects Completing the Bioequivalence Study

		Study No. 20-219-5A	
		Treatment Groups	
		Test Product N = 23	Reference Product N = 23
Age (years)	Mean ± SD	31 ± 10	31 ± 10
	Range	18 - 52	18 - 52
Age Groups	< 18	0 (0.00%)	0 (0.00%)
	18 - 40	18 (78.26%)	18 (78.26%)
	41 - 64	5 (21.74%)	5 (21.74%)
	65 - 75	0 (0.00%)	0 (0.00%)
	> 75	0 (0.00%)	0 (0.00%)
Sex	Female	14 (60.87%)	14 (60.87%)
	Male	9 (39.13%)	9 (39.13%)
Race	Asian	1 (4.35%)	1 (4.35%)
	Black	3 (13.04%)	3 (13.04%)
	Caucasian	19 (82.61%)	19 (82.61%)
	Hispanic	0 (0.00%)	0 (0.00%)
	Other	0 (0.00%)	0 (0.00%)
BMI (kg/m ²)	Mean ± SD	25.1 ± 2.8	25.1 ± 2.8
	Range	20.3 - 29.8	20.3 - 29.8
Height (cm)	Mean ± SD	168.9 ± 11.1	168.9 ± 11.1
	Range	146.5 - 196.5	146.5 - 196.5
Weight (kg)	Mean ± SD	72.0 ± 13.9	72.0 ± 13.9
	Range	49.8 - 100.5	49.8 - 100.5

Table A-2: Demographic Profile of Subjects Completing the Bioequivalence Study

Study No. 20-220-SA			
		Treatment Groups	
		Test Product N =24	Reference Product N =24
Age (years)	Mean ± SD	33 ± 13	33 ± 13
	Range	18 - 55	18 - 55
Age Groups	< 18	0 (0.00%)	0 (0.00%)
	18 - 40	17 (70.83%)	17 (70.83%)
	41 - 64	7 (29.17%)	7 (29.17%)
	65 - 75	0 (0.00%)	0 (0.00%)
	> 75	0 (0.00%)	0 (0.00%)
Sex	Female	16 (66.67%)	16 (66.67%)
	Male	8 (33.33%)	8 (33.33%)
Race	Asian	0 (0.00%)	0 (0.00%)
	Black	4 (16.67%)	4 (16.67%)
	Caucasian	19 (79.17%)	19 (79.17%)
	Hispanic	0 (0.00%)	0 (0.00%)
	Other	1 (4.17%)	1 (4.17%)
BMI (kg/m ²)	Mean ± SD	25.0 ± 2.9	25.0 ± 2.9
	Range	20.1 - 29.6	20.1 - 29.6
Height (cm)	Mean ± SD	167.9 ± 7.8	167.9 ± 7.8
	Range	161.0 - 201.5	161.0 - 201.5
Weight (kg)	Mean ± SD	70.4 ± 9.2	70.4 ± 9.2
	Range	55.1 - 92.9	55.1 - 92.9

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b(4)

Table A-3: Adverse Events and Severity (20-219-SA)

Event Number	Subject	Subject Initials	Treatment ID	Period	Total Dose	Adverse Reaction	Date of Reaction	Time After Dose	Severity
1	205	[REDACTED]	A	1	10mg	Headache	8/20/2007	17h3m	Mild
2	209		A	1	10mg	Headache	8/21/2007	24h56m	Mild
3	210		B	1	10mg	Abdominal wall pain	8/20/2007	1h23m	Mild
4	212		A	1	10mg	Headache	8/25/2007	12h50m	Mild
5	216		B	1	10mg	Abnormal taste	8/20/2007	0h58m	Mild
6	216		B	1	10mg	Flushing	8/20/2007	0h59m	Mild
7	216		B	1	10mg	Nausea	8/20/2007	0h59m	Mild
8	217		B	2	10mg	Headache	8/27/2007	1h5m	Mild
9	217		B	2	10mg	Dizziness	8/27/2007	1h10m	Mild

Treatment A: Cetirizine Capsule Treatment B: Zyrtec tablet
 Sponsor's table

b(6)

Table A-4: Adverse Events Data (20-219-SA)
 (Drug Relatedness and Resolution)

Event Number	Subject	Subject Initials	Treatment ID	Period	Associate with Drug	Resolution	Time to Resolution	Action Taken
1	205	[REDACTED]	A	1	Probable	Resolved	8h1m	None
2	209		A	1	Possible	Resolved	35h15m	None
3	210		B	1	Possible	Resolved	3h1m	None
4	212		A	1	Unlikely	Resolved	8h0m	None
5	216		B	1	Probable	Resolved	0h33m	None
6	216		B	1	Probable	Resolved	0h32m	None
7	216		B	1	Probable	Resolved	0h32m	None
8	217		B	2	Probable	Resolved	12h50m	None
9	217		B	2	Probable	Resolved	5h30m	None

Treatment A: Cetirizine Capsule Treatment B: Zyrtec tablet
 Sponsor's table

b(6)

b(4)

Table A-5: Adverse Event Data (20-220-SA)

Event Number	Subject	Subject Initials	Treatment ID	Period	Total Dose	Adverse Reaction	Date of Reaction	Time After Dose
1	304	F J	A	2	10mg	Somnolence	8/27/2007	4h24m
2	304		A	2	10mg	Polyuria	8/27/2007	4h24m
3	308		B	1	10mg	Headache	8/21/2007	25h51m
4	315		B	2	10mg	Somnolence	8/27/2007	3h32m
5	316		B	2	10mg	Broken tooth	8/27/2007	4h28m
6	318		A	1	10mg	Left arm pain with venipuncture	8/27/2007	167h21m
7	321		A	1	10mg	Nausea	8/21/2007	33h50m
8	321		A	1	10mg	Headache	8/21/2007	34h0m

b(6)

Treatment A: Cetirizine Capsule Treatment B: Zyrtec tablet
 Sponsor's table

Table A-6: Adverse Event Data (20-220-SA)
 (Severity, Drug Relatedness and Resolution)

Event Number	Subject	Subject Initials	Treatment ID	Period	Severity	Associate with Drug	Resolution	Time to Resolution	Action Taken
1	304	F J	A	2	Mild	Probable	Resolved	6h0m	None
2	304		A	2	Mild	Possible	Resolved	12h0m	None
3	308		B	1	Mild	Possible	Resolved	2h0m	Other: ice pack
4	315		B	2	Mild	Probable	Resolved	10h0m	None
5	316		B	2	Moderate	Not related	Resolved	47h22m	Other: tooth repair
6	318		A	1	Mild	Not related	Resolved	0h1m	None
7	321		A	1	Mild	Unlikely	Resolved	2h30m	None
8	321		A	1	Mild	Unlikely	Resolved	1h20m	None

b(6)

Treatment A: Cetirizine Capsule Treatment B: Zyrtec tablet
 Sponsor's table

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Table A-7: Nonfatal Serious Adverse Events for Cetirizine from AERS (6/07 to 3/08).^a
 (214 cases)

Preferred Term	Total	Dose 5 mg	Dose 10 mg	Dose Unknown
Convulsion	21	.	3	18
Hypersensitivity	13	.	6	7
Somnolence	12	1	4	7
Pruritus	10	.	4	6
Abnormal behaviour	9	1	3	5
Depression	9	.	3	6
Drug ineffective	9	.	3	6
Fatigue	9	.	4	5
Dizziness	8	.	3	5
Drug interaction	8	.	3	5
Feeling abnormal	8	.	1	7
Urticaria	7	.	2	5
Aggression	6	.	2	4
Drug exposure during pregnancy	6	.	5	1
Dry mouth	6	.	.	6
Headache	6	.	2	4
Insomnia	6	.	4	2
Loss of consciousness	6	.	2	4
Tremor	6	.	4	2
Anger	5	.	1	4

Table A-7 continued:

Preferred Term	Total	Dose 5 mg	Dose 10 mg	Dose Unknown
Balance disorder	5	.	1	4
Disturbance in attention	5	.	1	4
Drug dependence	5	.	1	4
Dysgeusia	5	.	.	5
Gait disturbance	5	.	.	5
Irritability	5	.	4	1
Nausea	5	.	4	1
Oedema peripheral	5	.	.	5
Pain	5	.	.	5
Premature baby	5	.	4	1
Sleep disorder	5	.	2	3
Suicidal ideation	5	.	1	4
Vomiting	5	.	1	4
Weight increased	5	.	.	5
Abdominal pain upper	4	.	.	4
Alanine aminotransferase increased	4	.	2	2
Aspartate aminotransferase increased	4	.	2	2
Blood glucose increased	4	.	1	3
Coma	4	.	.	4
Dyspnoea	4	.	.	4
Fall	4	.	2	2
Hallucination	4	.	1	3
Hernia	4	.	1	3
Malaise	4	.	1	3
Nightmare	4	.	1	3
Overdose	4	1	.	3
Pharyngolaryngeal pain	4	.	2	2
Suicide attempt	4	.	.	4
Swelling face	4	.	.	4
Abdominal pain	3	1	1	1
Activities of daily living impaired	3	.	.	3
Adrenogenital syndrome	3	.	2	1
Anxiety	3	.	2	1
Arnold-Chiari malformation	3	.	2	1
Chest discomfort	3	.	.	3
Chills	3	.	.	3
Developmental delay	3	.	2	1
Drug effect decreased	3	1	1	1
Drug withdrawal syndrome	3	.	1	2
Dry eye	3	.	1	2
Eating disorder	3	.	.	3
Gamma-glutamyl transferase increased	3	.	2	1
Gastric disorder	3	.	.	3
Hepatic function abnormal	3	.	2	1
Hypoaesthesia	3	.	1	2
Ill-defined disorder	3	.	2	1
Liver disorder	3	.	2	1
Mobility decreased	3	.	.	3

b(4)

Table A-7 continued:

Preferred Term	Total	Dose 5 mg	Dose 10 mg	Dose Unknown
Mood swings	3	.	1	2
Muscle spasms	3	.	.	3
Myalgia	3	.	.	3
Pain in extremity	3	.	.	3
Rash	3	.	1	2
Sinusitis	3	.	1	2
Speech disorder developmental	3	.	2	1
Stress	3	.	1	2
Unevaluable event	3	.	1	2
Viral infection	3	.	2	1
Weight decreased	3	.	1	2
White blood cell count decreased	3	.	2	1
Withdrawal syndrome	3	1	1	1
Abdominal distention	2	.	.	2
Abnormal dreams	2	.	1	1
Adrenal insufficiency	2	.	1	1
Ageusia	2	.	.	2
Allergic granulomatous angitis	2	.	.	2
Alopecia	2	.	.	2
Anaphylactic reaction	2	.	1	1
Anosmia	2	.	.	2
Apathy	2	.	1	1
Arrhythmia	2	.	1	1
Asthenia	2	.	.	2
Asthma	2	.	.	2
Blood alkaline phosphatase increased	2	.	2	.
Blood cholesterol increased	2	.	.	2
Blood lactate dehydrogenase increased	2	.	2	.
Blood pressure increased	2	.	.	2
Caesarean section	2	.	2	.
Cataract operation	2	.	.	2
Condition aggravated	2	.	1	1
Confusional state	2	.	1	1
Constipation	2	.	.	2
Contusion	2	.	1	1
Crying	2	.	.	2
Dermatitis	2	.	1	1
Diabetes mellitus	2	.	.	2
Disorientation	2	.	.	2
Drug toxicity	2	.	.	2
Dyspepsia	2	.	1	1
Dysphemia	2	1	.	1
Dysuria	2	1	.	1
Eye swelling	2	.	.	2
Eyelid oedema	2	.	.	2
Facial palsy	2	.	1	1
Feeling hot	2	.	.	2
Flatulence	2	.	.	2

b(4)

Table A-7 continued:

Preferred Term	Total	Dose 5 mg	Dose 10 mg	Dose Unknown
Fluid retention	2	.	.	2
Foetal distress syndrome	2	.	2	.
Fungal infection	2	.	.	2
Hallucination, auditory	2	.	.	2
Hangover	2	.	1	1
Heart rate increased	2	.	.	2
Hypersomnia	2	.	2	.
Hypotension	2	.	.	2
Impaired driving ability	2	.	2	.
Intentional overdose	2	1	.	1
Maternal condition affecting fetus	2	.	2	.
Medication error	2	.	.	2
Mental disorder	2	.	.	2
Nasal congestion	2	.	1	1
Oppositional defiant disorder	2	.	1	1
Panic disorder	2	.	.	2
Paraesthesia	2	.	.	2
Parosmia	2	.	.	2
Pharmaceutical product complaint	2	.	1	1
Poor venous access	2	.	2	.
Psychomotor hyperactivity	2	.	.	2
Pyrexia	2	.	.	2
Rash erythematous	2	.	.	2
Rash pruritic	2	.	1	1
Respiratory disorder	2	.	1	1
Rhinorrhoea	2	.	.	2
Road traffic accident	2	.	1	1
Sinus headache	2	.	.	2
Skin burning sensation	2	.	.	2
Skin exfoliation	2	.	2	.
Sneezing	2	.	1	1
Thinking abnormal	2	.	1	1
Tinnitus	2	.	1	1
Urinary tract infection	2	.	.	2
Vertigo	2	.	2	.
Vision blurred	2	.	.	2
Visual disturbance	2	.	.	2
Vulvovaginal discomfort	2	1	.	1
Wheezing	2	.	.	2
Total	544	10	166	368

a Reported in >1 case
 Sponsor's Table 3.1-5, ISS version 2 pp. 16-19.

List of scenarios included in the NPDS data.

Any events that fall outside of these scenarios would not be captured within these data.

- Incorrect dosing route
- dispensing cup error
- 10-fold dosing error
- Inadvertently
- took/was given someone else's medication
- inadvertently took/was given medication twice
- incorrect formulation or concentration given
- incorrect formulation or concentration dispensed
- wrong medication taken/given
- health professional iatrogenic error
- exposure through breast milk
- more than one product containing same ingredient taken
- medication doses given/taken too close together
- confused units of measure
- other incorrect dose
- drug interaction
- other/unknown therapeutic error
- product temporarily open because product was in use and caregiver was momentarily distracted
- child or pet accessed medication/product from purse
- child or pet accessed medication/product from suitcase
- child caused exposure (e.g., gave to sibling or pet)
- stored in unlocked, low cabinet in kitchen or bathroom
- stored within sight of child
- product always left out
- product stored inappropriately, other
- patient confused or mentally incompetent
- container transfer involved
- patient thought product or pill was a food
- patient thought non-medication was a pill
- exposure was the result of a dare or similar behavior in a patient otherwise old enough to know better and mentally competent

10.1 Review of Individual Study Reports

N/A

10.2 Line-by-Line Labeling Review

See section 9.4.

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/s/

Lolita Lopez
4/8/2009 06:50:39 AM
MEDICAL OFFICER

Daiva Shetty
4/8/2009 08:51:35 PM
MEDICAL OFFICER



NDA Fileability Checklist

Department of Health and Human Services
 Food and Drugs Administration
 Center for Drug Evaluation and Research
Division of Nonprescription Clinical Evaluation

NDA: NDA 22-429
Drug Name: Cetirizine 5 and 10 mg Capsules
Product Name: Cetirizine 5 and 10 mg Capsules
Indication: Treatment of Allergic Rhinitis
 Relief of Hives
Sponsor: Banner Pharmacaps, Inc. (BPI)
Reviewer: Lolita A. Lopez, M.D.
Team Leader: Daiva Shetty, M.D.
CDER Stamp Date: August 1, 2008
Filing Meeting: September 10, 2008
PDUFA Due Date: June 1, 2008

Item	Yes	No
1. Is the clinical section of the NDA organized in a manner to allow substantive review to begin?	x	
2. Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	x	
3. Is the clinical section of the NDA legible so that substantive review can begin?	x	
4. If needed, has the sponsor made an appropriate attempt to determine the most appropriate dosage and schedule for this product through appropriately designed dose-ranging studies?	N/A	
5. Do there appear to be the requisite number of adequately and well-controlled studies in the application?	N/A	
6. Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?	N/A	
7. Are all data sets for pivotal efficacy studies complete for all indications requested?	N/A	
8. Do all pivotal 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	
9. Has the applicant submitted line listings in a format to allow reasonable review of the patient data and in the format agreed to previously by the Division?	x	
10. Has the application submitted a rationale for the applicability of foreign data (disease specific, microbiologic specific) in the submission to the U.S. population?	N/A	

11. Has the applicant submitted all additional required case record forms, in addition to deaths and drop-outs, previously requested by the Division?	N/A	
12. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division?		x
13. Has the applicant presented the safety assessment based on all current world-wide knowledge regarding this product?		x
14. Has the applicant submitted adequate and well-controlled actual usage trial(s) 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?	N/A	
15. Has the applicant submitted adequate and well-controlled labeling comprehension trial(s) 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?	N/A	
16. Has the applicant submitted draft labeling consistent with 201.5 and 201.56, current divisional policies, and the design of the development package?		x
17. Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	N/A	
18. Has PREA been addressed?	x	
19. From a clinical perspective, is this NDA file-able? In no, please explain below.		x

Reviewer Comments:

- This is a 505(b)(2) application, the reference listed drug is Zyrtec® Tablets, 5 mg and 10 mg (NDA19-835). This NDA relies on the Agency's finding of safety and effectiveness for Zyrtec® Tablets for the pharmacology, toxicology, microbiology, statistical and clinical information.
- There are no clinical efficacy nor safety studies conducted by the sponsor. Bioavailability studies were conducted comparing the sponsor's cetirizine 10-mg capsule to Zyrtec® 10-mg tablets (reference drug). The sponsor did not conduct bioavailability studies for the 5 mg strength and is requesting a biowaiver for this dosage strength.
- The sponsor did not provide a detailed narrative description and analysis of the extent of exposure of subjects to the test drugs, adverse events, physical examination, vital signs and laboratory findings from their PK studies. These will be a potential review issue.
- This NDA submission has an incomplete clinical data section required as specified in 21 CFR 314.50(d)(5). It does not contain an integrated summary of all available information about the safety of the drug product. An integrated summary of the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling was not provided. This is a potential filing issue.
- The application does not contain a statement for each clinical study that it was conducted in compliance with the institutional review board regulations, and that it was conducted

in compliance with the informed consent regulations [21 CFR 314.101 (d)(7)]. This is a filing issue.

Recommendations:

- This reviewer recommends that the Division refuse to file this NDA due to an incomplete clinical data section, specifically safety information as required in 21 CFR 314.50(d)(5)(vi). In order to assess safety of the proposed formulation, postmarketing safety surveillance information for cetirizine from the following databases listed below should be submitted. The time period for a safety database should start at least one year prior to the NDA submission. Data from all sources should be summarized and analyzed by formulation, marketing status (Rx vs. OTC) dose, duration of use, year of reporting, age.
 - FDA Adverse Event Reporting System (AERS) database
 - World health Organization (WHO) International Drug Monitoring program
 - Medical Literature Review
 - Drug Abuse and Overdose Data:
 - American Association of Poison Control Centers (AAPCC)
 - Drug Abuse Warning Network (DAWN)
- The sponsor must provide a statement for each clinical study that it was conducted in compliance with the institutional review board regulations, and that it was conducted in compliance with the informed consent regulations, refer to 21 CFR 314.101 (d)(7)].
- The following non-filing issues should also be conveyed to the sponsor:
 - Submit a 4-month safety update information in accordance to 21 CFR 314.50(d)(5)(vi)(b)].
 - Provide information whether this product has been approved, marketed, and/or withdrawn in the U.S. or any foreign countries.
 - The adequacy of the narrative description and analysis of adverse events from their PK studies will be a review issue.

Addendum:

On September 10, 2008, DNCE sent an early communication (via email) to the sponsor conveying the above potential filing and review issues for their application. The sponsor subsequently requested a teleconference to discuss these issues. On September 29, 2008, a teleconference was held; DNCE and the sponsor discussed the above issues. DNCE explained the importance of the integrated safety summary (ISS) portion of the NDA, specifically postmarketing information. The sponsor committed to submitting the required information that addresses the potential filing issues.

On September 25, 2008, BPI submitted an amendment to NDA 22-429 providing a letter of commitment for the additional safety information. This amendment provides for the following commitments:

- An ethical conduct of compliance statement according to 21 CFR Part 56 and 50 (including Subpart B informed consent of human subjects) to be submitted by 09/26/08.

- An amended study report, which includes detailed safety information and the ethical conduct of compliance statement to be submitted by 10/31/08.
- Integrated safety assessment (ISS) which will include description, analysis and interpretation of the safety information from the studies Banner conducted, and from the following postmarketing safety databases for cetirizine products by 10/31/08.
 - FDA Adverse Event Reporting System (AERS) database
 - World health Organization (WHO) International Drug Monitoring Program
 - Medical Literature Review (provide references and articles)
 - Drug Abuse and Overdose Data from:
 - American Association of Poison Control Centers (AAPCC)
 - Drug Abuse Warning Network (DAWN)

In addition, the sponsor stated that mock-up labeling for all SKU's for each strength and both indications will be submitted by 09/26/08.

The sponsor's commitment as listed above is acceptable. Therefore, this reviewer recommends that this application be filed from a clinical safety perspective.

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/s/

Lolita Lopez
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Daiva Shetty
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