CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-835/S022

21-621/S005

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-155 (Zyrtec Syrup) 19-835/S-022 (Zyrtec Tablets) 21-621/S-005 (Zyrtec ChewableTablets)
Submission Code	N, 000 SE-6, S-022 SE-6, S-005
Letter Date	January 15, 2007
Stamp Date	January 16, 2007
PDUFA Goal Date	November 16, 2007
Reviewer Name	Lolita A. Lopez, M.D.
Team Leader	Daiva Shetty, M.D.
Review Completion Date	September 4, 2007
Established Name	Cetirizine Hydrochloride
(Proposed) Trade Name	Zyrtec
Therapeutic Class	H-1 Receptor Antagonist
Applicant	Pfizer, Inc./McNeil Consumer Healthcare
Priority Designation	S
Formulation	Syrup 1mg/mL (NDA 22-155) Tablets 5, 10 mg (NDA 19-835/S-022) Chewable Tabs 5, 10 mg (NDA 21-621/S-005)
Dosing Regimen	2.5 to 10 mg Once Daily Depending on Age and Symptom Severity
Indications	Treatment of Allergic Rhinitis (AR) Symptoms, Relief of Itching Due to Hives
Intended Population	Adults and Children ≥2 y/o (AR) Adults and Children ≥6 y/o (Hives)

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The sponsor provided adequate data to support the efficacy and safety of its proposed Zyrtec® line of single-ingredient cetirizine products: syrup 1mg/mL (NDA 22-155); tablets 5, 10 mg (NDA 19-835/S-022) and chewable tablets 5, 10 mg (NDA 21-621/S-005) for the following indications:

- 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) due to dust mites, animal dander and molds) and ragweed, grass and tree pollens) upper respiratory allergies in adults and children aged 2 years and older.
- relief of itching due to hives (urticaria) in adults and children aged 6 years and older.

Therefore, from a clinical safety perspective, this reviewer recommends approval of these applications as long as the sponsor incorporates the labeling recommendations for the different formulations of the cetirizine products (see section 9.4 of this review).

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

Pfizer, Inc/McNeil Consumer Healthcare is seeking the Agency's approval for an over-the-counter (OTC) switch of its Zyrtec® line of cetirizine products. Cetirizine is currently approved and marketed as prescription only for the following indications: seasonal allergic rhinitis (SAR) in adults and children ≥ 2 years old, perennial allergic rhinitis (PAR) in adults and children ≥ 6 months old, and chronic idiopathic urticaria (CIU) in adults and children ≥ 6 months old. The following single-ingredient cetirizine products will be covered in this review: tablets and chewable tablets (5 and

10 mg) and syrup (1mg/ml). The combination of cetirizine and pseudoephedrine (Zyrtec-D®) will be reviewed separately.

The proposed indications for these applications for OTC marketing will be similar to the already approved prescription indications for cetirizine with a narrower age indication in children: relief of allergic rhinitis (AR) symptoms in adults and children ≥ 2 years old, and relief of uncomplicated hives in adults and children ≥ 6 years old. Other than the difference in the intended population for the OTC cetirizine syrup, the proposed OTC products will have the same strength, indications, dosage and administration as the respective prescription products. No new indications are being proposed for these single ingredient products; therefore, no additional clinical efficacy studies were submitted with these NDAs. There are other available products in the same class of drugs (loratadine products) that are marketed OTC for the same indications.

1.3.2 Efficacy

No new indications are being proposed for these single-ingredient cetirizine products; therefore, no additional clinical efficacy studies were submitted with these applications. Data from clinical studies submitted with the original NDAs was referenced to support the efficacy of cetirizine in the treatment of symptoms of allergic rhinitis and hives. See the review from the Division of Pulmonary and Allergy Products (DPAP) for evaluation of efficacy.

1.3.3 Safety

The sponsor primarily relies on the information from clinical trials that has been previously submitted and evaluated for safety to support the prescription approval of the original single-ingredient cetirizine NDAs and postmarketing databases including review of literature.
Safety data submitted to this application include:

- Summaries of safety data (serious adverse events) from clinical trials previously submitted to and evaluated for safety to support the prescription approval of the original single-ingredient cetirizine applications
- Current cetirizine prescription label and loratadine OTC labels.
- Analysis of all post marketing serious adverse events received by Pfizer (1986 to 2007).
- A report summarizing adverse event reporting to the FDA from the Spontaneous Reporting System (SRS) and the Adverse Event Reporting System (AERS) (1969 to 2006).
- Analysis of reports to the American Association of Poison Control Centers' Toxic Exposure Surveillance System (TESS) database (1995 to 2005).
- A report of the Drug Abuse Warning Reports (DAWN) for cetirizine (1995 to 2006).
- A report summarizing adverse event reporting to the World Health Organization's (WHO) International Drug Monitoring Program.
- A review of medical literature relevant to the safety of cetirizine (1966 to 2006).

Controlled (15) and uncontrolled (10) clinical trials were conducted in the United States and Canada which included more than 6,000 patients aged 12 years and older in which more than 3,900 patients received Zyrtec 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. Most adverse reactions reported during therapy with Zyrtec were mild or moderate. The most common adverse events in adults and patients aged 12 years and older (N=3,646; Zyrtec=2,034, Placebo=1,612) receiving Zyrtec 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; the latter was dose related (6% in placebo, 11% at 5 mg and 14% at 10 mg). The most commonly reported serious adverse events from the sponsor clinical trial database (N=216) were asthma (36, 9.2%); vomiting (14, 3.6%); pyrexia (14, 3.6%) and bronchitis (11, 2.8%).

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 Zyrtec 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 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). A total of 168 patients aged 2 to 5 years received Zyrtec, the majority received single daily doses of 5 mg. The adverse experiences reported in pediatric patients aged 2 to 5 years in placebo-controlled trials were similar in nature and frequency to those reported in trials with children 6 to 11 years old. The majority of adverse reactions reported in patients aged 2 to 11 years with Zyrtec were mild or moderate.

The safety databases from TESS, AERS/FDA, WHO, and DAWN did not reveal any specific trend or signal detected with the use of cetirizine. TESS reported a total of 48,386 exposures with 13,184 associated clinical effect (CE) terms from January 1995 to December 2005. Of these, 84% were pediatric cases and 14% were adult cases, 2% had no age data. The most frequently reported clinical effects in both adults and children were: drowsy/lethargy 29%, agitated/irritable 8.5%, and tachycardia 8%. The FDA/SRS database had a total of 4,444 cases reported with 13,509 associated AE terms (1969 to 2006) for reports involving cetirizine as a suspect medication. Overall, the most common AEs reported were drug ineffective 3.3%, sedation 1.9%, urticaria 1.7%, and pruritus 1.4%. In the WHO database, there were 6,232 cases involving 12,318 AE terms reported for cetirizine, half of these cases (3,124 involving 5,225 AE terms) were reported from outside the U.S. and the most frequently reported AE terms were somnolence 8.5%, fatigue 6.5%, headache 5%, dizziness 3.6% and nausea 2.9%. The DAWN data did not reveal any signal that cetirizine is being abused or misused. The medical literature also did not reveal any safety signal or trends in serious adverse events.

In the sponsor's postmarketing database, there were a total of 14,921 cases received by Pfizer involving single-ingredient cetirizine products with associated 30,508 coded adverse event (AE) terms from sources other than clinical trials entered into its database from January 1, 1980 to May 10, 2006. Majority (12,456; 83%) of the cases were non-serious; 14% (2,110) were serious and 2.4% (355) were reports of death. The most commonly reported AE terms were drug ineffective (8.13%) and somnolence (7.83%). The following AEs terms were reported as having > 1% rate of all terms: rash (2.4%), fatigue (2.2%), urticaria (2.1%), dizziness (2%), headache (1.8%), pruritus and hypersensitivity (1.7% each), nausea (1.1%) and insomnia (1%).

The types of adverse events that were noted in the postmarketing safety databases for cetirizine and the medical literature are generally similar to those noted in clinical trials. There were no conclusive evidence of a causal relationship between the use of cetirizine and any previously unidentified serious or life-threatening adverse events from postmarketing experience. A safety update submitted on May 18, 2007 that covers the period from May 11, 2006 to January 16, 2007 for single-ingredient cetirizine HCl did not reveal any new safety concerns. In addition, the postmarketing safety data from Canada and the United Kingdom, where cetirizine is available as a nonprescription product, reveal no safety signal that precludes this drug's OTC switch in the United States.

1.3.4 Dosing Regimen and Administration

The proposed indications are for the temporary relief of allergic rhinitis symptoms (runny nose, sneezing, itchy, watery eyes, itching of the nose or throat) in adults and children ≥ 2 years old, and for the relief of itching due to hives/urticaria in adults and children ≥ 6 years old. The dosing regimen is generally similar except for some inconsistencies in the current prescription label and the proposed OTC label. The following is the proposed OTC dosing:

Cetirizine 1 mg/mL Syrup

adults and children 6 years and over:	use dosing cup provided. 1 teaspoonful (5 mL) or 2 teaspoonfuls (10 mL) once daily depending upon severity of symptoms; do not take more than 2 teaspoonfuls (10 mL) in 24 hours.
children 2 to under 6 years of age:	use dosing cup or syringe provided. ½ teaspoonful (2.5 mL) once daily. If needed, dose can be increased to a maximum of 1 teaspoonful (5 mL) once daily or ½ teaspoonful (2.5 mL) every 12 hours. Do not give more than 1 teaspoonful (5 mL) in 24 hours.
children under 2 years of age:	ask a doctor
consumers with liver or kidney disease:	ask a doctor

Cetirizine 5 mg Tablet/Chewable Tablet

adults and children 6 years and over:	1 or 2 tablets once daily depending upon severity of symptoms; do not take more than 2 tablets in 24 hours.
children under 6 years of age:	ask a doctor *(for tablet only)*
children 2 to under 6 years of age:	1 chewable tablet once daily *(for chewable tablet only)*

Cetirizine 10 mg Tablet/Chewable Tablet

adults and children 6 years and over:	1 tablet once daily; do not take more than 1 tablet in 24 hours. A 5 mg product may be appropriate for less severe symptoms.
children under 6 years of age:	ask a doctor
consumers with liver or kidney disease:	ask a doctor

The dosing for the *relief of itching due to hives (urticaria)* is the same as that of the allergic rhinitis except that for children under 6 years of age, the consumer is instructed to "ask a doctor".

The dosing for the formulations of cetirizine for OTC use is consistent with the current prescription label except for the 5 mg chewable tablet in children 2 to under 6 years of age (allergy relief indication). The proposed dose of 5 mg once daily in this age group does not communicate a lower initial recommended dose of 2.5 mg once daily as stated in the prescription label. This dosing

recommendation was based from a review of Pediatric Supplement of Zyrtec® (cetirizine) syrup for children 2 to 5 y/o submitted by Pfizer on 5/15/97 under NDA 20-346/S-002. In this supplement, it was noted that after administration of a 5-mg oral dose of cetirizine, the systemic exposure (Cmax and AUC) of cetirizine in pediatrics 2 to 5 y/o is (1) approximately 3 to 4-fold higher than that in adults, and (2) approximately 2 to 2.5-fold higher than that in children 7 to 12 y/o.

The sponsor's proposed OTC labels does not include a dose adjustment in elderly patients. The prescription label recommends a dose adjustment of 5 mg once daily for the elderly (77 years and older). This dose adjustment was based on a pharmacokinetic study which showed that elderly patients (≥65 years old, mean age=77) had increased Cmax and AUC. Therefore, OTC labels should include a dose adjustment of 5 mg once daily in patients ≥65 years of age, this include the full range of ages at risk supported by the data.

In addition, the OTC label should state that the use of this drug in nursing mothers is not recommended as stated in the prescription label.

1.3.5 Drug-Drug Interactions

There are no new drug-drug interactions evaluated with these applications. There is also no new significant information on drug interactions that warrants any changes in the cetirizine label. The prescription label states 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 Zyrtec 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.

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). The label also states to avoid alcoholic drinks, and that alcohol, sedatives and tranquilizers may increase drowsiness when using the product.

1.3.6 Special Populations

No new information regarding special populations was submitted with these NDAs. Cetirizine is currently listed as Pregnancy Category B. The proposed OTC label include appropriate warnings to certain consumers such as pregnant women and those with renal or kidney problems. However, similar to the prescription label, a dosage adjustment should be included for geriatric patients who are 65 years of age and older. Similarly, it should be communicated in the OTC label that the product is not recommended in breastfeeding mothers and should ask a doctor.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Cetirizine hydrochloride (Zyrtec®) 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. Zyrtec® was approved for prescription use on December 8, 1995 and is currently indicated for the relief of symptoms associated with allergic rhinitis (seasonal and perennial) and treatment of chronic idiopathic urticaria. It is available in the following formulations: tablet (5 and 10 mg), chewable tablet (5 and 10 mg), and syrup (1 mg/1 mL). The table below lists the historical product approvals for the Zyrtec® products.

The current prescription (Rx) indications for cetirizine are:

- Relief of symptoms associated with *seasonal allergic rhinitis* (SAR) due to allergens such as ragweed, grass and tree pollens in adults and children 2 years of age and older.
- Relief of symptoms associated with *perennial allergic rhinitis* (PAR) due to allergens such as dust mites, animal dander and molds in adults and children 6 months of age and older.
- Treatment of the uncomplicated skin manifestations of *chronic idiopathic urticaria* (CIU) in adults and children 6 months of age and older.

Table 1: Approval History of Zyrtec® Products

Approval Date (Rx)	NDA #	Formulation	Indications	Population
Dec 8, 1995	**NDA 19-835**	**tablets 5, 10 mg**	**SAR, PAR, CIU**	**adults & children ≥ 12 y/o**
Sept 27, 1996	**NDA 20-346**	**syrup 1 mg/mL**	**SAR, PAR, CIU**	**adults & children ≥ 6 y/o**
May 15, 1998	**sNDA 19-835/S-005 sNDA 20-346/S-002**	**tablets syrup**	**SAR, PAR, CIU**	**adults children 2 to 6 y/o**
Aug 10, 2001	**NDA 21-150**	**cetirizine HCl 5 mg w/ PSE 120 mg (Zyrtec-D 12 Hr®)**	**Relief of nasal & non-nasal symptoms asso. w/ SAR or PAR**	**adults & children ≥ 12 y/o**
Oct 21, 2002	**sNDA 19-835/S-015 sNDA 20-346/S-008**	**tablets syrup**	**SAR, PAR, CIU**	**adults & children ≥ 6 m/o**
Mar 16, 2004	**NDA 21-621**	**chewable tabs 5, 10 mg**	**SAR, PAR, CIU**	***SAR:* adults & children ≥ 2 y/o *CIU & PAR:* adults & children ≥6 m/o**

PSE-Pseudoephedrine

Table 2: Recommended Dosage for Prescription Cetirizine (Zyrtec®)

Age Group	Recommended Dose
Adults & children ≥ 12 y/o	5 mg or 10 mg once daily depending on symptom severity
Children 6 to 11 y/o	5 mg or 10 mg once daily depending on symptom severity
Children 2 to 5 y/o	initial dose of 2.5 mg (½ tsp) syrup once daily. Dosage can be increased to a maximum dose of 5 mg/day, given as 1 tsp syrup once a day or ½ tsp syrup every 12 hrs, or 1 chewable tablet once daily
Children 6 months to <2 y/o	2.5 mg (½ tsp) once daily. The dose in children 12 to 23 mos. of age can be increased to a maximum dose of 5 mg/day, given as ½ teaspoon (2.5 mg) every 12 hours
Renal & Hepatic Impaired	Use the lower recommended dose, i.e., • patients ≥ 12 y/o should use 5 mg once daily • patients aged 6 to 11 y/o, use the lower recommended dose • <6 y/o not recommended
Geriatric Patients ≥ 77 y/o	5 mg once daily

In this submission, Pfizer, Inc./McNeil Consumer Healthcare is seeking for the approval of cetirizine (Zyrtec®) tablets, syrup and chewable tablets for over-the-counter (OTC) use. The proposed indications will be similar to the already approved cetirizine Rx indications. This drug would offer consumers additional treatment options for the OTC treatment of allergic rhinitis and hives. The proposed indications for this drug are similar to the indications of the currently marketed second generation antihistamine, loratadine (Claritin®, Alavert®) for OTC use.

2.2 Currently Available Treatment for Indications

There are other currently available medical treatments for the relief of allergic rhinitis symptoms. These are the first and second generation H_1-antagonist antihistamines marketed both prescription and OTC. The only second-generation antihistamine currently available for OTC use is loratadine, 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. Fexofenadine (Allegra®) is another second generation antihistamine used for the same indication but is currently available for prescription use only.

The first generation antihistamine products available for OTC use are either 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:[1] 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 NDA approval process if the formulation is other than that

[1] 21CFR 341.12

specified in the monograph (e.g., extended-release) or if marketed in combination with a non-monograph ingredient.

The indications for antihistamines in the monograph[2] include: "*Temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever or other upper respiratory allergies or allergic rhinitis*". Monograph antihistamines are generally labeled down to 6 years old, however, there is a professional labeling provided to health professionals but not to the general public for the use of antihistamines in children under 6 years of age.

Clemastine (Tavist®, Allerhist®), a first generation antihistamine, was approved under an NDA and was originally approved as a prescription-only drug in 1977 but has been switched to OTC status in 1997.

2.3 Availability of Proposed Active Ingredient in the United States

Cetirizine has been available in the United States since 1995, and a cetirizine/pseudoephedrine combination product since 2001. There are no other marketed products containing cetirizine hydrochloride for OTC use in the United States.

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.[3]

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) 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. So far, there has been no reports of the Torsades de Pointes with cetirizine as the single suspect drug.

2.5 Presubmission Regulatory Activity

On June 27, 2006, a meeting was held between the sponsor and the Agency to discuss the necessary data and information to support the marketing of Zyrtec® products from prescription to over-the-counter status (Rx-to-OTC switch) including the OTC labeling for use in children 6 months of age and older for the indication of allergic rhinitis and hives relief. The Agency expressed concerns about the ability of parents/caregivers to diagnose PAR in children 6 months to 2 years of age and/or diagnose hives in children ages 2 to 6 years old without the supervision of a physician. The sponsor

2 21CFR 341.72
3 Clinical Pharmacology Online accessed 8-1-07.

was advised that the appropriateness of OTC labeling down to the age of 6 months for the allergic rhinitis and hives indications will be a review issue (see meeting minutes entered in DFS). Based on discussions at the Nonprescription Advisory Committee meeting dated May 11, 2001 (http://www.fda.gov/ohrms/dockets/ac/cder01.htm), 6 years of age was chosen as the minimum age for the nonprescription hives indication even though at that time prescription loratadine was approved for children less than 6 years old for hives.

On January 16, 2007, the sponsor submitted the following NDA and supplement NDAs:

- 22-155: Zyrtec® syrup 1mg/ml (NDA 20-346 remains prescription)
- 19-835/S-022: Zyrtec® tablets, 5 & 10 mg
- 21-621/S-005: Zyrtec® chewable Tablets, 5 & 10 mg
- 21-150/S-007: Zyrtec-D 12 Hr® tablets (this NDA will be the subject of a separate review)

There are no new indications being proposed for either the single ingredient or combination products. The sponsor is seeking for an Rx-to-OTC switch of the syrup formulation for children aged 2 years and older for allergic rhinitis, and for children 6 years and older for urticaria/hives relief. Note that the Zyrtec syrup formulation which was originally approved under NDA 20-346 is being referenced to support NDA 22-155 (a new NDA). NDA 20-346 will remain prescription for the indication of hives/urticaria relief in less than 6 years of age. Therefore, the proposed indications for the above applications for OTC marketing will be similar to the already approved prescription indications for cetirizine with a narrower age indication in children:

- relief of allergic rhinitis(AR) symptoms in adults and children 2 years and older
- relief of uncomplicated hives in adults and children 6 years and older

Allergic rhinitis is an OTC indication that consumers can self-diagnose and treat. The Agency has determined that no new clinical studies would be required to support the OTC switch for the allergic rhinitis/hay fever indication because of the extensive pre-approval and post-approval database for this drug. In addition, data from clinical studies previously performed to support the original approval of these products supports the efficacy of cetirizine in the treatment of symptoms of allergic rhinitis and chronic idiopathic urticaria (hives).

2.6 Other Relevant Background Information

The non-clinical development of cetirizine was begun in Europe by UCB, a Belgian pharmaceutical company. Following the completion of sufficient studies to demonstrate antihistaminic activity and acceptable toxicity, the clinical development was initiated. The initial studies of H-1 blocking activity examined this drug's ability to inhibit histamine-induced wheal and flare of the skin. Cetirizine has been marketed globally for almost 20 years (International Birthdate: Belgium, 1986). It was first available as a prescription product in other countries; it is now available for OTC use in adults and children two years and older. UCB Pharma is a sponsor of all cetirizine approvals and

submissions in more than 100 countries; the product has either OTC (or global equivalent) or general sales status in 46 of these countries. Cetirizine formulations are marketed under the trade name Zyrtec®, Reactine®, etc. Cetirizine is currently available for prescription use in the U.S., Italy and Venezuela.

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. When the committee members were asked question, "Does cetirizine have a safety profile acceptable for OTC marketing; i.e., can it be used safely without a learned intermediary?" There were "*19-Yes*" and "*4-No*" votes.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The sponsor makes reference to the applications from the original NDA submissions of the single-ingredient prescription cetirizine products for the Chemistry, Manufacturing and Controls (CMC) information. See Chemistry review for details.

Microbiology review was not necessary for these applications.

3.2 Animal Pharmacology/Toxicology

There are no new data or toxicology information submitted with this NDA. The sponsor refers to the Nonclinical Pharmacology and Toxicology information in their previously submitted NDAs for the single-ingredient prescription cetirizine products. The following information is reflected in the prescribing information for cetirizine:

PRECAUTIONS section, Carcinogenesis, Mutagenesis and Impairment of Fertility:

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 dose in adults on a mg/m^2 basis, or approximately 7 times the maximum recommended daily oral dose in infants on a mg/m^2 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 maximum recommended daily oral dose in adults on a mg/m^2 basis, or approximately 3 times the maximum recommended daily oral dose in infants on a mg/m^2 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 maximum recommended daily oral dose in adults on a mg/m^2 basis, or approximately equivalent to the maximum recommended daily oral dose in infants on a mg/m^2 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 maximum recommended daily oral dose in adults on a mg/m^2 basis)."

In preclinical studies, the acute minimal lethal oral doses were 237 mg/kg in mice (approximately 95 times the maximum recommended daily oral dose in adults on a mg/m^2 basis, or approximately 40 times the maximum recommended daily oral dose in infants on a mg/m^2 basis) and 562 mg/kg in rats (approximately 460 times the maximum recommended daily oral dose in adults on a mg/m^2 basis, or approximately 190 times the maximum recommended daily oral dose in infants on a mg/m^2 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 are no new clinical studies conducted by the sponsor to support these applications. The clinical data utilized in this review include summaries of efficacy and safety data from clinical trials conducted to support the prescription approval of the original single-ingredient cetirizine applications: NDAs 20-346 (Zyrtec syrup), 19-835 (Zyrtec tablets) and 21-621 (Zyrtec chewable tablets) and worldwide postmarketing safety data. The integrated review of safety information for the three single-ingredient cetirizine products submitted by the sponsor were essentially identical. The sponsor also refers to their approved prescription applications for information on chemistry, nonclinical, human pharmacokinetics and bioavailability.

4.2 Tables of Clinical Studies

There were no new clinical studies performed to support these applications. The sponsor makes reference to the clinical studies (pivotal and supportive) that led to the approval of cetirizine for prescription use. See table A-1 for a list of pivotal studies submitted under the original NDA applications.

4.3 Review Strategy

The data from clinical trials submitted to support the Rx-to-OTC switch of cetirizine have been previously submitted and evaluated for safety by the Agency. It has been previously determined that these products are safe and effective as prescription drugs for their respective indications. The efficacy of these NDAs will be evaluated by the Division of Pulmonary and Allergy Products (DPAP). This review will evaluate the safety of cetirizine for OTC use. This safety review will focus primarily on the new information accumulated since the initial approval of the drug in 1995.

This safety review includes an analysis of all post marketing serious adverse events including information from:

- Pfizer's Drug Safety Database
- Spontaneous Reporting System (SRS) and Adverse Event Reporting System (AERS)
- World Health Organization (WHO) International Drug Monitoring Program
- Toxic Exposure Surveillance System (TESS) database maintained by the American Association of Poison Control Centers (AAPCC)
- Drug Abuse Warning Network (DAWN) database
- Medical literature

A reviewer from the Division of Nonprescription Regulation Development (DNRD) will be reviewing the OTC label in detail.

4.4 Data Quality and Integrity

This is an Rx-to-OTC switch without any new clinical studies; therefore, no DSI inspection was requested.

4.5 Compliance with Good Clinical Practices

There were no new clinical studies performed or original study reports submitted to support these applications. However, for the 25 clinical trials previously conducted to support the prescription marketing of cetirizine, the sponsor states that the 24 studies sponsored by Pfizer were conducted in accordance with the Good Clinical Practice Guidelines (21 CFR 50, 21 CFR 56, 21 CFR 312) and the current ICH Good clinical Practices. One study was sponsored by UCB and conducted in Europe in accordance to local regulations.

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.

5 CLINICAL PHARMACOLOGY

There is no new clinical pharmacology information submitted with these submissions. The sponsor refers to the information submitted to their prescription cetirizine to support these NDAs. The clinical pharmacology information in the following sections is reflected in the prescribing information for cetirizine.

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. The following pharmacokinetics (pk) information below can be found in the prescription label for cetirizine.

Cetirizine was rapidly absorbed with a time to maximum concentration (Tmax) of approximately 1 hour following oral administration of tablets, chewable tablets or syrup in adults. Comparable bioavailability was found between the tablet and syrup dosage forms. Comparable bioavailability was also found between the (Zyrtec®) tablet and chewable tablet taken with or without water. When healthy volunteers were administered multiple doses of cetirizine (10 mg tablets once daily for 10 days), a mean peak plasma concentration (Cmax) 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 Tmax was delayed by 1.7 hours and 2.8 hours respectively, and Cmax was decreased by 23% and 37%, respectively in the presence of food.

The mean plasma protein binding of cetirizine is 93%, independent of concentration in the range of 25-1000 ng/mL, which includes the therapeutic plasma levels observed. A mass balance study in 6 healthy male volunteers indicated that 70% of the administered radioactivity was recovered in the urine and 10% in the feces. Approximately 50% of the radioactivity was identified in the urine as unchanged drug. Cetirizine is metabolized to a limited extent by oxidative O-dealkylation to a metabolite with negligible antihistaminic activity, the enzyme or enzymes responsible for this metabolism have not been identified. The mean elimination half-life in 146 healthy volunteers across multiple pharmacokinetic studies was 8.3 hours and the apparent total body clearance for cetirizine was approximately 53 mL/min.

Pharmacokinetic interaction studies with cetirizine in adults were conducted with pseudoephedrine, antipyrine, ketoconazole, erythromycin and azithromycin. No interactions were observed. 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.

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

Pediatric Patients
In pediatric patients, when 7 to 12 y/o children received a single, 5-mg oral cetirizine capsule, the mean Cmax was 275 ng/mL. Based on cross-study comparisons, the weight-normalized, apparent total body clearance was 33% greater and the elimination half-life was 33% shorter in this pediatric population than in adults. In pediatric patients 2 to 5 y/o who received 5 mg of cetirizine, the mean Cmax was 660 ng/mL. Based on cross-study comparisons, the weight-normalized apparent total body clearance was 81 to 111% greater and the elimination half-life was 33 to 41% shorter in this pediatric population than in adults. In pediatric patients aged 6 to 23 months who received a single dose of 0.25 mg/kg cetirizine oral solution (mean dose 2.3 mg), the mean Cmax was 390 ng/mL. Based on cross-study comparisons, the weight-normalized, apparent total body clearance was 304%

greater and the elimination half-life was 63% shorter in this pediatric population compared to adults. The average $AUC_{(0-t)}$ in children 6 months to <2 years of age receiving the maximum dose of cetirizine solution (2.5 mg twice a day) is expected to be two-fold higher than that observed in adults receiving a dose of 10 mg cetirizine tablets once a day.

Geriatric Patients
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 decrease renal function. A dose adjustment may be necessary in patients 77 years of age and older.

Medical Officer Comments: A study [no. 85-N-0073: (CP-8)] was conducted to compare serum and urine levels after administration of single dose of cetirizine 10 mg capsules to healthy volunteers of different ages. The objective of the study was to determine the pharmacokinetics of cetirizine in subjects of different ages, especially the geriatric population. A total of 30 volunteers 37 to 86 years old were assigned to two groups:

- *<65 y/o (called adult group): 14 subjects, 6 males and 8 females (Mean age: 53 ± 9 years)*
- *>65y/o (called geriatric group): 7 males and 9 females (Mean age: 77 ± 5 years)*

The results have shown that there was a significant differences in AUC, Cmax and T½ between the adult and geriatric groups. The extent of absorption in the (AUC) for the geriatric group was about 70% more when compared to the adult group. An increase of about 20% was seen in the Cmax for the geriatric group compared to the adult group. These differences were significantly different. Therefore, it was concluded that the pharmacokinetics profile of cetirizine for the geriatric age group (>65 y/o) was considerably different than the profile obtained for the adult group (<65 y/o) in that the normal geriatric subjects cleared the drug slower than the normal adult volunteers.

In addition, it was also noted that females had a higher mean AUC and mean Cmax values when compared to males (17% and 26% respectively).

Table 3: Study No. 85-N-0073 (CP-8)
Pharmacokinetics Profile in Healthy Adults and Geriatric Subjects

Parameter	Adult Subjects	Geriatric Subjects	p-value
AUC (0-72), ng.hr/ml	3317 (903)	5593 (1773)	0.01
AUC (0-inf), ng.hr/ml	3318 (903)	5653 (1824)	0.01
C max, ng/ml	384 (103)	460 (59)	0.02
T max, hr	1.0 (0.5)	0.9 (0.3)	0.55
t 1/2, hr	7.4 (1.6)	11.0 (3.0)	0.01

From NDA 19-835 Action Package filed in DFS

Renal Impairment
In patients with renal impairment, the kinetics of cetirizine were studied following multiple, oral, 10-mg daily doses of cetirizine for 7 days in 7 normal volunteers (creatinine clearance 89-128 mL/min), 8 patients with mild renal function impairment (creatinine clearance 42-77 mL/min) and 7 patients with moderate renal function impairment (creatinine clearance 11-31 mL/min). The pk of cetirizine were 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.

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. Dosing adjustment may be necessary in patients with hepatic impairment.

5.2 Pharmacodynamics

There are no new pharmacodynamic data submitted with this NDA. The following information is included in the prescription label for cetirizine.

Studies in 69 adult normal volunteers (aged 20 to 61 years) showed that cetirizine at doses of 5 and 10 mg strongly inhibited the skin wheal and flare caused by the intradermal injection of histamine. The onset of this activity after a single 10-mg dose occurred within 20 minutes in 50% of subjects and within one hour in 95% of subjects; this activity persisted for at least 24 hours. Cetirizine at doses of 5 and 10 mg also strongly inhibited the wheal and flare caused by intradermal injection of histamine in 19 pediatric volunteers (aged 5 to 12 years) and the activity persisted for at least 24 hours. In a 35-day study in children aged 5 to 12, no tolerance to the antihistaminic (suppression of wheal and flare response) effects of cetirizine was found. In 10 infants 7 to 25 months of age who received 4 to 9 days of cetirizine in an oral solution (0.25 mg/kg bid), there was a 90% inhibition of histamine-induced (10 mg/mL) cutaneous wheal and 87% inhibition of the flare 12 hours after administration of the last dose. The clinical relevance of this suppression of histamine-induced wheal and flare response on skin testing is unknown.

The effects of intradermal injection of various mediators or histamine releasers were also inhibited by cetirizine, as was response to a cold challenge in patients with cold-induced urticaria. In mildly asthmatic subjects, cetirizine at 5 to 20 mg blocked bronchoconstriction due to nebulized histamine, with virtually total blockade after a 20-mg dose. In studies conducted for up to 12 hours following cutaneous antigen challenge, the late phase recruitment of eosinophils, neutrophils and basophils, components of the allergic inflammatory response, was inhibited by cetirizine at a dose of 20 mg.

In four clinical studies in healthy adult males, no clinically significant mean increases in QTc were observed in cetirizine treated subjects. In the first study, a placebo-controlled crossover

trial, cetirizine doses up to 60 mg per day, 6x the maximum clinical dose were given for 1 week, and no significant mean QTc prolongation occurred. In the second study, a crossover trial, cetirizine 20 mg and erythromycin (500 mg every 8 hours) were given alone and in combination. There was no significant effect on QTc with the combination or with cetirizine alone. In the third trial, also a crossover study, cetirizine 20 mg and ketoconazole (400 mg/day) were given alone and in combination. Cetirizine caused a mean increase in QTc of 9.1 msec from baseline after 10 days of therapy. Ketoconazole also increased QTc by 8.3 msec. The combination caused an increase of 17.4 msec, equal to the sum of the individual effects. Thus, there was no significant drug interaction on QTc with the combination of cetirizine and ketoconazole. In the fourth study, a placebo-controlled parallel trial, cetirizine 20 mg was given alone or in combination with azithromycin (500 mg as a single dose on the first day followed by 250 mg once daily). There was no significant increase in QTc with cetirizine 20 mg alone or in combination with azithromycin.

5.3 Exposure-Response Relationships

There is no new exposure-response relationship information submitted with these applications.

6 INTEGRATED REVIEW OF EFFICACY

There were no new efficacy trials for the current single-ingredient cetirizine NDAs submitted. Reference is made by the sponsor to their previously submitted single-ingredient cetirizine NDAs 19-835, 20-346 and 21-621 for efficacy information in this Rx-to-OTC switch.

The sponsor has reviewed and analyzed 25 clinical studies, which establish the efficacy of 5 mg and 10 mg per day doses of cetirizine in the treatment of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), and chronic idiopathic urticaria (CIU) (see Table A-1 in the Appendix section for a list of studies). All studies were conducted in the United States (US), with the exception of study A160, a European trial conducted by UCB in children 2 to 6 years of age. The 25 studies include 15 pivotal trials and 10 supportive trials.

See the Clinical Efficacy Review from the Division of Pulmonary and Allergy Products.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This safety review addresses single-ingredient cetirizine (Zyrtec®) only; the safety of cetirizine/ pseudoephedrine combination product (Zyrtec-D®) will be reviewed separately. Information regarding the safety of cetirizine for the proposed indications has been previously submitted to the approved prescription NDAs for single-ingredient cetirizine products. The sponsor provided an integrated review of safety that included safety information from clinical trials and postmarketing databases. The clinical data utilized in the review of safety include:

- Summaries of safety data (SAEs) from clinical trials previously submitted and evaluated for safety to support the prescription approval of single-ingredient cetirizine applications
- Current prescription labels (U.S.) and foreign OTC labels for cetirizine
- Current prescription and OTC labels for loratadin.
- Proposed cetirizine OTC labels including package inserts
- Analysis of all post marketing serious adverse events received by Pfizer (January 1986 to January 2007)
- A report summarizing adverse event reporting to the FDA from the Spontaneous Reporting System (SRS) and the Adverse Event Reporting System (AERS) (1969 to March 31, 2006)
- Analysis of reports to the American Association of Poison Control Centers' Toxic Exposure Surveillance System (TESS) database (1995 to 2005)
- A report of the Drug Abuse Warning Reports (DAWN) for cetirizine (1995 to September 2006)
- A report summarizing adverse event reporting to the World Health Organization's (WHO) International Drug Monitoring Program
- A review of medical literature relevant to the safety of cetirizine (1966 to July 2006)

A summary of consolidated serious adverse events (SAEs) was provided by the sponsor from company sponsored clinical trials conducted in support of cetirizine submissions from January 1, 1986 and May 10, 2006. There were a total of 25 clinical studies conducted that established the efficacy of 5 mg and 10 mg per day doses of cetirizine in the treatment of SAR, PAR, and CIU. These clinical trials have previously been submitted to and evaluated for safety by the Agency. All studies were conducted in the US, with the exception of a study in children 2 to 6 years of age which was conducted in Europe. The sponsor states that many were UCB Pharma trials completed more than 10 years ago and in these studies, data, such as protocol number and causality assessment, were not available. Adverse events for cetirizine will be discussed in the following subsections.

7.1.1 Deaths

There were seven deaths reported among the 223 serious adverse events (SAEs) reported in clinical trials using cetirizine. In two of the reports, the patients were taking placebo and two cases involved pregnancy which will be discussed in section 7.1.14.

- Case 9505901 was a 75-year-old female with a history of chronic respiratory insufficiency, who accidentally fell, had a cranial injury and died that night.
- Case 9505902 was a 72-year-old male with a history of cerebrovascular insufficiency, who had a sudden coma and died shortly thereafter.
  *The above two cases were from the same investigator of the "long-term (6 month) study of the efficacy and tolerance of cetirizine in patients with senile pruritus". Both of these cases were assessed by the investigator as not related to the study drug.
- Case N-00615 provided limited information. This patient with lymphoma and hepatitis had liver enzyme abnormalities while taking cetirizine. As per the sponsor, liver failure was probably due to lymphoma, the investigator did not provide a causality assessment.
- Two cases (N-00034 and N-01075) from two separate protocols died of a myocardial infarction while taking placebo.

Deaths reported during postmarketing will be discussed in section 7.1.17 of this review.

7.1.2 Other Serious Adverse Events

The sponsor searched its corporate safety database, ARISg, for SAE cases from sponsored cetirizine clinical trials received by Pfizer and entered into the databases between January 1, 1986 and May 10, 2006. Controlled and uncontrolled clinical trials were conducted in the United States and Canada which included approximately 7,900 patients (6,000 aged 12 years and older, more than 1,300 aged 6 to 11 y/o, 168 aged 2 to 5 y/o, 399 aged 12 to 24 months, and 42 aged 6 to 11 months old).

There were 223 serious AE reports (SAEs) from clinical trials (including 7 deaths as discussed in section 7.1.1) coded with 404 terms for single ingredient oral cetirizine. The sponsor states that many were UCB Pharma trials completed more than 10 years ago in which studies, data, such as protocol number and causality assessment were not available.

There were 148 cases (66%) in patients under 12 years of age, 102 of these (45% of total SAEs) were from the Early Treatment of the Atopic Child clinical trial (ETAC Protocol #9322). It is reported that majority of events from this trial occurred after the study drug was discontinued and in many reports, the events occurred 6 months or longer after study drug was stopped. These adverse event terms were assessed by the investigator and/or the company as not related to study drug but related to either an intercurent illness or a pre-existing condition. The sponsor stated that many of the UCB Pharma trials were completed more than 10 years ago and in these studies, data, such as protocol number and causality assessment, were not available.

Of the 223 SAEs, 57% were in males, 40% were in females and unknown gender in 3%; the mean age was 14.5 years. There were 93 (42%) reports in the 2 to <6 year age group, 49 (22%) in the 18 to 64 year age group, and 39 (17%) in the 12 month to <2 year age group. Majority (174, 78%) of the patients recovered or were recovering, 8 (3.6%) did not recover; 7 (3%) died. See table below.

Table 4: Characteristics of Serious Cetirizine Clinical Trial Cases

		Cetirizine Overall
Total Number of Case Reports		223
Total Number of Adverse Event Terms		404
Age, years	N	216
	Mean[a]	14.48
	Range	1-88
		Count (%)
Age Group, years	12 months to <2 years	39 (17.49)
	2 to <6 years	93 (41.70)
	6 to <12 years	16 (7.17)
	12 to <18 years	8 (3.59)
	18 to <65 years	49 (21.97)
	65 to <77 years	7 (3.14)
	> 77 years	4 (1.79)
	Unknown	7 (3.14)
Gender	Female	89 (39.91)
	Male	127 (56.95)
	Unknown	3 (7)
Case Seriousness	Serious	216 (96.86)
	Death	7 (3.14)
Report Type	Clinical Study	223 (100.00)
Case Outcome	Unknown	10 (4.48)
	Not recovered	8 (3.59)
	Recovering	9 (4.04)
	Recovered	165 (73.99)
	Recovered with sequelae	1 (0.45)
	Not applicable[b]	23 (10.31)
	Death	7 (3.14)
Report Source[c]	Patient/consumer	1 (0.45)
	Pfizer Study	21 (9.42)
	Non-Pfizer Study	200 (89.69)
	Literature	1 (0.45)

a Mean age was based on the number of cases in which age was reported (not total number of cases).
b Not applicable – reflects data migrated from historical databases.
c Report Source – where multiple report sources are identified, only one is recorded in this table.
Table adapted from sponsor's submission ITEM 8, Volume 33 Page 14

The most commonly reported serious adverse events from the sponsor clinical trial database (N=216) were asthma (36, 9.2%); vomiting (14, 3.6%); pyrexia (14, 3.6%) and bronchitis (11, 2.8%). Below is a table of serious adverse events with a reporting rate of 1% or greater among all 388 AE terms reported for the 216 serious clinical trial AE reports (excluding deaths).

Table 5: Most Commonly Reported Serious AE terms at a Rate ≥1% Among all 388 AE terms from Clinical Trials (N=216)

SAE	Rate
asthma	36 (9.2%)
vomiting	14 (3.6%)
pyrexia	14 (3.6%)
bronchitis	11 (2.8%)
gastroenteritis	9 (2%)
wheezing	9 (2%)
cough	9 (2%)
abdominal pain	8 (2 %)
dehydration	7 (1.8%)
otitis media	6 (1.5%)
eczema	6 (1.5%)
viral infection	5 (1.2%)
urinary tract infection	5 (1.2%)
diarrhea	5 (1.29%)
fall	5 (1.2%)
toxic skin eruption	5 (1.2%)
dyspnea	4 (1%)
status asthmaticus	4 (1%)
constipation	4 (1%)
accidental overdose	4 (1%)
alanine aminotransferase increased	4 (1%)
asparte aminotranferase increased	4 (1%)
febrile convulsion	4 (1%)
cytolytc hepatitis	4 (1%)

Reviewer's table

The following is the causality assessment of the SAEs:

Table 6: Causality Assessment of SAEs

	Investigator	Company
not related	88 (39%)	199 (89%)
unlikely	78 (35%)	1 (0.5%)
unknown	53 (24%)	2 (1%)
possibly related	2 (1%)	4 (2%)
related	1 (0.5%)	
not probably	1 (0.5%)	
not applicable		17 (7.5%)[a]
Total	**223 (100%)**	**223 (100%)**

a: randomized to placebo
Reviewer's table

Of the SAEs, the Investigator's causality assessment was reported as not related in 88 (39%) of the reports and unlikely in 78 (35%) while the Company's causality assessment was not related in majority 199 (89%) and not applicable in 17 (7.6%) of the cases. See table above.

7.1.3 Dropouts and Other Significant Adverse Events

There were no information on dropouts or other significant adverse events included in the sponsor's summary of serious adverse events.

7.1.4 Other Search Strategies

This section is not applicable.

7.1.5 Common Adverse Events

Controlled and uncontrolled clinical trials were conducted in the United States and Canada which included more than 6,000 patients aged 12 years and older, more than 3,900 received Zyrtec at doses of 5 to 20 mg per day. Most adverse reactions reported were mild or moderate. These trials were conducted for the approval of prescription Zyrtec; this adverse event information can be found in the adverse event section of the prescription label for Zyrtec.

The most commonly reported adverse events in patients aged 12 years and older (n=2034 Zyrtec, n=1612 placebo) in clinical trials using a maximum dose of 10 mg were somnolence, fatigue, dry mouth, pharyngitis and dizziness (see table below). The most common adverse event that occurred more frequently on placebo than Zyrtec was somnolence. The incidence of somnolence associated with Zyrtec was dose related; 6% in placebo, 11% at 5 mg and 14% at 10 mg. Fatigue and dry mouth also appeared to be treatment-related adverse reactions. There were no differences by age, race, gender or by body weight with regard to the incidence of adverse reactions. The table below lists adverse events in patients aged 12 years and older which were reported for Zyrtec 5 and 10 mg in controlled clinical trials in the United States and that were more common with Zyrtec than placebo.

Table 7. AEs More Common with Zyrtec than Placebo in ≥12 years old (Max Dose of 10mg) at Rates of ≥ 2%

Adverse Event	Zyrtec (N=2034)	Placebo (N=1612)
Somnolence	13.7	6.3
Fatigue	5.9	2.6
Dry Mouth	5.0	2.3
Pharyngitis	2.0	1.9
Dizziness	2.0	1.2

Adapted from Zyrtec Rx label

Headache and nausea occurred in more than 2% of the patients, but were more common in placebo patients.

Pediatric studies were also conducted in more than 1,300 pediatric patients aged 6 to 11 years; more than 900 were treated with Zyrtec at doses of 1.25 to 10 mg per day (controlled and uncontrolled clinical trials). The duration of treatment ranged from 2 to 12 weeks.

See table below for a list of adverse events which were reported for Zyrtec 5 and 10 mg in pediatric patients aged 6 to 11 years in placebo-controlled clinical trials in the United States and were more common with Zyrtec than placebo. Of these, 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.

Table 8. AEs in Pediatric Patients 6 to 11 y/o which Occurred at a Frequency of ≥ 2% (5-mg or the 10-mg) Zyrtec Group, and more Frequently than in the Placebo Group (U.S Trials)

Adverse Events		Zyrtec	
	Placebo (N=309)	5 mg (N=161)	10 mg (N=215)
Headache	12.3%	11.0%	14.0%
Pharyngitis	2.9%	6.2%	2.8%
Abdominal pain	1.9%	4.4%	5.6%
Coughing	3.9%	4.4%	2.8%
Somnolence	1.3%	1.9%	4.2%
Diarrhea	1.3%	3.1%	1.9%
Epistaxis	2.9%	3.7%	1.9%
Bronchospasm	1.9%	3.1%	1.9%
Nausea	1.9%	1.9%	2.8%
Vomiting	1.0%	2.5%	2.3%

Placebo-controlled trials up to 4 weeks duration included 168 pediatric patients aged 2 to 5 years who received cetirizine, the majority of whom received single daily doses of 5 mg. The adverse experiences reported in pediatric patients aged 2 to 5 years in placebo-controlled trials were reported to be qualitatively similar in nature and generally similar in frequency to those reported in trials with children aged 6 to 11 years.

7.1.6 Less Common Adverse Events

The following are the adverse events that were observed infrequently (<2%), in almost 4,000 adults and children 12 years and older, or in 659 pediatric patients aged 6 to 11 years who received cetirizine 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.

Autonomic Nervous System: anorexia, flushing, increased salivation, urinary retention.
Cardiovascular: cardiac failure, hypertension, palpitation, tachycardia.
Central and Peripheral Nervous Systems: abnormal coordination, ataxia, confusion, dysphonia, hyperesthesia, hyperkinesia, hypertonia, hypoesthesia, leg cramps, migraine, myelitis, paralysis, paresthesia, ptosis, syncope, tremor, twitching, vertigo, visual field defect.
Gastrointestinal: abnormal hepatic function, aggravated tooth caries, constipation, dyspepsia, eructation, flatulence, gastritis, hemorrhoids, increased appetite, melena, rectal hemorrhage, stomatitis including ulcerative stomatitis, tongue discoloration, tongue edema.
Genitourinary: cystitis, dysuria, hematuria, micturition frequency, polyuria, urinary incontinence, urinary tract infection.
Hearing and Vestibular: deafness, earache, ototoxicity, tinnitus.

Metabolic/Nutritional: dehydration, diabetes mellitus, thirst.
Musculoskeletal: arthralgia, arthritis, arthrosis, muscle weakness, myalgia.
Psychiatric: abnormal thinking, agitation, amnesia, anxiety, decreased libido, depersonalization, depression, emotional lability, euphoria, impaired concentration, insomnia, nervousness, paroniria, sleep disorder.
Respiratory System: bronchitis, dyspnea, hyperventilation, increased sputum, pneumonia, respiratory disorder, rhinitis, sinusitis, upper respiratory tract infection.
Reproductive: dysmenorrhea, female breast pain, intermenstrual bleeding, leukorrhea, menorrhagia, vaginitis.
Reticuloendothelial: lymphadenopathy.
Skin: acne, alopecia, angioedema, bullous eruption, dermatitis, dry skin, eczema, erythematous rash, furunculosis, hyperkeratosis, hypertrichosis, increased sweating, maculopapular rash, photosensitivity reaction, photosensitivity toxic reaction, pruritus, purpura, rash, seborrhea, skin disorder, skin nodule, urticaria.
Special Senses: parosmia, taste loss, taste perversion.
Vision: blindness, conjunctivitis, eye pain, glaucoma, loss of accommodation, ocular hemorrhage, xerophthalmia.
Body as a Whole: accidental injury, asthenia, back pain, chest pain, enlarged abdomen, face edema, fever, generalized edema, hot flashes, increased weight, leg edema, malaise, nasal polyp, pain, pallor, periorbital edema, peripheral edema, rigors.

Occasional instances of transient, reversible hepatic transaminase elevations have occurred during cetirizine therapy. Hepatitis with significant transaminase elevation and elevated bilirubin in association with the use of cetirizine has been reported.

The Adverse Reactions section of the prescription cetirizine label states that in the *post-marketing* period, the following additional rare, but potentially severe adverse events have been reported: aggressive reaction, anaphylaxis, cholestasis, convulsions, glomerulonephritis, hallucinations, hemolytic anemia, hepatitis, orofacial dyskinesia, severe hypotension, stillbirth, suicidal ideation, suicide and thrombocytopenia.

7.1.7 Laboratory Findings

During cetirizine therapy, 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

No information was provided on vital signs in these Rx-to-OTC switch submissions.

7.1.9 Electrocardiograms (ECGs)

No information was provided on electrocardiograms in these Rx-to-OTC switch submissions.

7.1.10 Immunogenicity

Not applicable to these submissions.

7.1.11 Human Carcinogenicity

There are no human carcinogenicity issues related to cetirizine.

7.1.12 Special Safety Studies

There were no special safety studies conducted for these Rx-to-OTC switch submissions.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

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

The Drug Abuse Warning Network (DAWN) Database reveals that from 1995 to 2002, the (old) DAWN sample hospital emergency departments reported 23,939 cases involving antihistamines. The rate of drug-related hospital visits for antihistamines was estimated at 1 to 2 cases per 100,000 population per year; there were no cases specifically for cetirizine, fexofenadine, and loratadine. No mention of cetirizine, loratadine or fexofenadine was found in the 2000, 2001 and 2002 DAWN mortality data reports.

From 2003 to September 2006, emergency departments at (new) DAWN sample hospitals reported 6,096 antihistamine-related cases. Over this period, cetirizine accounted for 15%, fexofenadine 12% and loratadine 19%, of reported antihistamine cases. Their share of antihistamine cases varied from year to year and followed no pattern. There was no mention of cetirizine, loratadine, and fexofenadine in the 2003 DAWN mortality data report.

Medical Officer Comments: Both the old and new 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. 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/m^2 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/m^2 basis). There are, however, 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.

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/m^2 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 two deaths involving pregnancy among 223 serious adverse events reported in clinical trials and 10 reported deaths from postmarketing data related to drug exposure during pregnancy.

Deaths related to drug exposure during pregnancy in clinical trials:

- Case 9404367 was inadvertently coded in the database as a company-sponsored clinical trial. A 25 y/o female was enrolled in a clinical trial for 9 days and then found to be pregnant a month later. She was taking other medications including flunitrazepam[4], a contraceptive (unspecified) and a topical steroid. Ten days after learning she was pregnant, the death of twin fetuses was discovered. A curetting was performed.
- Case 9500761 (age not specified) with asthma was treated with cetirizine 15 mg BID for one month. The patient discovered she was pregnant; treatment was discontinued. During the pregnancy, she was treated with inhaled salbutamol and oral theophylline SR. On the seventh month of pregnancy, she developed eclampsia, was hospitalized for six days and treated with methyldopa and diazepam. Two weeks later, a stillborn child was delivered. The investigator assessed the event as no relationship to cetirizine.

Deaths related to drug exposure during pregnancy during postmarketing:

There were 4 fetuses that had congenital anomalies for which pregnancies were electively terminated by the mother:

- The first case was reported by the French Health Authority, the causality assessment with the relationship between cetirizine and the congenital anomalies was doubtful. No further detail on this case was provided.
- A 34 y/o female with allergies was treated with cetirizine 10 mg during early pregnancy. The fetus was found to have kidney malformation and rotation of the left foot on routine ultrasound. The pregnancy was electively terminated. According to the Swedish Health Authority, although there is no known teratogenic effect of cetirizine and the malformation frequency in children born after maternal use of cetirizine is normal, a causal relationship could not be excluded.
- A pregnant female with a history of two spontaneous abortions and exposure to anesthetic gasses during the pregnancy took cetirizine for several years and had an elective abortion after an echography showed left cardiac hypoplasia of the fetus. No further details were available.
- A 41y/o patient with a medical history of asthma took cetirizine, prednisone, acetylcysteine, enspiride, cefodoxime, montelukast and albuterol during her first trimester of pregnancy. The fetus was diagnosed with spina-bifida and Arnold-Chiari malformation leading to an elective abortion. No causality was provided.

4 a benzodiazepine more potent than valium

In the remaining 6 drug exposure during pregnancy cases, 3 had a causality assessment provided:

- A pregnant patient took cetirizine 10 mg daily for approximately 10 days, 3 weeks after discontinuing treatment; she delivered a stillborn (gestational age unspecified). The Danish Health Authority assessed a causality as possible.
- A patient was treated with antibiotics (fosfomycin) for cystitis in the first month of pregnancy. From the 3rd to 5th month of pregnancy, she was treated with cetirizine and minocycline for cutaneous allergy. She delivered a female with anophthalmia and esophageal atresia; infant died at 4 days of age. A teratogenic cause could not be excluded.
- A mother with thyroid deficiency took cetirizine for 10 days during the first trimester of pregnancy. At 33 weeks of gestation she delivered a female infant with Pierre Robin's Syndrome who subsequently died an hour later. The reporting physician assessed the relationship of cetirizine and the Pierre Robins' Syndrome as unlikely.

The three remaining drug exposure drug pregnancy cases are further discussed below:

- A 24 y/o pregnant woman who took cetirizine and ketoconazole during weeks 2 and 5 of pregnancy had hemolysis, elevated liver fuction tests and decreased platelets (HELLP syndrome) with fetal retardation at 25 weeks of pregnancy. She delivered a male infant who died a week later. The reporter did not provide a causality assessment.
- A pregnant female taking cetirizine 10 mg daily for pruritus. At 35 weeks of gestation, an unexplained intrauterine death was noted. The reporter did not provide a causality assessment.
- A 35 y/o female with history of five previous miscarriages used cetirizine (dose and indication unspecified) for about two weeks during the third trimester of her pregnancy, and delivered a male infant at 32 weeks. The infant was diagnosed with a severe combined immunodeficiency and died at the age of 6 months.

Medical Officer Comments: The above serious adverse events or deaths related to the exposure to cetirizine involving pregnancy were confounded with intake of concomitant medications, underlying medical conditions or had limited clinical information to assess causality. The information provided does not preclude the OTC use of cetirizine nor warrant any changes in the current label. The OTC label appropriately directs pregnant women to consult a health professional before using cetirizine.

7.1.15 Assessment of Effect on Growth

No information was submitted regarding the effect of cetirizine on growth. The proposed OTC cetirizine will not be indicated in children <2 years old.

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 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]

Summary of Human Exposure Data from the AAPCC's Toxic Exposure Surveillance System (TESS) Database

The sponsor has provided for cetirizine exposure based on data from the American Association of Poison Control Centers' (AAPCC) Toxic Exposure Surveillance System (TESS) database. The report tabulates information on all cases reported to a participating poison control center (PCC) in the United States involving a human exposure to cetirizine for 10 years (1995 to 2005).

There were a total of 48,386 exposures with 13,184 associated clinical effect (CE) terms reported from January 1995 to December 2005. Of these, 84% (40,659/48,386) were pediatric cases and 14% (6,674/48,386) were adult cases; 2% (1,053/48,386) had no age data. Unintentional exposures accounted for 89% (42,849/48,386) of the cases. This proportion was higher among pediatric cases ≤ 11 years old, 94% (38,395/40,659), than among reports for adults of 57% (3,779/6,674). There were more intentional-suspected suicide reports in the adult category 31% (2,043/6,674) compared to the pediatric category 3% (1,334/40,659) and relatively more reports of adverse reaction drug 8% (521/6,674) among adults compared to the pediatric reports 1% (454/40,659).

There were 7 (0.01%) reported deaths, all were adults and categorized as Intentional-Suspected Suicide; 5 involved multiple substance ingestions. Majority (95%) of the cases were categorized as having one of the following medical outcomes: Minimal effects, No effects, Minor effects, Nontoxic exposures and Unrelated effects. For both adult and pediatric population, the four most frequently reported clinical effects were: drowsy/lethargy 29% (3,830/13,184), agitated/ irritable 8.5% (1126/13,184), other 8% (1108/13,184) and tachycardia 8% (1075/13,184).

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

7.1.17 Postmarketing Experience

Cetirizine (Zyrtec) 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. Six reports based on post-marketing experience with cetirizine were provided in these submissions. These reports are based on data from Pfizer's AE database, FDA AERS databases, WHO Database, AAPCC TESS database, Drug Warning (DAWN) database, and a review of the medical literature.

Sponsor's Database for Postmarketing Experience

There were a total of 14,921 cases received by Pfizer involving single-ingredient cetirizine products with associated 30,508 coded adverse event (AE) terms from sources other than clinical trials entered into its database from January 1, 1980 to May 10, 2006. Majority (12,456; 83%) of the cases

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

were non-serious; 14% (2,110) were serious and 2.4% (355) were reports of death. Most (96%) were spontaneous cases from healthcare professionals (50%) or patients/consumers (43%). Forty-nine percent (49%) originated from the US, 22% from Canada, and 11% from Japan; 41% were in adults 18 to 65 years old and 13% were in children < 18 years old, age was unknown in 36% of the cases. An outcome of recovered or recovering was reported for 26% of the cases, and outcome was unknown for 43%, not recovered for 17%.

The vast majority of adverse event terms for most age categories (i.e. >12 months old) occurred within the following six System Organ Class (SOCs): General, Nervous, Skin, Gastrointestinal, Psychiatric and Respiratory. Among all 30,508 AE terms associated with all 14,921 cases, the most commonly reported AE terms were drug ineffective and somnolence. The most commonly reported AEs having > 1% rate of all terms were the following:

- General disorders and administration-site conditions:
    - **drug ineffective** (2,481; **8.13%**)
    - fatigue (659; 2.16%)
- Nervous-system disorders:
    - **somnolence** (2,389; **7.83%**)
    - dizziness (624; 2.05%)
    - headache (547; 1.79%)
- Skin and subcutaneous disorders:
    - urticaria (647; 2.12%)
    - pruritus (517; 1.70%)
    - rash (719; 2.36%)
- Immune system disorders: hypersensitivity (518; 1.70%)
- Gastrointestinal disorders: nausea (344; 1.13%)
- Psychiatric disorders: insomnia (324; 1.06%)

Table 9: AE Terms Associated with all or Nonserious Cases Reported ≥ 0.5% for Cetirizine Cases other than Clinical Trials

MedDRA SOC/ Preferred Term	Cetirizine	
	Nonserious, Count (%)[c]	Overall, Count (%)[b]
General Disorders and Administration Site Conditions	**4,937 (21.69)**	**5,957 (19.53)**
Drug ineffective[a]	2,392 (10.51)	2,481 (8.13)
Fatigue	594 (2.61)	659 (2.16)
Malaise	212 (0.93)	272 (0.89)
Drug Interaction[a]	199 (0.87)	287 (0.94)
Feeling abnormal	188 (0.83)	203 (0.67)
Irritability	130 (0.57)	148 (0.49)
Unevaluable event[a]	128 (0.56)	204 (0.67)
Oedema Peripheral	124 (0.54)	151 (0.49)
Nervous System Disorders	**4,293 (18.86)**	**5,263 (17.25)**
Somnolence[a]	2,282 (10.03)	2,389 (7.83)
Dizziness[a]	534 (2.35)	624 (2.05)
Headache	487 (2.14)	547 (1.79)
Skin and Subcutaneous Disorders	**2,437 (10.71)**	**3,014 (9.88)**
Urticaria[a]	552 (2.43)	647 (2.12)
Pruritus[a]	443 (1.95)	517 (1.69)
Rash[a]	616 (2.71)	719 (2.36)
Face Oedema	163 (0.72)	202 (0.66)
Gastrointestinal Disorders	**1,949 (8.56)**	**2,362 (7.74)**
Nausea	306 (1.34)	344 (1.13)
Dry Mouth	255 (1.12)	273 (0.89)
Abdominal Pain[a]	234 (1.03)	282 (0.92)
Diarrhoea	208 (0.91)	234 (0.77)
Vomiting	151 (0.66)	184 (0.60)
Psychiatric Disorders	**1,636 (7.19)**	**2,089 (6.85)**
Insomnia	289 (1.27)	324 (1.06)
Aggression[a]	88 (0.39)	105 (0.34)
Agitation	110 (0.48)	129 (0.42)
Anxiety	109 (0.48)	140 (0.46)
Respiratory, Thoracic and Mediastinal Disorders	**1,524 (6.70)**	**2007 (6.58)**
Cough	173 (0.76)	200 (0.66)
Rhinorrhoea	166 (0.73)	177 (0.58)
Dyspnoea[a]	171 (0.75)	261 (0.86)
Nasal Congestion	140 (0.62)	152 (0.50)
Sneezing	119 (0.52)	124 (0.41)
Investigations	**1,055 (4.64)**	**1,705 (5.59)**
Weight Increased[a]	230 (1.01)	258 (0.85)
Injury, Poisoning and Procedural Complications	**697 (3.06)**	**1,050 (3.44)**
Drug Administration Error[a]	292 (1.28)	358 (1.17)
Intentional Overdose	113 (0.50)	194 (0.64)
Immune System Disorders	**675 (2.97)**	**863 (2.83)**
Hypersensitivity	437 (1.92)	518 (1.70)
Cardiac Disorders	**386 (1.70)**	**744 (2.44)**
Palpitations	175 (0.77)	198 (0.65)
Tachycardia[a]	138 (0.61)	191 (0.63)
Vascular Disorders	**216 (0.95)**	**370 (1.21)**
Hypertension[a]	159 (0.70)	216 (0.71)
Blood and Lymphatic System Disorders	**185 (0.81)**	**352 (1.15)**
Thrombocytopenia[a]	156 (0.69)	229 (0.75)
Total No. of AE Terms	22,757	30,508
Total No. of Cases	12,456	14,921
Total No. of AE Terms/ Total No. of Cases	1.83	2.04

Adapted from Sponsor's submission Item 8 Vol 34, p 20

Medical Officer Comments: In general, the adverse events that were noted in the postmarketing safety database are similar to those noted in clinical trials. Somnolence, fatigue, dizziness and headache were also among the most common adverse events noted in the postmarketing database.

Deaths from Postmarketing Data

There were 355 reports of death; 229 (64%) were received from a source solicited through Pfizer post-marketing programs (e.g., "Pfizer for Living", "Zyrtec® [cetirizine] Disease Management Program"). The sponsor cannot determine a clear temporal relationship between the use of cetirizine and death in majority of the cases because the typical information reported in the cases was that the use of cetirizine was at unknown time and the patient was deceased at the time of the solicitation request. In addition, many of the patients had a significant underlying medical condition such as cancer, coronary artery disease, renal failure, and advanced Parkinson's disease.

Of the remaining 126/355 unsolicited reports of death, 98 were excluded from this discussion due to concurent illness or limited clinical information. A total of 10/355 of the reported death cases were related to drug exposure during pregnancy, 4 of these were fetuses that had congenital anomalies and were electively terminated by the mother; these will be discussed in section 7.1.14. The sponsor further stated that of the remaining cases, 31 were medically confirmed and one was a consumer case (total of 32 deaths).

Medical Officer Comment: There is a discrepancy in which the number of deaths was tallied. The exclusion of 98 cases from a total of 355 should result in 28 remaining cases, not 32 as reported by the sponsor. It is possible that the 4 fetal deaths electively terminated by the mother were counted twice.

Of the medically confirmed cases, 5 were children <12 years of age:

- A 3y/o female patient took cetirizine (unspecified time and indication) and experienced an unspecified cardiac arrhythmia while riding a tricycle and died. Causality assessment of reporting physician was possible.
- A male child (age unspecified) with a history of being allergic to antihistamines, who had a cortisone injection for an unknown indication, took cetirizine and had an anaphylactic reaction; he died 30 minutes later. Causality of the event with cetirizine use was assessed as probable.
- A 2 y/o male, who had taken cetirizine 2 teaspoons daily for 3 weeks fell forward while watching television and died. No further clinical information or causality assessment provided.
- A 3 y/o male was treated for a cold with cetirizine 2.5 mL for two days and a decongestant (pseudoephedrine/diphenhydramine) syrup for several doses. He died of fulminant hepatic failure associated with liver necrosis leading to death. Autopsy showed cerebral and pulmonary hypoxia with bleeding and massive liver necrosis which were assessed as being of a medical or viral origin. The reporting physician did not provide a causality assessment.
- A 6½ months old infant died of sudden infant death syndrome two days after being treated with cetirizine (dose and indication unspecified). No causality assessment was provided.

There were 16 of the medically confirmed cases identified patients over 12 years of age. Of these 16 cases, 6 provided an assessment of possible or probable and 3 of these cases where the causality was

possible or probable identified a diagnosis of Steven Johnson's syndrome (SJS). With regard to the remaining 10 medically confirmed cases, three provided a causality of unlikely related or dubious, the remaining seven medically confirmed cases, clinical details were limited and a causality assessment was not provided for any of these cases.

Medical Officer Comments: In addition to limited clinical information provided on theses cases, a clear temporal relationship between the use of cetirizine and death cannot be determined in majority of the cases. It is likely that the underlying medical conditions and/or concomitant use of multiple medications were the cause of death or contributed to the cause of death in these patients.

Adverse Events Associated with Serious Cases (Postmarketing)

There were 2,110 (14%) reported serious cases which include 7,057 AE terms (which could include both serious and non-SAE terms). The most commonly (>0.3% rate) reported serious AE terms are tabulated in table below.

Overall, the Nervous System had the highest number of adverse event terms reported with a total of 5,263 (17%) events. Among the most common serious adverse events (>1% rate), convulsion was the most frequently reported (156, 2.2%), followed by somnolence, rash, loss of consciousness, urticaria, dizziness, drug ineffective, dyspnea, drug interaction, hypersensitivity, intentional, overdose and pruritus. The table below is a list of serious adverse event terms from sources other than clinical trials that were reported at a rate of 0.3% or more.

Table 10: AE terms Associated with Serious Cases Other than Clinical Trials Reported at a Rate of at Least 0.3% for Cetirizine

MedDRA SOC/ Preferred Term	Cetirizine Count (%)[b]
Nervous System Disorders	**925 (13.11)**
Convulsion[a]	156 (2.21)
Somnolence[a]	107 (1.52)
Loss of Consciousness[a]	96 (1.36)
Dizziness[a]	90 (1.27)
Headache	60 (0.85)
Cerebral Vascular Accident[a]	39 (0.55)
Tremor	34 (0.48)
General Disorders and Administration Site Conditions	**746 (10.57)**
Drug Ineffective[a]	89 (1.26)
Drug Interaction[a]	82 (1.16)
Unevaluable Event[a]	70 (0.99)
Fatigue	65 (0.92)
Malaise	57 (0.81)
Pyrexia	55 (0.78)
Pain	37 (0.52)
Asthenia	31 (0.44)
Oedema Peripheral	26 (0.37)
Chest Pain	26 (0.37)
Investigations	**632 (8.96)**
Weight Increased[a]	28 (0.40)
Blood Cholesterol Increased	25 (0.35)
Weight Decreased	25 (0.35)
Electrocardiogram QT Prolonged	21 (0.30)
Skin and Subcutaneous Tissue Disorders	**552 (7.82)**
Rash[a]	101 (1.43)
Urticaria[a]	91 (1.29)
Pruritus[a]	74 (1.05)
Angioneurotic Oedema	39 (0.55)
Swelling Face[a]	39 (0.55)
Stephen-Johnson's Syndrome[a]	26 (0.37)
Respiratory, Thoracic and Mediastinal Disorders	**451 (6.39)**
Dyspnoea[a]	86 (1.22)
Asthma	64 (0.91)
Cough	27 (0.38)
Psychiatric Disorders	**428 (6.06)**
Confusional State	35 (0.50)
Insomnia	34 (0.48)
Depression	34 (0.48)
Anxiety	31 (0.44)
Gastrointestinal Disorders	**388 (5.50)**
Abdominal Pain [a]	47 (0.67)
Nausea	37 (0.52)
Vomiting	31 (0.44)
Diarrhoea	25 (0.35)
Injury, Poisoning and Procedural Complications	**337 (4.78)**
Drug Administration Error[a]	66 (0.94)
Intentional Overdose	78 (1.11)
Fall	31 (0.44)
Road Traffic Accident	22 (0.31)

Table continued:

Table 11: AE terms Associated with Serious Cases other than Clinical Trials Reported at a Rate of at Least 0.3% for Cetirizine

MedDRA SOC/ Preferred Term	Cetirizine Count (%)[b]
Cardiac Disorders	**311 (4.41)**
Ventricular Arrhythmia[a]	57 (0.81)
Tachycardia[a]	52 (0.74)
Arrhythmia	23 (0.33)
Palpitations	23 (0.33)
Myocardial Infarction	22 (0.31)
Surgical and Medical Procedures	**307 (4.35)**
Surgery	35 (0.50)
Hospitalization	34 (0.48)
Sinus Operation	30 (0.43)
Musculoskeletal and Connective Tissue Disorders	**278 (3.94)**
Arthralgia	25 (0.35)
Arthritis	21 (0.30)
Infections and Infestations	**239 (3.39)**
Sinusitis	24 (0.34)
Eye Disorders	**198 (2.81)**
Blindness[a]	31(0.44)
Immune System Disorders	**181 (2.56)**
Hypersensitivity	78 (1.11)
Anaphylactic Reaction	26 (0.37)
Blood and Lymphatic System Disorders	**157 (2.22)**
Thrombocytopenia[a]	70 (0.99)
Metabolissm and Nutrition Disorders	**113 (1.60)**
Diabetes mellitus	24 (0.34)
Social Circumstances	48 (0.68)
Disability	25 (0.35)
Hepatobiliary Disorders	**157 (2.22)**
Hepatitis[a]	101 (1.43)
Vascular Disorders	**134 (1.90)**
Hypertension[a]	53 (0.75)
Hypotension[a]	28 (0.40)
Congenital, Familial and Genetic Disorders	**86 (1.22)**
Congenital Anomaly	23 (0.33)
Ear Disorder	**76 (1.08)**
Deafness[a]	26 (0.37)
Total No. of AE Terms (Serious/Nonserious)	7,057
Total No. of Serious Cases	2,110
Total No. of AE Terms/ Total No. of Cases	3.34

(continued)

Sponsor's submission Item 8 Vol. 34 p.23

Medical Officer Comments: In the prescribing information for cetirizine, the following central and peripheral nervous system adverse events were observed infrequently (<2%), in either 3,982 adults and children 12 years and older or in 659 pediatric patients aged 6 to 11 years who received cetirizine in U.S. trials, including an open adult study of six months duration: abnormal coordination, ataxia, confusion, dysphonia, hyperesthesia, hyperkinesia, hypertonia, hypoesthesia, leg cramps, migraine, myelitis, paralysis, paresthesia, ptosis, syncope, tremor, twitching, vertigo, visual field defect. A causal relationship of these infrequent events with cetirizine administration

has not been established. In addition, convulsions have been reported in the post marketing experience with cetirizine as rare but potentially severe adverse event. [6]

Convulsion, somnolence, rash, urticaria, dizziness, dyspnea and pruritus are already noted in the list of adverse events for cetirizine and are included in the current cetirizine prescription label. Convulsion was noted in the postmarketing of cetirizine but was not as prominent as noted in this database. Note that the most commonly reported serious adverse event from the sponsor clinical trial database were asthma (9.2%), vomiting (3.6%), pyrexia (3.6%), and bronchitis (2.8%).

Similar to the other second generation antihistamines, loratadine and fexofenadine, convulsion, and cardiac events are adverse events of interest (see CDER OTC Switch Review Team's Memo); these will be further discussed below.

Convulsion (Postmarketing)

Overall, there were a total of 187 cases reporting convulsion[7] and it was the most frequently reported term associated with serious cases. A total of 152 (81%) cases were classified as serious; 64 of these involved patients with either a significant medical history of convulsions, concurrent illness, other medications considered primary suspect, limited clinical information provided, or associated with an overdose or medication error. The rest of the 88 cases, 66 were medically confirmed (14 involved children <12 years old) and 22 were consumer reports. This discussion will mainly focus on the medically confirmed cases of convulsion. Of the 14 cases of children <12 years old, 6 had causality assessment of possibly or probably related; with regard to outcome: 8 recovered, 3 unknown and 3 not recovered. The following is a short narrative of the cases where causality assessment was possibly or probably related:

- A 9 y/o male took cetirizine 10 mg daily for urticaria, 5 days later had convulsions and was hospitalized.
- A 3 y/o male with a history of questionable febrile seizure at one year of age, recurrent bronchitis and allergies. He developed myoclonic seizure disorder within 2 months of cetirizine treatment (dose unknown).
- A 10 y/o female had convulsion the day she took cetirizine (unknown dose and indication) and Celestamine (betamethasone, dexchlorpheniramine).
- A 7 y/o male on cetirizine 10 mg daily for allergies and Seretide (fluticonasone + salmeterol) for asthma. Medications were discontinued after 3 epileptic crises. Later, medications were restarted and had an absence attack with trismus; patient recovered.
- Two cases: 10 y/o and 7 y/o males had seizure while using cetirizine, and recovered after cetirizine was discontinued.

In a total of 74 cases reported for those over 12 years of age (or unknown age), 27 had outcome of recovered, 24 unknown (mostly due to limited information regarding the case) and 1 not recovered (CAT scan showed a possible brain tumor). A causality of possibly related was provided for 5 cases,

6 Cetirizine Prescribing Information, Post-marketing Experience section
7 Includes combined MedDRA terms convulsion, epilepsy, grand mal convulsion, petit mal epilepsy, partial seizures myoclonus, complex partial seizures, myoclonic epilepsy, clonic convulsion, tonic convulsion, clonus, status epilepticus hypotonic-hyporesponsive episode.

3 recovered after discontinuing cetirizine use and a fourth recovered although it is not clear if cetirizine use was discontinued. The fifth case is a 38 y/o male with a history of cryptogenic partial epilepsy who took cetirizine 10 mg; he was also taking gabapentin, lamotrigine and carbamazepine. That day, he developed two partial convulsive crises. The reporting physician's causality was possible, while the French Authority's assessment was dubious. Further details on these cases were not provided. There were 3 reported cases of convulsion that identified the concomitant use of use of alcohol with cetirizine and 3 patients who had previously existing seizure disorders and seizure activity coincident with the use of cetirizine. Causality was probable for 4 cases:

- A 68 y/o female was treated with cetirizine 10 mg daily for contact dermatitis who drank some alcohol had and convulsion. She lost her hearing, consciousness, had cramps in her hands, abnormal eye movement and urine incontinence. She discontinued the cetirizine and recovered.
- A 53 y/o female was taking multiple unspecified drugs for multiple medical conditions including hepatitis and hyperlipidemia. She took cetirizine for chronic rhinitis and 2 days later had convulsions; she was treated and recovered.
- A 37 y/o female took cetirizine 10 mg daily for allergic rhinitis and bronchitis, one day later, she developed convulsions and recovered.
- A 26 y/o male was on unknown dose of cetirizine for an unknown indication for the past 6 months experienced impaired concentration, memory loss and seizure. The physician reported that the seizure was due to cetirizine.

Medical Officer Comments: Seizures/convulsions were the most common serious CNS adverse event noted during the postmarketing of loratadine single-ingredient products.[8] *The current prescription label for cetirizine states that convulsion has been reported in the post marketing experience as rare but potentially severe adverse event. Based on the postmarketing database, there are no conclusive evidence of a clear causal relationship or safety trend with the use of cetirizine and seizure events.*

A Postmarketing Safety Review to evaluate cetirizine use and Nervous System and Psychiatric Events was conducted by the Division of Drug Risk Evaluation on March 28, 2001. In this review, the Safety Evaluator stated that causality in the seizure cases is difficult to assess and is less certain. An overview of Psychiatric and Nervous system AERS cases for non-sedating antihistamines was also conducted and results showed that a similar profile for the non-sedating antihistamines, cetirizine, loratadine, fexofenadine, (except for clemastine) in both the types of events reported and in the percentage of total reports. These events occurred about twice as often in adult patients age 17 to 60 as in pediatric patients or in older adults. It appears that seizure is likely an AE common to the antihistamine drug class.[9]

This Medical Officer requested DDRE/OSE for AERS crude counts of seizure reports for all postmarketing data for single-ingredient cetirizine and seizure/convulsion adverse events in comparison with loratadine. There is no significant difference in the AERS crude counts of seizure reports for cetirizine (All=193, U.S. only=115) and loratadine (All=193, U.S. only=157). Similar to loratadine, there is no reason to believe that cetirizine will not be compatible for OTC marketing as far as seizures are concerned.

8 See Medical Officer Review for Claritin Rx-to-OTC Switch (NDA 19-658, section 7.6.3.5)
9 See DDRE Review dated 3-28-01 (NDA 20-346 and 19-835).

Cardiac Events (Postmarketing)

The cardiac disorders SOC had an overall total of 744/30,508 (2.4%) AE terms reported for cetirizine. With respect to the serious cases reported, 311/7,057 (4.4%) were serious AE terms. There were no AEs reported at a rate of 1% or greater for this SOC and the most frequently reported events were ventricular tachycardia (57/7057; 0.8%) followed by arrhythmia (23/7057; 0.3%); both of these terms were consolidated with other MedDRA terms. There were 128 AE reports classified as serious where the primary event term was categorized in the cardiac disorders SOC. Cardiac events are discussed below.

There were a total of 191cases reporting *tachycardia*; of these, 52 cases were classified as serious. Of the 52 cases, 35 were excluded from the discussion due to: concurrent illness, another clinically relevant term classified the case as serious, another medication was the primary suspect drug, drug overdose, drug interaction, suicide or medication error. The remaining were 17 medically confirmed cases, of which 4 were consumer reports and 2 were cases in children <12 y/o:

- A 3 y/o male with atopy was prescribed cetirizine as a prophylaxis for an unspecified allergy. He was also on paracetamol/clorfenamine (antihistamine?) 5 ml daily for 5 days for symptoms of rhinitis; weeks later he developed sinus tachycardia and excessive somnolence. ECG showed sinus tachycardia (120/min), arrhythmia and normal QT interval. The reporting physician attributed the excessive drowsiness to both medications and attributed tachycardia to the psychological reaction of the child to the parent's agitation and concern.
- A 5 y/o male took cetirizine 5 mg had difficulty breathing and tachycardia, cetirizine was discontinued and the event abated. Causality was not provided.

The remaining 11 medically confirmed cases were in patients 12 years or older or classified as unknown age. The following cases had a causality assessed as probable.

- A female (unspecified age) patient took cetirizine 10 mg daily for allergies, 45 minutes later had increased heart rate (from 70 to 140/min) and palpitations, this occurred several times with cetirizine intake. The event resolved after 10 minutes.
- A 55 y/o male took cetirizine 10 mg as needed for hay fever for two years and had extrasystoles, palpitations and a racing heart (unspecified rate). The drug was discontinued and patient recovered.

The outcome of the 11 above cases were as follows: 6 recovered, 4 unknown and 1 not recovered. The latter is a 28 y/o male patient who took cetirizine 10 mg daily for allergic rhinitis for 2 years, had dyspnea and palpitations and was hospitalized. He had tachycardia (200/min) and ECG showed an enlarged QRS complex and a right bundle branch block (RBBB). Cetirizine was stopped and amiodarone was administered. The patient has not recovered at the time of report and causality was not provided.

There were a total of 64 cases that contained the term *arrhythmia*, 23 (0.3%) of these were classified as serious. Of these 23 serious cases, 12 were excluded from the discussion due to a concurrent illness; another clinically relevant term classified the cases as serious or due to drug interaction. Of the remaining 11 cases, 8 were medically confirmed, and 2 of these were in the <12y/o:

- A 7 y/o male had taken loratadine and cetirizine in the past and experienced chest pain. He took cetirizine at a later time and was hospitalized with chest pain with irregular heart rate and PVCs every 3-4 beats. Outcome is unknown and causality was not provided.
- A 3 y/o male was on respiratory therapy and unspecified dose of cetirizine. Arrhythmia was noted; cetirizine was discontinued and arrhythmia resolved. No causality was provided.

In the remaining 6 cases in cases aged >12y/o or unknown age, the outcome was recovered in 3 cases, unknown in 2 cases and not recovered in one case. The last case was a 13 y/o who was on cetirizine for an unspecified indication and dose and was diagnosed with a second degree heart block. Work-up was negative and cetirizine was discontinued. Outcome was not recovered and no causality was provided.

There were 74 cases that reported the term *ventricular arrhythmia*, 50 were classified as serious. Of these, 23 involved patients with either a significant concurrent illness; another clinically relevant term reported, classifying the case as serious; poor documentation with limited clinical information; or an association with overdose or drug interaction. Of the remaining 27 cases, 24 were medically confirmed and 3 were consumer reports. Out of the 24 cases, 3 were pediatric cases (see below) and 21 were adult cases or no age designated; 7 of the 21 cases were classified as probable or possible causality (see below) and 14 had no causality assessment. The following are the 3 pediatric cases <12 years old:

- A 5 y/o girl developed tachycardia 1½ weeks after starting cetirizine 5 mg for an ear effusion and was diagnosed to have supraventriculer tachycardia (SVT). She was treated with adenosine and patient recovered. This was assessed as possibly related to cetirizine.
- A 4 y/o boy who was on cetirizine 10 mg daily for allergies developed tachycardia 2 years later. He was diagnosed with SVT, cetirizine was not believed to be the cause.
- An 8 y/o girl who took cetirizine 10 mg for allergies (duration unknown) and was diagnosed with SVT most likely secondary to concealed accessory pathway vs. atrioventricular pathway reentry; she was put on digoxin. Outcome of the events was unknown and causality was not provided.

There were 7 ventricular arrhythmia cases (in >12 y/o) that were assessed as probably or possibly related to cetirizine use.

- A 40 y/o male on cetirizine 10 mg daily for unknown reason was diagnosed with paroxysmal SVT. No other details provided.
- An 86 y/o male took cetirizine 5 mg 2x/day for senile pruritus developed paroxysmal SVT. He had history of angina pectoris, multiple cerebral infarctions, coronary artery disease, sinus bradycardia, left bundle branch block (BBB) and prostate hypertrophy. He was on chlorpheniramine, digoxin, aspirin and crotamiton. Cetirizine was discontinued and outcome is unknown.
- A 66 y/o male with history of type II diabetes, hypercholesterolemia, ischemic heart disease and MI took cetirizine 10 mg daily (unknown duration). He collapsed during exercise in a cardiac rehabilitation class and was diagnosed with ventricular fibrillation and tachycardia; outcome was unknown at the time of report.
- A 58 y/o male took cetirizine 10 mg for urticaria; 10 days later collapsed and was found to have atrial fibrillation and frequent PVCs and admitted to an intensive care unit. Outcome is unknown.

- A 30 y/o female took cetirizine 10 mg for allergic rhinitis, three days later fainted and was diagnosed with AV block and SVT. Patient recovered; no further details provided.
- A 76 y/o male on cetirizine 10 to 20 mg daily for allergic rhinitis developed mild chest tightness and fatigue 2 years later, ECG showed severe AV block and multiple ventricular extrasytoles, a cardiac pacemaker was inserted.
- A 77 y/o male with a history of hypertension and drinking alcoholic beverage (unknown amount) while taking cetirizine 5 mg every other day for allergies had cardiac arrest secondary to torsades de pointes.

A total of 27 cases were identified containing the term *QT prolongation*; 21 of these were classified as serious. Of the 21 cases, 7 were excluded due to: another clinically relevant term classified the case as serious, concurrent illness, overdose or drug interaction. Of the remaining 14 cases, 13 were medically confirmed (2 reports in <12 y/o) and 1 with unknown reporter status. The outcome in 5 of these 13 cases was recovered, 5 unknown, and 3 not recovered. The following is a list of the two cases in <12 y/o:

- An 8 y/o girl on cetirizine 5 mg intermittently for allergies for one year; she had a low-grade fever and had a positive strep screen. ECG revealed QT prolongation with asymptomatic bigamy and trigeminy. Cetirizine was discontinued for a few days and ECG returned to normal.
- A child with unspecified age with a history of asthma was taking cetirizine and turned blue during exercise. Cardiac evaluation revealed a prolonged QT interval, cetirizine was discontinued; outcome is unknown. No causality assessment was provided by the physician.

The following 4 of the 13 cases were classified as probably or likely related to cetirizine:

- A 45 y/o female patient with tinea blanca, gastric ulcer and urticaria was taking various medications and took cetirizine 10 mg daily for urticaria. A prolonged QT complex was identified during a check-up. Cetirizine was discontinued and other drugs were continued. The event has not resolved at report time.
- A 43 y/o female took 10 mg cetirizine tablet daily for allergies; one week later, she collapsed on the floor. ECG showed bradycardia and long QT interval. Cetirizine was discontinued, the events resolved.
- A 12 y/o female took cetirizine 10 mg daily for pollinosis, 3 weeks later, had cardiac arrhythmia diagnosed as ventricular extrasystoles, ECG showed QT prolongation. Cetirizine was discontinued and the event resolved.
- A 65 y/o female on cetirizine 10 mg for urticaria with history of chronic hepatitis C, dizziness, cough and treated with unknown Chinese medicines. She developed palpitations, ECG revealed prolonged QT syndrome. Cetirizine was discontinued and the event did not reappear.

There were a total of 198 cases reporting *palpitations*, 23 were classified as serious. Of the 23 cases, 18 cases were excluded from the discussion due to another clinically relevant term classified the case as serious, concurrent illness, overdose or drug interaction. Of the remaining 5 cases, 2 were medically confirmed and 1 with unknown reporter status. No patient was <12 y/o. One case was classified as probably related to cetirizine:

- A 34 y/o male started taking cetirizine 10 mg and ebastine 10 mg (H-1 antihistamine) daily for urticaria, 2 months later was hospitalized for palpitations and diagnosed with first degree AV block. Cetirizine was discontinued and patient recovered.

Medical Officer Comments: The adverse reactions section of the prescription label of cetirizine includes cardiac failure, hypertension, palpitation and tachycardia. Loratadine, a drug that belongs to the same class (second generation antihistamines) with similar indications had the same adverse events listed in its prescription label; in addition, loratadine had hypotension and supraventricular tachyarrhythmias. Loratadine is now marketed for OTC use and has not had any cardiac safety concerns. Due to the limited clinical information small number of cases, a clear temporal relationship between the use of cetirizine and cardiac events cannot be determined in majority of the cases. It is likely that the underlying medical conditions or concomitant use of multiple medications were the cause or contributed to the occurrence of these events.

Cardiovascular diseases are the leading cause of death in adults and the third leading cause of death in the United States. [10] *Taking into consideration of the amount of exposure to cetirizine, the above reported cardiac events for cetirizine are well below the reported incidence in the general population. There appears to be no specific trend or signal detected with the use of cetirizine and the occurrence of cardiac serious adverse events from these data.*

Adverse Events in Subpopulations

The summary of data suggests that the adverse event profile for both genders were generally similar. There were more female cases identified (8,449) compared to males (5,002). A significant number (41%) of cases were in patients who were 18 to 65 year of age. The reported pediatric cases (<18 y/o) involved 1,060 males and 771 females who ranged in age from <1 month old to 17 y/o (mean age=7.3 years). The majority (83%) were non-serious. The outcome of death (which were previously discussed) varied for all age categories.

Table 12: Postmarketing AEs Terms (at Least 1%) in <18 years old [11]
(Cases other than Clinical Trials)

Adverse Event	%	Adverse Event	%
Drug ineffective	5.4%	Headache	1.5%
Somnolence	3.8%	Convulsion	1.4%
Drug Administration Error	3.5%	Cough	1.3%
Rash	2.8%	Insomnia	1.3%
Urticaria	1.9%	Diarrhea	1.2%
Overdose	1.9%	Fatigue	1.3%
Abdominal pain	1.7%	Psychomotor hyperactivity	1.1%
Vomiting	1.7%	Pruritus	1.1%
Hypersensitivity	1.6%	Intentional overdose	1%
Accidental Overdose	1.5%	Aggression	1%

10 TDR data.com, Incidence and Prevalence database (http://www.tdrdata.com/IPD/ipd_init.aspx (ICD code 427.5).
11 Adapted from sponsor's table 9a

Table 13: AE Terms Reported at Rate of at Least 1% in adults >18 years old: [12]

Adverse Event	%	Adverse Event	%
Somnolence	9.3%	Headache	1.9%
Drug Ineffective	6.8%	Face edema	1.8%
Dizziness	2.5%	Hypersensitivity	1.5%
Rash	2.4%	Nausea	1.3%
Fatigue	2.4%	Nasal Congestion	1.2%
Urticaria	2%	Malaise	1%
Hepatitis	2 %	Dry mouth	1%

Medical Officer Comments: The postmarketing data show that the adverse events in the adult and pediatric population are generally similar to the adverse events reported from the clinical trials.

Comparison of Adverse Events in Rx and OTC Markets (Canada and U.S.)
(see Table A-2 in the Appendix section)

Cetirizine has been used as an antihistamine for 20 years and is available in more than 100 countries worldwide. It is available as nonprescription (OTC or general sales status) in many countries (see table A-3) including Canada. Cetirizine has been marketed as a prescription drug in Canada from May 28, 1991 to September 20, 1994, and OTC thereafter. In order to assess product risk as an OTC product, the sponsor reviewed the safety profile of cetirizine OTC in Canada (a market that is comparable to the U.S.) and compared it to the cetirizine prescription safety profile in the U.S. from September 21, 1994 through May 10, 2006.

There were over ——— units of cetirizine distributed in Canada and over ——— of cetirizine distributed in the U.S. during this period. In Canada, there were 3,277 case reports involving cetirizine, describing 5,267 AE terms in a period of 12 years. In the United States, there were 7,259 cases involving 17,020 AE terms. The majority of reports in both markets were non-serious (Canada 98% and US 78%). In the Canadian market, 64/3,277 (1.95%) were classified as serious and 1,235/7,259 (17%) in the U.S.were classified as serious. There were 301 (4%) reports of death in the US and none in Canada. The sponsor stated that 229 of these reports of death in the US were from a solicited source such as "Pfizer for Living", "Zyrtec (cetirizine) Disease Management Program" and other Pfizer marketing programs. The characteristics of both the Canadian and US cases are summarized in Table A-2 (see Appendix). The significant difference in unit distribution should be noted which reflects the reporting rate between the two countries.

When the reports were analyzed by system organ class (SOC), the majority of AE terms were categorized under the General Disorders and Nervous System SOC for both the Canadian and U.S. market; this is similar to the AE profile for all cetirizine reports. The most frequently reported adverse events for the Canadian and U.S. market were similar, i.e. drug ineffective and fatigue.

12 Adapted from sponsor's table 9b

Of the overall serious adverse event terms reported, the most frequently reported adverse events were convulsion (Canada 15, 10%; U.S. 84, 1.8%) and somnolence (Canada 4, 2.6%; US 70; 1.5%). 1.5%).

Medical Officer Comments: It appears from the data that there are no clinically significant differences in reporting patterns and nature of AEs reported from the general sales market (Canada) when compared to the prescription only market (U.S.). The sponsor did not explain the difference in the reporting rates for serious AEs between Canada and the U.S. (1.95% vs. 17%). It was not explained how data was collected in Canada compared to the U.S., this could have affected reporting rates for serious AEs. Healthcare professionals were the source of reports in 50.6% of cases in the U.S and only 3.2% in Canada; while the consumer is the source of 88% reports in Canada and 42% in the U.S. Of note, of the overall serious adverse event terms reported, the most frequently reported serious adverse events for both Canada and U.S. were convulsion and somnolence. However, Canada had a much higher reporting rate for convulsion as a serious adverse event compared to the U.S. (10% vs. 1.8%).

Summary of Safety Data Derived from the FDA's SRS and AERS Databases

A total of 4,444 cases were reported with 13,509 associated AE terms derived from the FDA's SRS and AERS Databases from 1969 to March 2006 for reports involving cetirizine as a suspect medication. A total of 18% of cases (817/4,444) were from the SRS and 82% (3,438/4,444) from the AERS database. Of these cases, 15% (671/4,444) were reports in the pediatric patients, and 46% (2,054/4,444) were in the adult age range; 39% (1,719/4,444) had no age data. The overall the mean age was 40 years. There were 29% (1,304/4,444) serious cases and 3.5% (156/4,444) deaths, 3% (129/4,444) had no outcome data. Reports made by health professionals comprised 62% (2,737/4,444) and consumers accounted for 42% (1,849/4,444). The sponsor notes that a single report could have more than one source. Overall, the AE terms were broadly distributed across the SOCs and those with the highest reporting rates were:

- General disorders and administration site conditions (14%; 1,943/13,509)
- Nervous System disorders 13% (1,814/13,509)
- Skin and Subcutaneous Tissue disorders 9% (1,217/13,509)
- Psychiatric disorders 8% (1,088/13,509)

With respect to specific AEs, the overall most common AEs reported were drug ineffective 3.3%, sedation 1.9%, urticaria 1.7%, and pruritus 1.4% (see table below). In the pediatric age group, four AE terms had higher reporting rates compared to overall: medication error 2.4% (overall 0.9%), convulsion 1.9% (overall 0.9%), vomiting 1.3 % (0.5), and drug administration error 1.2% (overall 0.6%).

Table 14: Most Frequent Adverse Event Terms for Cetirizine - All Reports by MedDRA Term and Age Category (frequency ≥ 0.5%) N (%)[a]

SOC Abbr[b]	MedDRA Preferred Term	Pediatric (≤ 17)	Adult (≥ 18)	No age data	Overall total
Genrl	Drug ineffective	54 (2.6)	211 (2.8)	186 (4.9)	451 (3.3)
Nerv	Sedation	21 (1.0)	129 (1.7)	110 (2.9)	260 (1.9)
Skin	Urticaria	27 (1.3)	113 (1.5)	83 (2.2)	223 (1.7)
Skin	Pruritus	21 (1.0)	109 (1.4)	57 (1.5)	187 (1.4)
Nerv	Somnolence	33 (1.6)	90 (1.2)	44 (1.2)	167 (1.2)
Genrl	Drug interaction	20 (0.9)	92 (1.2)	50 (1.3)	162 (1.2)
Nerv	Headache	25 (1.2)	95 (1.3)	42 (1.1)	162 (1.2)
Genrl	Asthenia	11 (0.5)	108 (1.4)	40 (1.0)	159 (1.2)
Skin	Dermatitis	26 (1.2)	76 (1.0)	57 (1.5)	159 (1.2)
Immun	Hypersensitivity	26 (1.2)	67 (0.9)	62 (1.6)	155 (1.1)
Psych	Insomnia	33 (1.6)	62 (0.8)	48 (1.3)	143 (1.1)
Nerv	Dizziness	13 (0.6)	86 (1.1)	36 (0.9)	135 (1.0)
Inj&P	Medication error	51 (2.4)	26 (0.3)	49 (1.3)	126 (0.9)
Resp	Dyspnoea	16 (0.8)	79 (1.0)	30 (0.8)	125 (0.9)
Nerv	Convulsion	41 (1.9)	44 (0.6)	32 (0.8)	117 (0.9)
Genrl	Condition aggravated	14 (0.7)	64 (0.8)	34 (0.9)	112 (0.8)
Gastr	Nausea	16 (0.8)	63 (0.8)	23 (0.6)	102 (0.8)
Infec	Rhinitis	15 (0.7)	44 (0.6)	32 (0.8)	91 (0.7)
Gastr	Dry mouth	2 (0.1)	56 (0.7)	30 (0.8)	88 (0.7)
Genrl	Pain	11 (0.5)	49 (0.6)	28 (0.7)	88 (0.7)
Genrl	Pyrexia	16 (0.8)	63 (0.8)	8 (0.2)	87 (0.6)
Inv	Weight increased	8 (0.4)	35 (0.5)	43 (1.1)	86 (0.6)
Vasc	Hypertension	3 (0.1)	40 (0.5)	42 (1.1)	85 (0.6)
Genrl	Malaise	8 (0.4)	56 (0.7)	19 (0.5)	83 (0.6)
Card	Palpitations	7 (0.3)	55 (0.7)	21 (0.5)	83 (0.6)
Gastr	Diarrhoea	17 (0.8)	54 (0.7)	11 (0.3)	82 (0.6)
Genrl	Fatigue	13 (0.6)	48 (0.6)	21 (0.5)	82 (0.6)
Gastr	Abdominal pain	19 (0.9)	47 (0.6)	14 (0.4)	80 (0.6)
Inj&P	Drug administration error	26 (1.2)	23 (0.3)	31 (0.8)	80 (0.6)
Nerv	Syncope	9 (0.4)	48 (0.6)	20 (0.5)	77 (0.6)
Genrl	Chest pain	5 (0.2)	53 (0.7)	17 (0.4)	75 (0.6)
Card	Tachycardia	8 (0.4)	45 (0.6)	20 (0.5)	73 (0.5)
Nerv	Loss of consciousness	8 (0.4)	46 (0.6)	15 (0.4)	69 (0.5)
Psych	Anxiety	10 (0.5)	31 (0.4)	27 (0.7)	68 (0.5)
Gastr	Vomiting	28 (1.3)	31 (0.4)	9 (0.2)	68 (0.5)
Resp	Asthma	13 (0.6)	26 (0.3)	28 (0.7)	67 (0.5)
Psych	Agitation	15 (0.7)	25 (0.3)	25 (0.7)	65 (0.5)
Psych	Confusional state	9 (0.4)	48 (0.6)	8 (0.2)	65 (0.5)
Resp	Cough	17 (0.8)	36 (0.5)	12 (0.3)	65 (0.5)
Psych	Depression	7 (0.3)	32 (0.4)	24 (0.6)	63 (0.5)
Genrl	Face oedema	6 (0.3)	47 (0.6)	10 (0.3)	63 (0.5)
Psych	Nervousness	18 (0.9)	25 (0.3)	20 (0.5)	63 (0.5)
Genrl	Oedema peripheral	4 (0.2)	34 (0.4)	25 (0.7)	63 (0.5)
	Total AE terms[c] (col %)	2110 (100)	7573 (100)	3826 (100)	13509 (100)
	Total AE terms[c] (row %)	2110 (15.6)	7573 (56.1)	3826 (28.3)	13509 (100)
	Total cases[c] (row %)	671 (15.1)	2054 (46.2)	1719 (38.7)	4444 (100)

a Unless otherwise indicated, the percent basis is the total number of terms in each age category.
b The full text of the SOC abbreviations is presented in the List of Abbreviations which follows the Table of Contents.
c The totals are those for the entire dataset, not just the data displayed in the table.
Adapted from sponsor's electronic submission Item 8, Vol. 35 p. 19.

Table 15: SRS/AERS Most Frequent AE Terms for Cetirizine Reports by MedDRA Term and Seriousness Category (≥ 0.5%) N (%)

SOC Abbr[b]	MedDRA Preferred term	Not Serious	Serious	Death	No Outcome Data	Overall Total
Genrl	Drug ineffective	402 (5.9)	40 (0.7)		9 (4.1)	451 (3.3)
Nerv	Sedation	220 (3.2)	38 (0.7)		2 (0.9)	260 (1.9)
Skin	Urticaria	160 (2.4)	56 (1.0)	4 (0.5)	3 (1.4)	223 (1.7)
Skin	Pruritus	125 (1.8)	57 (1.0)	4 (0.5)	1 (0.5)	187 (1.4)
Nerv	Somnolence	133 (2.0)	30 (0.5)		4 (1.8)	167 (1.2)
Genrl	Drug interaction	92 (1.4)	60 (1.0)	5 (0.7)	5 (2.3)	162 (1.2)
Nerv	Headache	113 (1.7)	49 (0.8)			162 (1.2)
Genrl	Asthenia	116 (1.7)	39 (0.7)		4 (1.8)	159 (1.2)
Skin	Dermatitis	131 (1.9)	22 (0.4)	3 (0.4)	3 (1.4)	159 (1.2)
Immun	Hypersensitivity	119 (1.8)	33 (0.6)	3 (0.4)		155 (1.1)
Psych	Insomnia	119 (1.8)	22 (0.4)		2 (0.9)	143 (1.1)
Nerv	Dizziness	79 (1.2)	50 (0.9)	1 (0.1)	5 (2.3)	135 (1.0)
Inj&P	Medication error	61 (0.9)	18 (0.3)	1 (0.1)	46 (20.7)	126 (0.9)
Resp	Dyspnoea	63 (0.9)	58 (1.0)	3 (0.4)	1 (0.5)	125 (0.9)
Nerv	Convulsion	42 (0.6)	64 (1.1)	10 (1.4)	1 (0.5)	117 (0.9)
Genrl	Condition aggravated	51 (0.8)	52 (0.9)	8 (1.1)	1 (0.5)	112 (0.8)
Gastr	Nausea	56 (0.8)	41 (0.7)		5 (2.3)	102 (0.8)
Infec	Rhinitis	89 (1.3)	2 (0.0)			91 (0.7)
Gastr	Dry mouth	79 (1.2)	9 (0.2)			88 (0.7)
Genrl	Pain	49 (0.7)	36 (0.6)	3 (0.4)		88 (0.7)
Genrl	Pyrexia	22 (0.3)	62 (1.1)	3 (0.4)		87 (0.6)
Inv	Weight increased	71 (1.0)	13 (0.2)		2 (0.9)	86 (0.6)
Vasc	Hypertension	52 (0.8)	32 (0.6)	1 (0.1)		85 (0.6)
Genrl	Malaise	36 (0.5)	42 (0.7)	5 (0.7)		83 (0.6)
Card	Palpitations	49 (0.7)	30 (0.5)	1 (0.1)	3 (1.4)	83 (0.6)
Gastr	Diarrhoea	49 (0.7)	31 (0.5)	1 (0.1)	1 (0.5)	82 (0.6)
Genrl	Fatigue	28 (0.4)	54 (0.9)			82 (0.6)
Gastr	Abdominal pain	52 (0.8)	27 (0.5)		1 (0.5)	80 (0.6)
Inj&P	Drug administration error	51 (0.8)	16 (0.3)		13 (5.9)	80 (0.6)
Nerv	Syncope	26 (0.4)	49 (0.8)	2 (0.3)		77 (0.6)
Genrl	Chest pain	38 (0.6)	37 (0.6)			75 (0.6)
Card	Tachycardia	48 (0.7)	24 (0.4)	1 (0.1)		73 (0.5)
Nerv	Loss of consciousness	18 (0.3)	42 (0.7)	9 (1.2)		69 (0.5)
Psych	Anxiety	51 (0.8)	16 (0.3)		1 (0.5)	68 (0.5)
Gastr	Vomiting	26 (0.4)	35 (0.6)	4 (0.5)	3 (1.4)	68 (0.5)
Resp	Asthma	35 (0.5)	30 (0.5)	1 (0.1)	1 (0.5)	67 (0.5)
Psych	Agitation	44 (0.6)	17 (0.3)	1 (0.1)	3 (1.4)	65 (0.5)
Psych	Confusional state	25 (0.4)	32 (0.6)	8 (1.1)		65 (0.5)
Resp	Cough	42 (0.6)	22 (0.4)		1 (0.5)	65 (0.5)
Psych	Depression	34 (0.5)	22 (0.4)	5 (0.7)	2 (0.9)	63 (0.5)
Genrl	Face oedema	41 (0.6)	22 (0.4)			63 (0.5)
Psych	Nervousness	57 (0.8)	4 (0.1)		2 (0.9)	63 (0.5)
Genrl	Oedema peripheral	44 (0.6)	19 (0.3)			63 (0.5)
	Total AE terms[c] (col %)	6771 (100)	5787 (100)	729 (100)	222 (100)	13509 (100)
	Total AE terms[c] (row %)	6771 (50.1)	5787 (42.8)	729 (5.4)	222 (1.6)	13509 (100)
	Total cases[c] (row %)	2855 (64.2)	1304 (29.3)	156 (3.5)	129 (2.9)	4444 (100)

a Unless otherwise indicated, the percent basis is the total number of terms in each age category.
b The full text of the SOC abbreviations is presented in the List of Abbreviations which follows the Table of Contents.
c The totals are those for the entire dataset, not just the data displayed in the table.
Adapted from sponsor's electronic submission Item 8, Vol. 33 p. 38

In the pediatric age ranges, frequencies of convulsion were 2.7% (6/220) in the >2-6 year age group and 4.1% (9/218) in the 7-11 years age group; while the overall rate was 1.1% (64/5,787). Other AEs with apparently higher rates when compared to the overall were:

- ≤ 1 year age range:
  - complications of maternal exposure to therapeutic drugs (6.2% vs. 0.6%)
- 12-17 age range:
  - headache (2.3% vs 0.8%)
  - nausea (2% vs. 0.7%)
- 18-40 year age range:
  - urticaria (2% vs. 1%)
- 65-77 age range
  - loss of consciousness (1.5% vs. 0.7%)
- > 77 year age range
  - drug interaction (2% vs 1%)
  - pruritus (2% vs 1%)
  - condition aggravated (2% vs 0.9%).

Deaths (SRS/AERS Data)

There were 156 reports of death with 729 associated adverse events terms. Of these, 10% were pediatric cases, 56% were the adult cases and 34% (53/156) had no age data. The six SOCs that had the highest reporting rates accounted for 48% of all the reported AE terms were: General disorders and administration site conditions (11%, 80/729), Nervous system disorders (9%, 66/729), Investigations (8%, 59/729), Skin and subcutaneous tissue disorders (7%, 53/729), Injury, poisoning and procedural complications (6%, 46/729) and Cardiac disorders (6%, 45/729). Overall, there is no single SOC or AE term that was consistently associated with reports of death across the age ranges under consideration. Below is a tabulation of the most frequently reported AE terms for deaths stratified by age category.

Table 16: Most Frequent Adverse Event Terms for Cetirizine – Deaths by MedDRA Term and Age Category (Frequency ≥ 0.7%) N (%)[a] (SRS & AERS)

SOC Abbr[b]	MedDRA Preferred Term	Pediatric (≤ 17)	Adult (≥ 18)	No Age Data	Overall Total
Genrl	Death	1 (1.9)	5 (0.9)	**18 (15.0)**	24 (3.3)
Nerv	Coma	**5 (9.4)**	7 (1.3)		12 (1.6)
Card	Cardiac arrest		9 (1.6)	1 (0.8)	10 (1.4)
Psych	Completed suicide		9 (1.6)	1 (0.8)	10 (1.4)
Nerv	Convulsion	**4 (7.5)**	6 (1.1)		10 (1.4)
Nerv	Loss of consciousness	1 (1.9)	7 (1.3)	1 (0.8)	9 (1.2)
Infec	Sepsis		9 (1.6)		9 (1.2)
Preg	Complications of maternal exposure to therapeutic drugs	1 (1.9)		**7 (5.8)**	8 (1.1)
Genrl	Condition aggravated		8 (1.4)		8 (1.1)
Psych	Confusional state		8 (1.4)		8 (1.1)
Hepat	Hepatic failure	1 (1.9)	6 (1.1)	1 (0.8)	8 (1.1)
Renal	Renal failure		7 (1.3)	1 (0.8)	8 (1.1)
Skin	Toxic epidermal necrolysis		7 (1.3)		7 (1.0)
Card	Cardio-respiratory arrest	1 (1.9)	4 (0.7)	1 (0.8)	6 (0.8)
Inj&P	Drug toxicity		6 (1.1)		6 (0.8)
Surg	Abortion induced			**5 (4.2)**	5 (0.7)
Skin	Blister		5 (0.9)		5 (0.7)
Hepat	Cholestasis		5 (0.9)		5 (0.7)
Psych	Depression		3 (0.5)	2 (1.7)	5 (0.7)
Genrl	Drug interaction		1 (0.2)	**4 (3.3)**	5 (0.7)
Nerv	Extrapyramidal disorder		5 (0.9)		5 (0.7)
Genrl	Malaise		5 (0.9)		5 (0.7)
Nerv	Metabolic encephalopathy		5 (0.9)		5 (0.7)
Inj&P	Multiple drug overdose	1 (1.9)	4 (0.7)		5 (0.7)
Infec	Nosocomial infection		5 (0.9)		5 (0.7)
Renal	Renal failure acute		4 (0.7)	1 (0.8)	5 (0.7)
Renal	Renal failure chronic		5 (0.9)		5 (0.7)
	Total AE terms[c] (col %)	53 (100)	556 (100)	120 (100)	729 (100)
	Total AE terms[c] (row %)	53 (7.3)	556 (76.3)	120 (16.5)	729 (100)
	Total cases[c] (row %)	16 (10.3)	87 (55.8)	53 (34.0)	156 (100)

a Unless otherwise indicated, the percent basis is the total number of terms in each age category.
b The full text of the SOC abbreviations is presented in the List of Abbreviations which follows the Table of Contents.
c The totals are those for the entire dataset, not just the data displayed in the table.
From sponsor's submission Vol. 33 p.43.

In the pediatric age category, coma (9.4%, 5/53 vs. 1.6%, 12/729) and convulsion (7.5%, 4/53 vs. 1.4%, 10/729) had a higher reporting rates compared to overall. It is to be noted that the absolute numbers are small. In the category without age data four terms had reporting rates notably higher than the corresponding overall rates: Death (15%, 18/120 vs. 3.3%, 24/729), Complications of maternal exposure to therapeutic drugs (5.8%, 7/120 vs. 1.1%, 8/729), Abortion induced (4.2%, 5/120 vs. 0.7%, 5/729) and Drug interaction (3.3%, 4/120 vs. 0.7%, 5/729).

Medical Officer Comments: Of the 156 reports of death, there was no single organ system or AE term that was consistently associated with reports of death in both adults and pediatric population.

There were no new adverse events identified that occurred at a significant frequency in the reports of death; reported AEs appear to be generally distributed over a broad range of conditions. In general, there was no consistent pattern among the reports of death for all age groups.

It is not clear why the rate for coma and convulsion were higher in the pediatric age category compared to adults; it is probably because the reported total AE terms for adults is much higher (10x) than in the pediatric group.

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, sedation, urticaria, pruritus, somnolence, drug interaction, headache, asthenia dermatitis are similar to those previously reported with the use of cetirizine both during clinical trials and from the sponsor's database. It is to be noted causality cannot be determined in most of the cases due to lack of more specific clinical information. In addition, reports regarding the same case may sometimes be received from several different sources at different times.

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

The sponsor obtained reports of AEs associated with cetirizine as a suspect medication from the WHO drug safety database maintained in Uppsala, Sweden tabulated and analyzed. The reports were segregated by country of origin; those originating outside the US were the focus of the report.

There were 6,232 cases involving 12,318 WHO AE terms reported for cetirizine; half of these cases (3,124) involving 5,225 AE terms were reported from outside the U.S. and were the primary focus of the report. A total of 64 cases were designated as serious with 102 associated AE terms. The 3,108 cases with 7,093 associated AE terms reported by the FDA to the WHO were also tabulated for completeness; however, cases of US origin are discussed in a separate document (in the FDA's SRS and AERS databases). Cases of exUS origin comprised half (3,124/6,232) of all WHO cases and another half from the US (3,108/6,232). For the exUS cases, 5 countries accounted for 76% (2375/3124) of the total reports. These were: Germany 20% (636/3,124), United Kingdom 19% (602/3,124), Canada 17% (541/3,124), France 12% (366/3,124) and the Netherlands 7% (230/3,124).

Adult reports accounted for 74.4% (3,889/5,225) of all reported terms, pediatric cases (≤ 17 years) accounted for 8.9% (464/5,225) of all reported terms and reports without age data involved 16.7% (872/5,225) of all reported terms.

The following 5 SOCs accounted for 75% (3913/5,225) of exUS cases:

- Psychiatric disorders 20% (1,037/5,225)
- Body as a whole, general disorders 17% (911/5,225)
- Central and peripheral nervous systems disorders 15% (791/5,225)
- Skin and appendages disorders 12% (609/5,225)
- Gastrointestinal system disorders 11% (565/5,225).

The most frequently reported individual AE terms were: somnolence 8.5% (446/5,225), fatigue 6.5% (341/5,225), headache 5% (250/5,225), dizziness 3.6% (190/5,225), and nausea 2.9% (151/5,225). These 5 AEs accounted for 26% (1,378/5,225) of all reported terms. Pediatric cases (≤ 17 years) accounted for 9% (464/5225) compared to 74% (3889/5225) in adults; reports without age data involved 17% (872/5225) of all reported terms. See table below.

Table 17: Most Frequently Reported ≥ 1% AEs (exUS) for All Reports by Age Group in Descending Order of Overall Frequency SOC N (%)[a]

WHOART SOC Abbreviation	WHOART Preferred Term	Pediatric Total (≤ 17 yrs)	Adult Total (≥ 18 yrs)	No age data	Overall Total
Psych	Somnolence	30 (6.5)	299 (7.7)	117 (13.4)	446 (8.5)
Body Genrl	Fatigue	13 (2.8)	289 (7.4)	39 (4.5)	341 (6.5)
CNS & PNS	Headache	14 (3.0)	198 (5.1)	38 (4.4)	250 (4.8)
CNS & PNS	Dizziness	11 (2.4)	145 (3.7)	34 (3.9)	190 (3.6)
Gastro	Nausea	8 (1.7)	117 (3.0)	26 (3.0)	151 (2.9)
Skin	Urticaria	10 (2.2)	95 (2.4)	14 (1.6)	119 (2.3)
Skin	Rash	13 (2.8)	74 (1.9)	16 (1.8)	103 (2.0)
Gastro	Mouth dry	0 (0.0)	77 (2.0)	11 (1.3)	88 (1.7)
Gastro	Abdominal pain	11 (2.4)	57 (1.5)	14 (1.6)	82 (1.6)
Heart rate/rhythm	Palpitation	2 (0.4)	64 (1.6)	9 (1.0)	75 (1.4)
Skin	Pruritus	5 (1.1)	60 (1.5)	9 (1.0)	74 (1.4)
Body Genrl	Therapeutic response decreased	5 (1.1)	33 (0.8)	34 (3.9)	72 (1.4)
Body Genrl	Asthenia	7 (1.5)	48 (1.2)	10 (1.1)	65 (1.2)
Body Genrl	Malaise	4 (0.9)	40 (1.0)	19 (2.2)	63 (1.2)
Skin	Rash erythematous	7 (1.5)	45 (1.2)	11 (1.3)	63 (1.2)
Gastro	Dyspepsia	1 (0.2)	47 (1.2)	11 (1.3)	59 (1.1)
Psych	Depression	3 (0.6)	46 (1.2)	7 (0.8)	56 (1.1)
Gastro	Diarrhoea	4 (0.9)	38 (1.0)	13 (1.5)	55 (1.1)
Respiratory	Dyspnoea	6 (1.3)	36 (0.9)	11 (1.3)	53 (1.0)
Psych	Confusion	5 (1.1)	40 (1.0)	7 (0.8)	52 (1.0)
Psych	Agitation	7 (1.5)	35 (0.9)	9 (1.0)	51 (1.0)
Body Genrl	Medicine ineffective	23 (5.0)	17 (0.4)	10 (1.1)	50 (1.0)
	Total AE Terms (row %)	464 (8.9)	3889 (74.4)	872 (16.7)	5225 (100)
	Total Case Reports (row%)	297 (9.5)	2318 (74.2)	509 (16.3)	3124 (100)

a Unless otherwise indicated, all percents are calculated based on the total number of terms for each age group.
Adapted from sponsor's submission Item 8, Vol. 33, p. 53

Among the most frequently reported terms, two had relatively higher frequencies in the pediatric population compared to the overall population, these were: medicine ineffective 5% (overall 1%) and abdominal pain 2.4% (overall 1.6%).

With regard to serious reports, there were a total of 64 cases with 102 associated AE terms and 5 SOCs accounted for 56% (57/102) of the exUS AE terms for serious cases:

- Skin and appendages disorders 14% (14/102)
- Body as a whole general disorders 13% (13/102)
- Central and Peripheral nervous systems disorders 12% (12/102)
- Heart rate and rhythm disorders 9% (9/102)

- Liver and biliary system disorders 9% (9/102)

Only two terms had more than 2 reported occurrences, coma (3%, 3/102) and dyspnea (3%, 3/102). According to the sponsor, the reporting rates for individual terms were too small to make meaningful comparisons between ages.

There were 9 reports of death with 17 associated AE terms; 7 involved adult patients, 1 infant and 1 fetal death. Sudden death was reported in 3 instances, 3 arrhythmias (1 cardiac arrest, 1 syncope). One of the cases of arrhythmia was ventricular fibrillation (with syncope) in a patient in the 18-40 year age range. There was one report of a fetus small for gestational age and another of multiple fetal malformations. No details were provided for these cases. No deaths were reported among the pediatric age groups for reports of exUS origin.

The sponsor states that there were no new or unexpected findings that have emerged from the analysis of the safety profile of cetirizine. The majority of the reported events were not serious and the most frequent events were related to the central or peripheral nervous system, Psychiatric SOCs or to allergic phenomena. The analysis is limited by the absence of exposure data for cetirizine and the absence of any valid comparison information to place the reporting rates for the three topics into a clinical perspective.

Medical Officer Comments: The types of adverse events from the WHO database: somnolence, fatigue, headache, dizziness and nausea are similar to those previously reported adverse events with the use of cetirizine both during clinical trials and postmarketing. This database did not reveal any new safety concerns 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

A total of 25 clinical trials (15 controlled/pivotal and 10 uncontrolled/supportive) were conducted in the United States and Canada for the marketing of prescription cetirizine (Zyrtec®). These trials included more than 6,000 patients aged 12 years and older; more than 3,900 patients received Zyrtec 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 Zyrtec 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. See Table A-1 for a table of all pivotal clinical studies submitted for the approval of prescription Zyrtec.

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

A total of 4,968 patients (3,900 aged ≥ 12 years; 1,068 aged 2 to 12 years) were exposed to Zyrtec in clinical trials. These trials have been previously submitted and evaluated for safety by the FDA. There were no major safety issues identified at the time of the original Zyrtec NDA applications.

The sponsor submitted exposure to cetirizine that was derived from "units of volume measurement" (tablets, mLs, etc.) from Intercontinental Marketing Services (IMS). The total number of volume units distributed globally by Pfizer only from April 1, 1994 through March 31, 2006 was approximately ——— units with approximately ——— patient exposures: ——— total mLs, ——— and ——— unknown formulation units.

The sponsor further states that definitive conversion of packages distributed into numbers of subjects exposed is not possible as the product is marketed OTC in majority of countries and may be used by more that one member of the family. Although the adverse event databases reflect all adverse events received by both Pfizer and UCB, the patient exposure information reflects product distributed by Pfizer only, therefore not a comprehensive representation of patient exposure.

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. It is approved for use at a higher dose for up to 20 mg in other countries and is available for OTC use in many countries. 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 to switch this drug from prescription to OTC use.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

There are no new animal studies submitted with this NDA.

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 was submitted with this NDA. The sponsor provided sufficient data to characterize the pharmacological profile of cetirizine during the original submission of the NDA. The prescription label notes that the pharmacokinetics 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. 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 alcohol, sedatives and tranquilizers may increase drowsiness, and to avoid alcoholic drinks when using the product. In addition, the label should also warn 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

From a clinical safety perspective, this application is adequate and complete. There were no new studies conducted to support these submissions; therefore, no DSI inspection was requested.

7.2.9 Additional Submissions, Including Safety Update

A safety update was submitted that covers the period from May 11, 2006 to January 16, 2007 for cetirizine HCl. The update provided summaries of postmarketing adverse events reported; there were no new clinical trials completed during this time. The total volume of cetirizine distributed globally by Pfizer was approximately —— units: —— total mL and —— tablets. The sponsor states that it is not possible to count the definitive number of subjects exposed because the product is marketed OTC in majority of countries; therefore the product may be used by more than one member of the family.

There were 946 cases involving a total of 1,816 adverse event terms (MEDRA) reported for the above reporting period in patients aged <6 months old to 88 years old. Of these adverse events, 263 (28%) cases were classified as serious with 753/1,816 associated adverse event terms (which could include both serious and non-serious adverse event terms) and 13 cases (1.3%) of death. The most frequently reported adverse event terms for all cases were[13]: drug ineffective 10.7%, somnolence 10.1%, dizziness 1.5%, fatigue 1.4%, drug exposure during pregnancy 1.3%, headache 1.3%, hypersensitivity 1.3% and rash 1%. The most commonly reported serious adverse event terms were[14]: surgery 2.3% [0.07%], drug ineffective 1.9% [0.07%], hypersensitivity 1.9% [0.07%], convulsions 1.6% [0.06%], dyspnea 1.5% [0.06%], food allergy 1.5% [0.05%], disability 1.5% [0.05%], dizziness 1.3% [0.05%], asthma 1.3% [0.05%], somnolence 1.2% [0.05%], pruritus 1.2%

13 These are expressed as% (n/1816).
14 These are expressed as% n/753, overall count expressed as [n/1816].

[0.05%] , hypertension 1.2% [0.05%] and urticaria 1% [0.04%]. Most of the deaths reported in this safety update are confounded with an underlying medical illness, concomitant use of multiple medications or limited information to make a meaningful clinical assessment.

There are no new safety issues identified in this safety update.

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 Zyrtec 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 U.S.) for over 10 years now and is available for OTC use in many countries (including Canada and U.K.). The safety profile of cetirizine is well-characterized; there should be no new unexpected safety issues if this drug is marketed for OTC use in the U.S.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

A total of 25 clinical studies (15 controlled and 10 uncontrolled) were conducted in the United States and Canada. These included more than 6,000 patients 12 years and older (3,900 patients received Zyrtec) and 1,468 patients aged 2 years and older (1,068 patients received Zyrtec). The most commonly adverse events in adults and patients aged 12 years and older (N=3,646; Zyrtec=2,034, Placebo=1,612) receiving Zyrtec 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. The adverse experiences reported in pediatric patients aged 2 to 5 years in placebo-controlled trials were similar in nature and frequency to those reported in trials with older children.

Pharyngitis and somnolence were consistently reported among the clinical studies in both adults and children. Somnolence is considered to be a treatment-related adverse event for both population 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.

7.4.2 Explorations for Predictive Factors

There were no explorations for predictive factors submitted with these applications.

7.4.3 Causality Determination

This section is not applicable.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The sponsor's proposed OTC indications are similar to those of the already approved indications for prescription cetirizine. These indications are for the temporary relief of allergic rhinitis symptoms (adults and children ≥ 2 years old) and relief of itching due to hives/urticaria (adults and children ≥ 6 years old). The dosing regimen is generally similar except for some inconsistencies in the current prescription (Rx) label and the proposed OTC label.

See table below for the proposed OTC dosing of the different dosage formulations compared with the prescription label.

Table 18: Proposed OTC Dosing and Current Rx Dosing for Cetirizine

Proposed OTC Dosing					
Dosage Form	**Adults & ≥ 6y/o**	**2 to 6 y/o**	**< 2 y/o**	**≥ 77 y/o**	**Liver/Kidney Ds.**
Syrup					
1mg/mL	5 or 10mL OD depending on symptom severity	2.5 OD may inc. to 5 mL OD or 2.5 mL q12 hrs	Ask a doctor		Ask a doctor
Tablets					
5mg	1 or 2 tab OD depending on symptom severity	<6 y/o: Ask a doctor			Ask a doctor
10mg	1 tab OD; a 5 mg product may be appropriate for less severe symptoms	<6 y/o: Ask a doctor			Ask a doctor
Chewable Tablets					
5mg	1 or 2 tab OD depending on symptom severity	1 tab OD	Ask a doctor		Ask a doctor
10mg	1 tab OD; a 5 mg product may be appropriate for less severe symptoms	<6 y/o: Ask a doctor			Ask a doctor
Rx Dosing					
	5 mg or 10 mg OD depending on symptom severity	2.5 to 5 mg OD or 2.5 mg every 12 hours	**6mo to <2y/o:** 2.5mg OD, can be inc to 2.5 mg 12hrs	5 mg OD	**≥ 12 y/o:** 5mg OD **6 to 11y/o:** use the lower recommended dose

OD-once daily, inc.- increase

The dose for OTC use should be consistent with the current dosing in the Rx label. The dosing for children 2 to 5 years old (chewable tablet) is inconsistent with the prescription label and across all dosage formulations (see table below).

Medical Officer Comments: The dosing for children 2 to under 6 years of age should be consistent not only with the prescription label but also across all dosage formulations. The proposed dosing of 5mg chewable tablet daily for children aged 2 to under 6 years of age is inconsistent with the Rx label. Consumers in this age group are not made aware of the initial recommended dose of 2.5 mg once daily as stated in the prescription label; this is particularly important to those who are going to take cetirizine for the first time or in children who are closer to two years of age and are lightweight. The dosing recommendation for this age group in the prescription label was based on a review of Pediatric Supplement of Zyrtec® (cetirizine) syrup for children 2 to 5 y/o submitted by Pfizer on 5/15/97 under NDA 20-346/S-002. In this supplement, it was noted that after administration of a 5-mg oral dose of cetirizine, the systemic exposure (Cmax and AUC) of cetirizine in pediatrics 2 to 5 y/o is (1) approximately 3 to 4-fold higher than that in adults, and (2) approximately 2 to 2.5-fold higher than that in children 7-12 y/o (see Biopharm review of Dr. Tien-Mien Chen in DFS). It was communicated to the sponsor that the Agency felt the recommended initial dose for children ages 2-5 years should be 2.5 mg once a day; Pfizer agreed (see Memorandum of Telecon dated 5/6/98 filed in DFS). The dosing of an initial 2.5 mg in children 2 to 5 y/o was based on pk data in this population and therefore should not be ignored.

In addition, in the practice of medicine, it is always prudent to use the lowest effective dose that causes the least side effects when a medication is prescribed to patients. This should not be any different when a product is used in an OTC setting or in any setting where there is no learned intermediary. It is also important that the OTC label for cetirizine be consistent with its prescription label to avoid confusion in patients who are already taking the drug and purchases the product when marketed OTC. If there is a lower effective dose, then the consumer should be made aware of this and be given the option to choose which dose is more appropriate for them. The most common adverse events noted with cetirizine use are somnolence, fatigue and dry mouth. In clinical trials, the incidence of somnolence associated with cetirizine was dose related.[15] Therefore, consumers who experience somnolence/ drowsiness might experience a lesser degree of this adverse event with a lower dosage strength that is efficacious as well.

Dosage Adjustment: The sponsor's proposed OTC label does not include a dose adjustment in elderly patients. Similar to the Rx label, a dose adjustment of 5 mg once daily for the elderly (>65 years old) should be included in all the OTC labels.

Medical Officer Comments: This dose adjustment was based on study for the original approval of Zyrtec under NDA 19-835 to support geriatric labeling (Study no. 85-N-0073: CP-8). This study showed that the pk profile of cetirizine for the geriatric age group (>65 y/o, mean age=77) was considerably different than the profile obtained for the adult group (<65 y/o) in that the normal geriatric subjects cleared the drug slower than the normal adult volunteers. The extent of absorption in the (AUC) was about 70% more and Cmax was 20% more for the geriatric group compared to the adult group (see also section 5.1). Therefore, a dose adjustment based on age that

15 Cetirizine Prescription Label, Adverse Reactions section.

includes the full range of ages at risk supported by the data (not just the mean age of 77y/o) is necessary to include in the OTC label. A warning for patients with kidney (and liver) problems to ask a doctor before use does not capture the elderly patients who may not be aware that they have a decrease in their renal function. It is to be noted that some foreign OTC labels for cetirizine (e.g. Reactine® in Canada) include a dose adjustment for consumers 65 years and older.

During a pre-NDA a meeting on June 27, 2006 with the sponsor (see meeting minutes filed in DFS), dosing in the elderly was discussed. FDA stated that based on information from the prescription Zyrtec label, 77 appears to be the mean age of individuals who demonstrated reduced clearance and higher serum levels of cetirizine. Thus, to make 77 years of age the minimum age for the dosage adjustment warning would not be appropriate. The dosage warning should include the full range of ages at risk and should be supported by the data. Pfizer stated that they agreed with FDA's comment about not using 77 years of age as an age cut off for potential dosing adjustment and have decided to focus this warning on the issue of renal function and not age. FDA stated that Pfizer may want to consider a warning that includes both age and renal function in order to capture the older population who may not be aware that they have a decrease in their renal function. An age-related dose adjustment should be based on data from studies in this age group. Pfizer agreed to reevaluate their proposed renal function warning and was going to provide alternate language in the label.

The dosing for the hives relief indication is the same as that of the allergic rhinitis except for children under 6 years of age, the consumer is instructed to "ask a doctor".

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 label contains similar warnings.

The prescription information for cetirizine states that there was 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 larger theophylline doses could have a greater effect. There are no drug interaction warning listed in the proposed OTC label.

There is no new information regarding drug interaction that precludes the switch of cetirizine for OTC use, or warrants additional warning in the proposed label.

8.3 Special Populations

No new information regarding special populations was submitted with these NDAs. 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/m^2 basis). There no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Zyrtec should be used during pregnancy only if clearly needed. The proposed OTC label directs pregnant women to ask 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 Zyrtec in nursing mothers is not recommended. The proposed OTC label directs nursing mothers to ask a health professional before using the product. However, the OTC label should be consistent to the prescription label and state 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 decreased 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 OTC label should include a dosage adjustment of 5 mg once daily in the elderly population. This should include the full range of ages at risk supported by the data, i.e., patients who are 65 years old (and not just a mean age of 77 years). See Medical Officer Comments on dosage adjustment in the Dosage and Administration (8.1) section of this NDA review.

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 use in Zyrtec in children below the age of 6 years with impaired renal or hepatic function is not recommended due to the difficulty in reliably administering doses of less than 2.5 mg (½ teaspoon) of Zyrtec syrup and in the absence of pharmacokinetic and safety information for cetirizine in children below the age of 6 years with impaired renal or hepatic function.

The pharmacokinetics 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.

Similar to the prescription label, the OTC label directs consumers with kidney and liver disease to ask a doctor.

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.

Similar to the prescription label, the OTC label directs consumers with kidney and liver disease to ask a doctor.

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.

8.4 Pediatrics

Cetirizine is currently available for prescription use in children as young as 6 months old. The sponsor has fulfilled the pediatric study requirement for this application for patients 6 months and older for the relief of the hives and for patients two years and older for allergic rhinitis under the prescription indications. Therefore, no new pediatric studies were required for these submissions.

The safety and effectiveness of cetirizine in pediatric patients under the age of 6 months have not been established. The safety of Zyrtec has been demonstrated in pediatric patients aged 6 months to 11 years. However, the effectiveness of Zyrtec 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 Zyrtec 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. See also section 5.1 and Medical Officer Comments on dosing in the Dosage and Administration (8.1) section of this NDA review for detailed pharmacokinetic information in the pediatric population.

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

The medical literature was surveyed to search for information that references to the safety profile of cetirizine. The sponsor performed an update of a comprehensive literature review for cetirizine using the MEDLINE Database from 1966 to July 2006. A total of 382 citations were identified when searched under the headings adverse effects, clinical trials and reviews. The review of safety citations were divided into 3 sections: clinical trials, case reports/series and review articles.

Articles involving cetirizine/pseudoephedrine combination, articles that did not contain information related to safety, or were published after the approval of cetirizine (1995) in the U.S. were reviewed but will not be discussed below. Full reference for these articles can be found in the Appendix section of this review.

Published Clinical Trials

1) *Day JH, et. al. (2005)* evaluated the comparative efficacy of cetirizine and fexofenadine for seasonal allergic rhinitis, 5-12 hours postdose, in the environmental exposure unit. Eligible ragweed allergic subjects were exposed to pollen in the Environmental Exposure Unit and randomized (n = 599) to a single dose of cetirizine, 10 mg; fexofenadine, 180 mg; or placebo (2.5:2.5:1). The authors concluded that cetirizine produced greater relief of seasonal allergic rhinitis symptoms than fexofenadine at 12 hours postdose and over the 5 to 12-hour postdose period. The incidence of treatment-emergent adverse events and somnolence were similar among groups: cetirizine, 25.3% and 0.8%, respectively; fexofenadine, 29.6% and 0%, respectively; placebo, 35% and 0%, respectively. Headache was the most common adverse event in each group. Somnolence occurred in 0.8% of subjects on cetirizine and in 0% on fexofenadine or placebo.

2) *Corren J, et. al. (2005)*. Evaluated the effectiveness of two selective histamine H-1 receptor antagonists, azelastine nasal spray compared with oral cetirizine in patients with seasonal allergic rhinitis. A total of 299 patients (12 to 74 y/o) with moderate to severe SAR completed 2 weeks of study treatment. Azelastine nasal spray produced significantly greater improvements in total nasal symptom score (TNSS) and total Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score compared with cetirizine. The most common adverse event was somnolence (2.6%). All other adverse events were reported in less than 1% of patients. One patient in the cetirizine group discontinued the study due to somnolence and 1 discontinued due to a skin rash.

3) *Hyo S, et.al (2005)* evaluated the efficacy of short-term administration of 3 antihistamines vs. placebo under natural exposure to Japanese cedar pollen in 113 adult patients. Patients were divided into 4 groups according to treatment assignment: cetirizine 10 mg/day, fexofenadine 120 mg/day, loratadine 10 mg/day, and placebo 2x/day. Symptoms were recorded hourly during the study and patients completed the Japanese version of the RQLQ before and after the trial. Cetirizine seems to be more effective than fexofenadine and loratadine at reducing subjective symptoms in this study population. No serious adverse effects were reported. The most frequently reported adverse effect was drowsiness, 2 each in the cetirizine, exofenadine, and loratadine groups, and 1 in the placebo group.

4) *Martinez-Cocera C, et. al. (2005)* evaluated a new antihistamine with antiplatelet-activating factor (PAF) activity, rupatadine 10 mg and cetirizine 10 mg in seasonal allergic rhinitis in 249 patients for two weeks. The main efficacy variable was the mean total daily symptom score (mTDSS) and was based on the daily subjective assessment of the severity of each rhinitis symptoms recorded by patients in their diaries. Results suggest that rupatadine 10 mg may be a valuable and safe alternative for the symptomatic treatment of SAR. Most (67%) reported adverse events were mild in terms of intensity. Somnolence was reported in 9.6% cetirizine and 8.5% rupatadine patients. Most frequent cetirizine-related adverse events were headache (19.7%), fatigue/asthenia (6.8%) and somnolence (8.5%).

5) *Purohit A, et. al. (2004)* investigated the onset of action and magnitude of effect of fexofenadine and cetirizine as assessed by inhibition of histamine-induced wheal-and-flare reaction in 42 adult volunteers. Skin prick tests were undertaken using histamine before and after treatment. The two drugs had comparable onset of action times and similar frequencies of inhibition, as evaluated by the occurrence of 95% inhibition of histamine-induced wheal and flare. There was no severe AE during fexofenadine treatment, whereas 2 subjects experienced a severe effect (fatigue and somnolence) during cetirizine treatment.

6) *Takahashi H, et. al. (2004)* evaluated the effects of the following antihistamines: bepotastine, cetirizine, fexofenadine, and olopatadine on histamine-induced wheal and flare response, sedation, and psychomotor performance. Bepotastine 10 mg 2x/day, cetirizine 10 mg once daily, fexofenadine 60 mg 2x/day, and olopatadine 5 mg 2x/day or placebo was given in a double-blind manner to 7 healthy volunteers before histamine challenge by iontophoresis. All active treatments yielded significant reduction of histamine-induced wheal and flare response compared to placebo ($P < 0.01$). Olopatadine, fexofenadine, and cetirizine showed a significant systemic sedative effect in this order with bepotastine showing the least sedative effect. Moreover, olopatadine affected psychomotor performance most markedly, which was followed by fexofenadine and cetirizine.

7) *Tashiro M, et. al. (2004)* evaluated the sedative profiles of fexofenadine and cetirizine by measurement of psychomotor performance, subjective sleepiness, and brain histamine H1-receptor occupancy (H1RO) using 11C-doxepin positron emission tomography in 20 healthy volunteers. Hydroxyzine 30 mg was included as a positive control. In psychomotor tests, fexofenadine was not significantly different from placebo and significantly less impairing than cetirizine on some tasks, as well as significantly less impairing than hydroxyzine on all tasks. For subjective sleepiness, fexofenadine was not significantly different from placebo, whereas cetirizine showed a trend toward increased sleepiness compared with fexofenadine and placebo. H1RO was negligible with fexofenadine (0.1%) but moderately high with cetirizine (26%). It is to be noted that the cetirizine dose was double than the approved dose (U.S.) and the fexofenedine was used at an approved dose, and therefore the result of this study will have to be interpreted with caution. It was reported that no other information regarding adverse events or safety data related to cetirizine were reported.

8) *Purohit A, et. al. (2004)* compared the activity of cetirizine and desloratadine on histamine-induced wheal-and-flare responses in 18 adult volunteers. Skin reaction to histamine by

3) *Conboy-Ellis K (2005)* reviewed the efficacy and safety of second-generation prescription antihistamines using selected published clinical trials to inform nurse practitioners (NP) in order to optimally manage patients presenting with SAR. The authors noted that cetirizine 10 mg daily had a significantly greater incidence of drowsiness and fatigue than fexofenadine HCl 120 and 180 mg in patients with SAR, and was therefore more likely to cause sedation and impairment. Cetirizine at recommended doses impaired performance in driving studies.

4) *Blaiss M (2004)* reviewed pertinent articles identified in the literature through a MEDLINE search (1990-2003) and provided an overview of the diagnostic and treatment challenges posed by allergic rhinitis (AR) in school-age children by comparing the available treatment modalities for this age group. It was noted that newer agents, such as cetirizine, loratadine, desloratadine, and fexofenadine are effective and safer than the older drugs, no cardiotoxicity and less sedation. The incidence of drowsiness due to cetirizine was reported to be approximately twice that seen with fexofenadine or placebo. Cetirizine, even at recommended doses, has been shown to impair driving ability and decrease scores on objective psychometric tests.

Medical Officer Comments: Similar to the adverse events database from the sponsor's clinical trials, the most commonly reported adverse events generally relate to the central nervous system and skin/cutaneous conditions. The most frequently reported adverse events in the clinical trials found in the literature were somnolence/drowsiness, fatigue and dry mouth. In the clinical studies of cetirizine in which laboratory testing was monitored, no clinically important changes in laboratory results were noted following exposure to cetirizine. In some studies, cetirizine at recommended doses did not produce higher rates of sedation than placebo or other non-sedating antihistamines (terfenadine, astemizole and loratadine). In four clinical studies and 3 review articles, sedation/ drowsiness due to cetirizine was reported to be higher than other second generation antihistamines.

The observed adverse events reported in the literature have been previously recorded in other safety databases; those that were not previously reported had limited clinical information or had no conclusive evidence of a causal relationship between the use of cetirizine and any previously unidentified adverse events with cetirizine use. A review of the published literature on cetirizine did not reveal any new serious, unusual, significant or new safety concerns that would preclude the OTC use of cetirizine.

8.7 Postmarketing Risk Management Plan

There is no postmarketing risk management plan recommended for these NDAs.

8.8 Other Relevant Materials

There are no other relevant materials submitted for the review.

9 OVERALL ASSESSMENT

9.1 Conclusions

Allergic rhinitis and hives are OTC indications that consumers can self-diagnose and treat. There is currently a similar second generation antihistamine, loratadine, marketed OTC for the same indications. Data from clinical studies, review of literature and postmarketing information support the safety of cetirizine in the treatment of symptoms of allergic rhinitis and relief of itching due to hives. Human exposure to all formulations of cetirizine is extensive, and in general, adverse events that were noted in the postmarketing safety database for cetirizine were similar to those noted in clinical trials, such as somnolence, fatigue, dizziness, and nausea. Postmarketing safety data from Canada where loratadine is available as a non-prescription product did not reveal any safety signal that would preclude the OTC marketing of cetirizine in the United States.

In a discussion at a Joint Nonprescription and Pulmonary Advisory Committee meeting held on May 11, 2001 (http://www.fda.gov/ohrms/dockets/ac/cder01.htm), it was determined that the second generation antihistamines, including cetirizine, have a safety profile acceptable for OTC marketing.

In summary, from a clinical perspective, the sponsor adequately supports the safety of the single-ingredient cetirizine products for OTC use. However, the OTC labels of these cetirizine products should be consistent with the prescription label. The sponsor should modify the proposed labels to include a dose adjustment of 5 mg once daily in patients 65 and older for all dosage formulations, and revise the 5 mg chewable tablet label to communicate a lower starting dose of 2.5 mg in children 2 to 6 y/o as recommended in the prescription label.

9.2 Recommendation on Regulatory Action

The sponsor adequately supports the efficacy and safety of its proposed Zyrtec® line of cetirizine products for the following indications:

- 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) due to [redacted] (dust mites, animal dander and molds) and [redacted] (ragweed, grass and tree pollens) upper respiratory allergies in adults and children aged 2 years and older.
- relief of itching due to hives (urticaria) in adults and children aged 6 years and older.

Therefore, from a clinical safety perspective, this reviewer recommends approval of these applications as long as the sponsor incorporates the reviewing team's labeling recommendations for the different formulations of the cetirizine products.

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

A member of the Interdisciplinary Scientist (IDS) group in the Division of Nonprescription Regulation Development (DNRD) will be reviewing the proposed label and package insert in detail.

The cetirizine OTC labels for all the dosage formulations of Zyrtec® (cetirizine) should be consistent with the prescription labels. This Medical Officer has the following general recommendations and comments to the proposed OTC labels:

- Similar to the Rx label, a dose adjustment of 5 mg once daily for the elderly (>65 years old) should be included in all the OTC labels.
- The dosing for children 2 to under 6 years of age (allergy relief) should be consistent not only with the prescription label but also across all dosage formulations.
- Similar to the Rx label, the OTC label should state that the use of this drug in nursing mothers is not recommended and to ask a health professional before use.
- The Package Insert (PI) should be revised to incorporate the following changes:
  - Under the heading "What is Zyrtec?" the phrase "*...so you can go anywhere life takes you.*" should be deleted. This phrase is misleading and unrelated to the indications of the drug product.
  - Under the heading "Who Should Not Take Zyrtec?", the following should be included:
    - If you are breast-feeding, this product is not recommended.
    - Liver and kidney disease < 6 years of age.

The sponsor had sent two sets of OTC labels. The first set was submitted during the submission of the Zyrtec Rx-to-OTC switch on January 16, 2007. These labels have been amended on July 19, 2007 after a teleconference held between the Office of Nonprescription Products (ONP) and the sponsor on May 23, 2007 wherein the sponsor was made aware of the labeling inconsistency between the proposed OTC labels and current Rx label, specifically regarding the directions of starting with an initial lower dose (see meeting minutes filed in DFS). The sponsor had revised the proposed OTC labels subsequent to this meeting. See section 8.1 for detailed comments on dosing and Appendix for proposed labels and package inserts.

9.5 Comments to Applicant

None.

10 APPENDICES

Table A-1: All Pivotal Clinical Studies Submitted under Rx Zyrtec NDAs

Trial Number/ Population	Treatment Duration	Treatment Arms	Number Subjects	Age (yr.) mean ± S.D.
SAR-1 Adults	1 week	Cetirizine 5 mg /day	102	36.8 ±13.5
		Cetirizine 10 mg /day	106	38.8 ± 13.1
		Cetirizine 20 mg /day	104	37.2 ± 12.8
		Placebo	103	39.6 ± 12.7
SAR-2 Adults	2 weeks	Cetirizine 10 mg QAM	49	38.5 ±10.8
		Cetirizine 10 mg QHS	50	40.5 ± 14.0
		Cetirizine 5 mg BID	50	41.6 ± 11.8
		Placebo	51	40.1 ± 14.3
SAR-3 Adults	2 weeks	Cetirizine 5 mg /day	77	30.6 ± 13.0
		Cetirizine 10 mg/day	79	30.7 ± 10.6
		Chlorpheniramine 16 mg/day	77	31.7 ± 13.8
		Placebo	77	35.1 ± 12.1
SAR-4 Adults	4 weeks	Cetirizine 5 mg /day	79	33.3 ± 12.8
		Terfenadine 120 mg/day	78	30.9 ± 12.6
		Placebo	75	33.2 ± 11.4
L-0362 Adults	2 weeks	Cetirizine 10 mg/day	431	37.8 ±10.8
		Placebo	431	36.5 ± 10.7
L-0364 Adults	2 weeks	Cetirizine 10 mg/day	201	35.8 ±10.6
		Placebo	197	37.5 ± 11.0
A1431009 Pediatric Age 6-12	2 weeks	Cetirizine 10 mg/day	228	8.6 ± 1.7
		Loratadine 10 mg/day	219	8.9 ± 1.6
		Placebo	229	8.9 ± 1.6
PED-2 Pediatric Age 6-12	2 weeks	Cetirizine 5 mg/day (low wt.)	11	7.4 ± 1.4
		Placebo (low wt.)	13	7.4± 0.8

Trial Number/ Population	Treatment Duration	Treatment Arms	Number Subjects	Age (yr.) mean ± S.D.
		Cetirizine 10 mg /day (high wt)	73	9.4 ± 1.3
		Placebo (high wt.)	73	9.4 ± 1.4
A160 (UCB 89) Pediatric Age 2-6	2 weeks	Cetirizine 5 mg/day	53	4.7 ±1.0
		Placebo	53	4.3 ± 1.2
PAR-1 Adults	4 weeks	Cetirizine 10 mg/day	72	34.1 ±11.2
		Cetirizine 20 mg/day	71	34.2 ± 12.3
		Placebo	73	35.5 ±12.5
PAR-3 Adults	4 weeks	Cetirizine 5-10 mg/day	75	36.2 ±12.6
		Diphenhydramine 75-150 mg /day	75	35.8 ± 12.1
		Placebo	76	38.2 ±12.6
PAR-4 Adults	8 weeks	Cetirizine 5 mg/day	80	37.8 ±12.2
		Cetirizine 10 mg /day	78	34.6 ± 13.1
L-0352 Adults	4 weeks	Placebo	80	35.8 ± 12.2
		Cetirizine 10 mg /day	158	37.5 ±11.6
		Placebo	162	37.2 ± 10.5
URT-2 Adults	4 weeks.	Cetirizine 5-10-20 mg /day	69	36.2 ±14.1
		Hydroxyzine 25-50-75 mg/day	72	36.2 ± 12.2
		Placebo	74	38.0 ±13.9
URT-3 Adults	4 weeks	Cetirizine 10 mg /day	61	34.4 ± 12.8
		Astemizole 10 mg /day	58	37.2 ± 14.4
		Placebo	58	41.8 ± 15.6

Adapted from sponsor's submission sNDA summary section 3.8.3

Table A-2: Characteristics of Cetirizine for Canada (OTC), U.S. (Rx) and All Cases

		Canada	United States	All Cases
Total Number of Case Reports		3,277	7259	14,301
Total Number of Adverse Event Terms		5,267	17,020	29,448
Age, years	N	2,303	3,773 (51.98)	9,174 (64.15)
	Mean[a]	40.08	37.01	39.75
	Range	< 1-95	< 1-103	<1 - 103
Age Group, years	<6 months	3 (0.09)	63 (0.87)	76 (0.53)
	6 months to <12 months	3 (0.09)	37 (0.51)	45 (0.31)
	12 months to <2 years	9 (0.27)	80 (1.10)	99 (0.69)
	2 to <6 years	79 (2.41)	479 (6.60)	641 (4.48)
	6 to <12 years	138 (4.21)	367 (5.06)	609 (4.26)
	12 to <18 years	123 (3.75)	156 (2.15)	413 (2.89)
	18 to <65 years	1600 (48.83)	1,956 (26.95)	5,814 (40.65)
	65 to <77 years	254 (7.75)	401 (5.52)	1,006 (7.03)
	≥ 77years	94 (2.87)	234 (3.22)	471 (3.29)
	unknown	974 (29.72)	3,486 (48.02)	5,127 (35.85)
Gender	Female	2,017 (61.55)	4,030 (55.51)	8,157 (57.04)
	Male	1,165 (35.55)	2,242 (30.89)	4,849 (33.91)
	Unknown	95 (2.90)	987 (13.60)	1,295 (9.06)
Case Seriousness	Nonserious	3,213 (98.05)	5,723 (78.84)	11,890 (83.14)
	Serious	64 (1.95)	1,235 (17.01)	2,057 (14.38)
	Death	0 (0.00)	301 (4.15)	354 (2.48)
Report Type	Spontaneous	8095 (95.81)	6,733 (92.75)	13,715 (95.90)
	Literature	34 (0.40)	8 (0.11)	68 (0.48)
	Otherδδ	320 (3.79)	518 (7.13)	518 (3.62)
Case Outcome	Unknown	1,293 (39.46)	3,813 (52.52)	6,325 (44.23)
	Not recovered	1,038 (31.68)	1,277 (17.59)	2,545 (17.80)
	Recovered	698 (21.30)	733 (10.65)	3,177 (22.22)
	Recovering	93 (2.84)	307 (4.23)	668 (4.67)
	Recovered with sequelae	1 (0.03)	1 (0.01)	5 (0.03)
	Not applicable[b]	154 (4.70)	787 (10.84)	1,227 (8.58)
	Death	0 (0.00)	301 (4.15)	354 (2.48)
Report Source[c]	Healthcare Professional	106 (3.23)	3,670 (50.56)	6,929 (48.45)
	Patient/consumer	2,885 (88.04)	3,066 (42.23)	6,402 (44.77)
	Health Authority	10 (0.31)	13 (0.18)	97 (0.68)
	Literature	3 (0.09)	17 (0.23)	78 (0.55)
	Sales Representative	240 (7.32)	32 (0.44)	275 (1.92)
	Attorney	6 (0.18)	12 (0.17)	19 (0.13)
	Solicited	0	433 (5.96)	433 (3.03)
	Spontaneous	27 (0.82)	16 (0.22)	66 (0.46)
	Non-Pfizer Study	0	0	2 (0.01)

a Mean age was based on the number of cases in which age was reported (not total number of cases).
b Not applicable - reflects data migrated from historical databases, as well as cases with the terms drug ineffective, exposure in utero, no adverse event, medication error, and accidental exposure.
c Report Source – where multiple report sources are identified only one is recorded in this table.

Adapted from Sponsor's submission Item 8 / Item 10 Vol. 34 p. 142

Table A-3: Countries where Cetirizine is either OTC or Pharmacy-only Restricted Status

Country
1. Australia
2. Austria
3. Belgium
4. Canada
5. Czech Republic
6. Denmark
7. Finland
8. France
9. Germany
10. Ireland
11. Italy
12. Korea
13. Netherlands
14. New Zealand
15. Norway
16. Philippines
17. Poland
18. Singapore
19. Slovak Republic
20. Slovenia
21. Spain
22. Sweden
23. Switzerland
24. United Kingdom

9 Page(s) Withheld

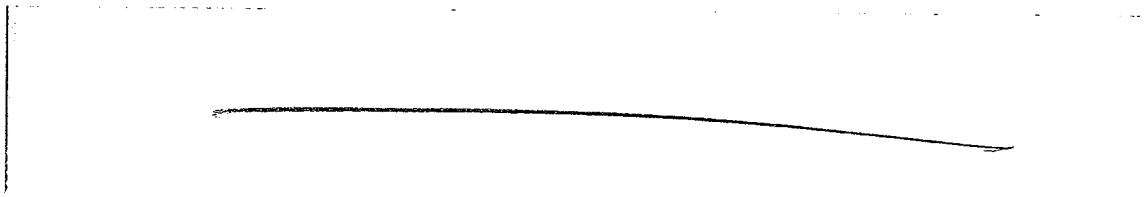
_____ Trade Secret / Confidential

6 Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Medical-*_____

Figure 12: Hives Relief Package Insert



10.1 Review of Individual Study Reports

Not applicable.

10.2 Line-by-Line Labeling Review

See section 9.4.

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CLINICAL REVIEW

Application Type	NDA
Submission Number	NDA 19-835/S-022 Zyrtec tablets NDA 21-150/S-007 Zyrtec-D NDA 21-621/S-005 Zyrtec Chewable tablets NDA 22-155 Zyrtec Syrup
Submission Code	SE06, S_002 SE06, S_007 SE06, S_005 N, 000
Letter Date	January 9, 2007
Stamp Date	January 11, 1007
PDUFA Goal Date	November 9, 2007
Reviewer Name	Susan Limb, MD
Review Completion Date	September 10, 2007
Established Name	Cetirizine Cetirizine hydrochloride 5mg/pseudoephedrine hydrochloride 120mg
(Proposed) Trade Name	Zyrtec Zyrtec-D
Therapeutic Class	Antihistamine Antihistamine/decongestant
Applicant	McNeil Consumer Healthcare
Priority Designation	S
Formulation	Oral tablets, chewable tablets, and oral syrup
Dosing Regimen	Once or twice daily (per formulation and age)
Indication	Symptoms of hay fever or other upper respiratory allergies: hives; nasal congestion hay fever, or other upper respiratory allergies (OTC indications)
Intended Population	2 years of age and older (allergic rhinitis) 6 years of age and older (hives)

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The Applicant proposes a partial Rx to OTC switch of cetirizine (Zyrtec®) and cetirizine/pseudoephedrine (Zyrtec-D 12-Hour Extended Release Tablets®).
For cetirizine, the Applicant proposes an OTC switch for the following indications: 1) treatment of nasal allergy symptoms in patients 2 years of age and older and 2) treatment of chronic hives in patients 6 years of age and older. Treatment of perennial allergic rhinitis (PAR) in children under the age of 2 years and treatment of chronic idiopathic urticaria (CIU) in patients under the age of 6 years will remain prescription-only indications. The Applicant also proposes an Rx to OTC switch for cetirizine/pseudoephedrine (Zyrtec-D 12-Hour Extended Release Tablets®) for the treatment of nasal allergy symptoms, including congestion in patients 12 years of age and older. For cetirizine/pseudoephedrine, the OTC switch will be complete; thus, there will be no prescription indications remaining.

At a meeting in May 2001, the Joint Advisory Committees on Nonprescription and Pulmonary-Allergy Drug Products concluded that cetirizine demonstrates a risk/benefit profile suitable for an OTC antihistamine. Because of the extensive pre-approval and post-approval database for cetirizine, no new clinical studies were required to support this application. Therefore, no new efficacy and safety studies were submitted for the proposed OTC switch of cetirizine and cetirizine/PSE. To support these applications, the Applicant references the efficacy and safety data previously reviewed in the original NDAs that supported the approval of Zyrtec and Zyrtec-D as well as post-marketing safety data. The referenced studies provide adequate efficacy and safety data to support the proposed partial OTC switch. Review of post-marketing safety data does not identify any new safety signals.

The recommended action is **Approval**.

1.2 Recommendation on Postmarketing Actions

No postmarketing actions are recommended.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Cetirizine is currently approved prescription for the following indications:

- relief of symptoms associated with seasonal allergic rhinitis due to allergens such as ragweed, grass, and tree pollens in adults and children 2 years of age and older
- relief of symptoms associated with perennial allergic rhinitis due to allergens such as dust mites, animal dander and molds in adults and children 6 months of age and older
- treatment of uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 months of age and older

Cetirizine/PSE is currently approved prescription for the following indication:

- relief of nasal and non-nasal symptoms associated with SAR or PAR in adults and children 12 years of age and older.

The application for the partial OTC switch of cetirizine and cetirizine/PSE was submitted under Section 505(b)(2) of the FD&C Act. The regulation permits an approval of such a switch to be based upon the Agency's previous findings of safety and efficacy for the drug. The Applicant must provide adequate support for the use of the product in the OTC setting. At a meeting in May 2001, the Joint Advisory Committees on Nonprescription and Pulmonary-Allergy Drug Products concluded that cetirizine demonstrates a risk/benefit profile suitable for an OTC antihistamine. Because of the extensive pre-approval and post-approval database for cetirizine, no new clinical studies are required to support this application. Therefore, no new efficacy and safety studies were conducted for the proposed switch of cetirizine and cetirizine/PSE.

1.3.2 Efficacy

The Applicant proposes the following OTC indications for cetirizine:

- temporary relief of symptoms of hay fever or other upper respiratory allergies (runny nose; sneezing; itchy, watery eyes; itching of the nose and throat)
- provides relief of the above symptoms due to —— dust mites, animal dander and molds) and —— (ragweed, grass and tree pollens) upper respiratory allergies
- relief of hives

The Applicant proposes the following OTC indications for cetirizine/PSE:

- temporary relief of symptoms of hay fever or other upper respiratory allergies (runny nose; sneezing; itchy, watery eyes; itching of the nose and throat)
- provides relief of the above symptoms due to —— dust mites, animal dander and molds) and —— ragweed, grass and tree pollens) upper respiratory allergies
- temporary relief of nasal congestion ———— hay fever or other upper respiratory allergies
- reduces swelling of nasal passages
- temporarily relieves sinus congestion and pressure
- temporarily restores freer breathing through the nose

As discussed above, no new efficacy studies were submitted with the application. The Applicant references data previously submitted in support of the original NDAs. These data support the efficacy of cetirizine and cetirizine/PSE for the proposed OTC switch. ————

. Although the prescription label for cetirizine includes specific allergens such as dust mites and ragweed, specific allergens are typically no longer included in prescription labeling because the specific allergen does not add any information to the indication, since the medication is assumed to be effective for all allergens regardless of the allergens studied in the pivotal trials.

1.3.3 Safety

The safety of cetirizine for OTC switch is supported by the referenced studies from the original NDA and an extensive post-marketing safety database. No new safety studies were required for this application. The CDER OTC Switch Review Team's review of safety information for cetirizine and the OTC monograph for nasal decongestants support the safety of OTC use of cetiririzine and cetirizine/PSE. The CDER OTC Switch Review Team conducted a review of worldwide safety information to determine whether there were safety concerns that would prevent the use of cetirizine (as well as loratadine and fexofenadine) in the OTC setting. Results of this review were presented at a joint meeting of the Nonprescription and Pulmonary-Allergy Drug Products Advisory Committees on May 11, 2001. The Advisory Committee determined that cetirizine has a safety profile acceptable for OTC marketing [http://www.fda.gov/ohrms/dockets/ac/cder01.htm, Pulmonary-Allergy Drugs Advisory Committee]. PSE is an OTC monograph oral nasal decongestant, and is considered to be safe and effective in adults and children 12 years and older at 60 mg every four to six hours, not to exceed 240 mg per day. The total daily dose of PSE in the proposed product is the same as the OTC monograph dose.

1.3.4 Dosing Regimen and Administration

Cetirizine is available in several oral formulations: 5- and 10-mg tablets, 5- and 10-mg chewable tablets, and 5mg/5ml syrup. The recommended OTC dose for the various indications is provided below. The remaining prescription indications and dosing are also shown below in the shaded areas.

Indication	≥12 years	6 to 11 years	2 to 5 years	12 months to < 2 years	6 to < 12 months
SAR	5 or 10 mg QD	5 or 10 mg QD	2.5 mg QD 2.5 mg BID 5 mg QD	Not indicated	Not indicated
PAR	5 or 10 mg QD	5 or 10 mg QD	2.5 mg QD 2.5 mg BID 5 mg QD	2.5 mg QD 2.5 mg BID	2.5 mg QD
CIU	5 or 10 mg QD	5 or 10 mg QD	2.5 mg QD 2.5 mg BID 5 mg QD	2.5 mg QD 2.5 mg BID	2.5 mg QD

1.3.6 Special Populations

The current Rx product label recommends a 5-mg dose in patients 12 years of age and older with decreased renal function (CrCl 11-31 mL/min), hepatic impairment, and patients on hemodialysis (CrCl <7 mL/Min). The OTC product label should advise patients with kidney or liver disease to consult with their healthcare professional prior to dosing.

Cetirizine/PSE contains 5 mg cetirizine/120 mg pseudoephedrine. The recommended dose is 1 tablet twice daily. For patients with decreased renal function or hepatic impairment, the current Rx product label recommends 1 tablet once daily. The OTC product label should advise patients with kidney or liver disease to consult with their healthcare professional prior to dosing.

The product label for prescription cetirizine recommends a dose adjustment for patients 77 years and older. The original geriatric PK study referenced in the label included comparative PK data on two groups: 1) <65 years and 2) 65 years and older. The mean age of the second group was 77 years and used as the cutoff age for the product label. Review of the data showed that age-related decreases in renal clearance accounted for the decreased clearance noted in older patients. The primary safety concern is an increased risk of sedation in patients with decreased creatinine clearance. To maintain consistency with the general guidelines of cetirizine prescription labeling as well as other OTC labels regarding age cut-offs for geriatric patients, the OTC labels for cetirizine should recommend the lower 5 mg dose for adults 65 years of age and older. For the 10 mg dose, patients should be advised to consult their physician.

Of note, the prescription label for cetirizine/PSE does not recommend any dose adjustment for geriatric patients; similarly, no age-based dose adjustments should be included on the OTC label for cetirizine /PSE. In general, the rate of sedation for cetirizine/PSE (1.9%) is much less than that observed for cetirizine (11-14% for 5 to 10 mg doses), presumably offset by the sympathomimetic effects of PSE. Separate geriatric studies were not performed with cetirizine/PSE; however, the Rx label does warn that elderly patients may be more likely to experience adverse reactions with sympathomimetic amine use.