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APPLICATION NUMBER:

21-150/S007

MEDICAL REVIEW(S)

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
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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 [redacted], 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)

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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. ———

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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 cetiriirizine 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.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Cetirizine hydrochloride is a selective H_1-receptor antagonist, approved for the following Rx indications:

- Relief of symptoms associated with seasonal allergic rhinitis (SAR) in adults and children 2 years of age and older
- Relief of symptoms associated with perennial allergic rhinitis (PAR) in adults and children 6 months of age and older
- Treatment of uncomplicated skin manifestations of chronic idiopathic urticaria (CIU) in adults and children 6 months of ages and older

Cetirizine/PSE is a combination antihistamine/decongestant drug product, approved for the following Rx indication:

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

2.2 Currently Available Treatment for Indications

In addition to avoidance of allergens, antihistamines are the first-line treatment for symptoms of allergic rhinitis. Several antihistamines are currently marketed as OTC monograph drugs in the US, including first-generation agents such as brompheniramine, chlorpheniramine, diphenhydramine, and doxylamine. These products are indicated for the treatment of symptoms of "hay fever or other upper respiratory allergies" [21 CFR 341.72]. The first-generation antihistamines are characterized by sedation as an adverse effect. There are also antihistamines marketed OTC in the US that were initially approved as NDA products, such as clemastine, and the second-generation antihistamine, loratadine and loratadine/PSE. Loratadine and other second-generation antihistamines typically have limited penetration of the CNS and are associated with less or minimal sedation. There are numerous antihistamines which are available only by prescription in the US, including hydroxyzine, cyproheptadine, fexofenadine, and desloratadine, in addition to cetirizine.

2.3 Availability of Proposed Active Ingredient in the United States

Cetirizine is currently marketed in the US in various oral formulations: 5- and 10-mg tablets, 1mg/ml syrup, and 5- and 10-mg chewable tablets.

2.4 Important Issues With Pharmacologically Related Products

As noted above, both first and second generation antihistamines can cause sedation, although the sedation is typically much less with second generation agents.

Two less-sedating antihistamines previously approved in the US, terfenadine and astemizole, were withdrawn from the market due to their association with fatal cardiac arrhythmias. These drugs prolonged the QTc interval and were associated with torsades de pointes. The second-generation antihistamines currently available on the market – loratadine, desloratadine, fexofenadine, and cetirizine – do not cause significant QT prolongation and have not been associated with similar cardiac events.

2.5 Presubmission Regulatory Activity

On June 6, 2006, a pre-IND meeting was held with the holder of the original NDA, Pfizer Consumer Healthcare, to discuss the planned Rx-to-OTC switch. Major points addressed during the meeting included the proposed indications and guidelines for use in pediatric and geriatric patients. [redacted]. Current pediatric age ranges for OTC antihistamines were also discussed, as well as the selection of appropriate dosing recommendations for elderly patients with age-related decreased creatinine clearance.

On December 12, 2006, a teleconference was held with Pfizer to discuss two environmental exposure unit studies to support a prevention claim for cetirizine. The Agency discussed the questionable scientific distinction between prevention and treatment of symptoms given the mechanism of action of antihistamines. In addition, a clinical development program would need to establish the optimum time for pre-exposure dosing, efficacy in a natural allergen exposure setting, and adequate label comprehension among consumers.

5 CLINICAL PHARMACOLOGY

No new clinical pharmacology studies were submitted with this application.

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. Furthermore, the product label for levocetirizine, the active enantiomenr of cetirizine, does not recommend dose adjustment based on age. Levocetirizine exposure levels are highly correlated with renal function as well. As the proposed OTC label for cetirizine already includes information on appropriate dose adjustment in renal impairment, the Clinical Pharmacology review team did not recommend inclusion of dose adjustment on the basis of age alone in the label.

6 INTEGRATED REVIEW OF EFFICACY

The efficacy of cetirizine and cetirizine/pseudoephedrine for OTC switch is supported by the studies conducted to support the original prescription approval of cetirizine and cetirizine/pseudoephedrine.

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 were required to support this application. Therefore, no new efficacy and safety studies were submitted for the proposed switch of cetirizine and cetirizine/PSE.

To support these applications, the Applicant references data previously submitted in support of the currently approved product, Zyrtec, for the treatment of the symptoms of SAR, PAR, and CIU. The data from the referenced studies are adequate to support the efficacy of cetirizine and cetirizine/PSE for the proposed partial OTC switch. The basis for the approval of the original cetirizine NDAs is summarized below.

Summary of Efficacy for Prescription NDAs

As part of the original application approval for allergic rhinitis, nine multicenter, randomized, double-blind, placebo-controlled clinical trials were reviewed. Doses ranging from 5 mg to 20 mg cetirizine were compared to placebo in patients 12 years of age and older with SAR or PAR. Of the nine studies, three demonstrated statistically significant reductions in symptoms of SAR (1 to 4 weeks duration) and 2 in PAR (8-week studies). In general, the 10-mg dose was more effective than the 5-mg dose and the 20-mg dose did not provide any additional benefit. The primary efficacy variable in the majority of these studies was the weekly Total Symptom Score, a composite endpoint of various allergic symptoms: sneezing, runny nose, eye itching, eye watering, eye redness, nose itching, and mouth itching. Nasal congestion was also assessed in the studies but was excluded from the TSS. Looking at individual component symptoms across

the studies, cetirizine seemed to relieve sneezing and runny nose most consistently; results for the other component symptoms were less consistent.

For the hives indications, two 4-weeks multicenter, randomized, double-blind, placebo-controlled trials in patients with chronic idiopathic urticaria were performed, examining doses of 5 to 20 mg once daily. The 10-mg dose was noted to be more effective than the 5-mg dose, and the 20-mg dose had no added benefit. Patients in these studies were 12 years of age and older.

In addition, four randomized, double-blind, placebo-controlled trials in 534 pediatric patient ages 6 to 11 years with SAR using doses from 1.25 to 10 mg cetirizine were conducted to establish efficacy in pediatric patients and were reviewed as part of the original NDA (NDA 20-346, Zyrtec Syrup, Approval date – September 27, 1996). These trials did not demonstrate a consistent, statistically significant benefit over placebo; however, based on the likelihood that the disease pathophysiology of allergic rhinitis is substantially similar between adult and pediatric populations, efficacy in children was extrapolated from the established efficacy in adults. Additional pharmacokinetic safety data from 168 children ages 2 to 5 years was submitted in a supplement (NDA 20-346, Zyrtec Syrup, Approval date – May 15, 1997) to extend the age range approved for cetirizine syrup formulation appropriate for this younger age group. For patients between 6 and 24 months, three randomized, double-blind, placebo-controlled trials and open-label long-term safety data in 724 patients were later submitted to support the safety of cetirizine. Efficacy in the different indications was again based on extrapolation from data in older children. The safety and efficacy of cetirizine in patients under 6 months of age have not been established.

For cetirizine/PSE, no separate efficacy studies were conducted. Two pivotal in vivo pharmacokinetic studies (143-006 and 143-007) and two supportive pharmacokinetic studies (9817 and 9831) addressing the comparative bioavailability between the proposed combination product versus the co-administration of the individual active ingredients and food interaction were reviewed as part of the original NDA submission.

For cetirizine chewable 10- and 5-mg tablets, no separate efficacy studies were conducted. Two pivotal bioequivalence studies (A1431019 and A1431018) and four other supportive pharmacokinetic studies (A1431016, A1431014, A1431007, and UCB A00332) established the bioequivalence between the 10-mg chewable tablet and the commercially available, non-chewable 10-mg tablet (NDA 21-621, Zyrtec Chewable Tablet). The Agency waived separate studies to establish the bioequivalence of the 5-mg tablet due to the similar dissolution profiles of the 10- and 5-mg products. These studies were reviewed as part of the original NDA submission.

These data are adequate to support the efficacy of cetirizine and cetirizine/PSE for the proposed partial OTC switch.

Proposed OTC Indications

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 [redacted] dust mites, animal dander and molds) and [redacted] 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 [redacted] dust mites, animal dander and molds) and [redacted] ragweed, grass and tree pollens) upper respiratory allergies
- temporary relief of nasal congestion [redacted] 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

Reviewer's comment: While the efficacy data from the original prescription NDAs are adequate to support the efficacy of cetirizine and cetirizine/PSE for the proposed partial OTC switch, the proposed indications should be modified to [redacted]

7 INTEGRATED REVIEW OF 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 cetiriirizine 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.

Safety data from clinical trials

In controlled and uncontrolled clinical trials, more than 6000 patients received cetirizine. More than 3900 patients received doses of 5 to 20 mg per day, with a mean exposure of 30 days (range of exposure from 1 week to 6 months). The rates of discontinuations due to adverse events were comparable between cetirizine 5 and 10 mg and placebo. The most common adverse reaction observed in patients 12 years of age and older was dose-related somnolence, occurring in 11% of the 5-mg dose group and in 14% of the 10-mg dose group compared to 6 % in the placebo. Other adverse reactions included fatigue (5.9%) and dry mouth (5.0%). For children ages 6 to 11 years (>1300 patients in pediatric studies) and children ages 2 to 11 years (n=168), the most common adverse reactions were abdominal pain (4.4 to 5.6%) and somnolence (1.9 to 4.2%). In children 6 to 24 months of age (n=399), insomnia (9.0% vs. 5.3% in placebo) was more commonly observed.

Seven hundred one patients received cetirizine/PSE in controlled clinical trials. The primary adverse reaction was insomnia (4.0% vs. 0.6% placebo). Somnolence was reported in 1.9% of patients, compared to 0.1% in the placebo group. The rate of discontinuation from the trial due to adverse events was slightly higher in the cetirizine/PSE group (2.0%) compared to placebo (1.1%).

Non-clinical trial safety data

The Applicant has submitted postmarketing safety data and 4-month safety updates in support of the OTC switch. These data cover the time periods from January 1, 1986, to January 16, 2007, (cetirizine) and September 21, 1999, to January 16, 2007 (cetirizine/PSE). The Applicant has also included a literature review of safety data on cetirizine from 1987 to 2006. A total of 14,921 cases involving single-ingredient cetirizine, comprised of 30,508 AE terms, are included in the Applicant's non-trial safety database. An estimated total number of patients exposed in unknown, as cetirizine is marketed OTC in many places, but the Applicant states that ——— total tablets, ——— mls, and ———total unknown-formulation units have been distributed globally from April 1, 1994, through March 31, 2006. For cetirizine/PSE, a total of 635 adverse events were reported, comprised of 1,497 AE terms. A total of ——— tablets have been sole from April 1, 1994, through March 31, 2006. Of note, another manufacturer, UCB, markets cetirizine/pseudoephedrine in over 70 countries; the Applicant is the marketing/registration holder in 10 countries. The safety data included in this application do not include data collected by UCB.

The summary reports for non-clinical trial, post-marketing data are generally consistent with the adverse event profile described in the current approved product labels. Other common adverse events for both cetirizine and cetirizine/PSE include fatigue, dry mouth, pharyngitis, and dizziness.

Overall, review of the provided case descriptions for serious adverse events (SAEs) in the most recent safety updates did not suggest any new safety signals. The most commonly reported

reported SAEs for cetirizine for the period of May 11, 2006, to January 16, 2007, included surgery (n=17), drug ineffectiveness (n=14), hypersensitivity (n=14), convulsions (n=12), disability (n=11), asthma (n=10), dizziness (n=10), and hypertension (n=9). In the majority of cases, there did not appear to be any clear correlation to use of the drug and comorbid conditions were present. Of 13 reports of death, most cases were medically complicated and characterized by serious comorbid conditions; the role of cetirizine in these cases is difficult to elucidate. In one of the 13 cases, however, cetirizine, appears to have played a central role: a teenage patient with a previous history of hypersensitivity to diphenhydramine and other antihistamines received cetirizine for poison ivy in an emergency room in 1999 and experienced fatal anaphylaxis 30 minutes later. Hypersensitivity to cetirizine, hydroxyzine, or any of the other ingredients of Zyrtec is listed as a contraindication on the current product label. For cetirizine/PSE, SAEs included increased heart rate (n=2) and increased blood pressure (n=2), both noted as possible adverse effects in the current product label. No deaths were reported during this time period for cetirizine/PSE.

Of note, cetirizine is currently available without prescription in 46 countries outside the United States.

Reviewer's comment: A more detailed review of post-marketing safety data is provided in the Division of Nonprescription Clinical Evaluation (DNCE) clinical team's reviews for both cetirizine and cetirizine/PSE.

8 ADDITIONAL CLINICAL ISSUES

The Applicant has proposed a partial Rx to OTC switch for cetirizine for the treatment of _____ allergy in patients 2 years of age and older and the treatment of chronic hives in patients 6 years of age and older. The treatment of PAR symptoms in patients under the age of 2 and CIU in patients under the age of 6 will remain as prescription-only indications. The proposed dosing regimens are shown in Table 1.

Table 1 Proposed OTC cetirizine dosing	
Age	**Dose**

Reviewer's comment: Due to restrictions on cross-referencing other products on an OTC label, the 10-mg chewable tablet label does not mention the 5-mg dose and likewise, the 5-mg chewable tablet label does not mention the possibility of a 2.5-mg dose. Cetirizine tablets are not scored and cannot be divided by the consumer to achieve a lower dose. As a result, the dosing recommendations do no correspond directly to the Rx dosing instructions. At the time of this review, the Division of Nonprescription Clinical Evaluation has requested that the Applicant provide wording to reconcile the discrepancy. That being said, it is common clinical practice to prescribe the 10-mg dose for adult patients and the 5-mg dose in children without any attempts to titrate to the lowest effective dose. The proposed dosing regimens are still within the currently approved dosing ranges and do not pose any additional safety risks, although use of lowest effective dose may minimize sedation in some individuals.

Final dosing recommendations for the OTC switch are pending at the time of finalization of this review.

The proposed dose for cetirizine/PSE for patients 12 years of age and older is 1 tablet twice daily, consistent with current prescription dosing. Patients with liver or kidney disease are advised to consult their healthcare provider prior to dosing.

9 OVERALL ASSESSMENT

9.1 Conclusions

The Applicant proposes a partial Rx to OTC switch cetirizine (Zyrtec®) for the following indications:

- Temporary relief of these symptoms due to hay fever or other upper respiratory allergies in patients 2 years of age and older: runny nose, sneezing, itchy watery eyes, and itching of the nose or throat. Relief of these symptoms due to [redacted] upper respiratory allergies.
- Relief of itching due to 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 following indications in patients 12 years of age and older:

- Temporary relief of these symptoms due to hay fever or other upper respiratory allergies in patients 2 years of age and older: runny nose, sneezing, itchy watery eyes, and itching of the nose or throat. Relief of these symptoms due to [redacted] upper respiratory allergies.
- Temporary relief of nasal congestion [redacted] hay fever, or other upper respiratory allergies.
- Reduction of swelling of nasal passages.
- Temporary relief of sinus congestion and pressure.
- Temporary restoration of freer breathing through the nose.

The Applicant refers to efficacy and safety data previously reviewed in the original NDA. No new efficacy and safety studies were conducted for the proposed OTC switch. Review of post-marketing safety data does not identify any new safety signals and the proposed indications and dosing regimens are acceptable for OTC use.

9.2 Recommendation on Regulatory Action

The recommended action is **Approval**.

9.3 Recommendation on Postmarketing Actions

No postmarketing actions are recommended.

9.4 Labeling Review

The labels for the OTC products are primarily under the purview of the Division of Nonprescription Products; however, the labels were reviewed by DPAP and the following is noted. The labeling is primarily based upon the monographs for antihistamines and

decongestants. However, in addition to Monograph indications for antihistamines, the Applicant proposes the addition of the following under Uses on the OTC product label:

> *"Provides relief of the above symptoms due to dust mites, animal dander, and molds) and ragweed, grass, and tree pollens) upper respiratory allergies."*

From the Division of Pulmonary and Allergy Product's perspective, are not recognized clinical conditions and these terms are not used in prescription labeling. Furthermore, the identification of specific allergens such as dust mites and ragweed are not typically permitted in prescription labeling.. To maintain consistency with prescription labeling for cetirizine and other antihistamines drug products, as well as consistency with other OTC antihistamine labels, this reviewer recommends striking the addition from the proposed OTC label.

Proposed OTC labeling for cetirizine/PSE is otherwise consistent with Monograph labeling for nasal decongestants.

Cetirizine for relief of itching due to hives has a separate product label. The proposed label is consistent with the OTC label for loratadine, which carries the same hives indication.

9.5 Comments to Applicant

None.

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/s/

Susan L Limb
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MEDICAL OFFICER

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I concur.

CLINICAL REVIEW

Application Type	sNDA
Submission Number	21-150, SE6-007
Submission Code	
Letter Date	January 10, 2007
Stamp Date	January 11, 2007
PDUFA Goal Date	November 11, 2007
Reviewer Name	Steven F. Osborne, M.D.
Review Completion Date	August 10, 2007
Established Name	cetirizine HCl 5 mg/ pseudoephedrine HCl 120 mg
(Proposed) Trade Name	Zyrtec-D Allergy & Congestion
Therapeutic Class	antihistamine-decongestant
Applicant	McNeil Consumer Healthcare
Priority Designation	Standard
Formulation	Tablet
Dosing Regimen	for adults and children 12 years of age and older, one tablet every 12 hours; not more than two tablets in 24 hours
Indication	for temporary relief of symptoms of hay fever and other upper respiratory allergies and for relief of nasal congestion [redacted] hay fever or other upper respiratory allergies.
Intended Population	age 12 and older

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The proposed sNDA 21-150, Zyrtec-D 12 Hour Extended Release Tablets (cetirizine HCl 5 mg / pseudoephedrine HCl 120 mg), has an acceptable safety profile for OTC marketing for the indication of the temporary relief of symptoms of hay fever and other upper respiratory allergies and for relief of nasal congestion due to hay fever or other upper respiratory allergies in adults and children 12 years of age and older. Therefore, this application is approvable from the safety standpoint.

While the data submitted do not directly support the sponsor's request to label the drug for the relief of nasal congestion due to the common cold, the OTC monograph permits this claim for nasal decongestant products. Therefore, this indication should be granted.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No special post-marketing risk management activities are recommended.

1.2.2 Required Phase 4

No special Phase 4 commitments are recommended.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

McNeil Consumer Healthcare, a Division of McNeil-PPC (McNeil-Pfizer partnership), is seeking approval to market OTC a combination tablet dosage form containing 5 mg of cetirizine HCl and 120 mg of pseudoephedrine HCl (hereafter cetirizine 5 mg/ pseudoephedrine 120 mg or Zyrtec-D) for the indication of the temporary relief of symptoms of hay fever and other upper respiratory allergies and for relief of nasal congestion _____, hay fever, or other respiratory allergies in adults and children 12 years of age and older. The Sponsor currently markets the product as a prescription for adults and children 12 years and older with the indication "for the relief of nasal and non-nasal symptoms associated with seasonal or perennial

allergic rhinitis in adults and children 12 years of age and older". The Sponsor also markets cetirizine single-ingredient 5 mg and 10 mg tablets, a 10 mg chewable tablet, and a 5 mg/5 mL syrup as prescription products. The cetirizine single-ingredient formulations are the subject of separate Rx-to-OTC switch applications.

1.3.2 Efficacy

No new clinical efficacy trials were conducted for this application. In support of efficacy, Pfizer provided an updated Integrated Summary of Efficacy (ISE) from the original NDA submission that included:

- data from the three clinical trials conducted with Zyrtec-D for the indications of Seasonal Allergic Rhinitis (SAR) and Perennial Allergic Rhinitis (PAR). See Table 2 (section 4.2) and the description of studies in section 6.1.4.
- data analyses and other information associated with the three pivotal studies
- a review of the published literature that describes the efficacy of cetirizine/pseudoephedrine in SAR and PAR.

The Sponsor's literature review supported efficacy in the target population and is discussed further in section 8.6. These data will be assessed by the reviewer from the Division of Pulmonary and Allergy Products.

1.3.3 Safety

An integrated review of safety was conducted at the time of the approval of Zyrtec-D for seasonal allergic rhinitis (SAR) on August 10, 2001, and was updated at the time of approval for Zyrtec chewable tablets in 2004. Safety data submitted to the current application consists of a review of the safety data from the pivotal efficacy studies for the original Zyrtec-D application, global post-marketing safety data in the Sponsor's database, a review of the published literature, and data from the following external databases:

- Toxic Exposure Surveillance System ("TESS", American Association of Poison Control Centers)
- Adverse Event Reporting System ("AERS", FDA)
- World Health Organization's International Drug Monitoring Program (WHO)
- Drug Abuse Warning Network ("DAWN" , Substance Abuse and Mental Health Services Administration, Department of Health and Human Services)

The pivotal efficacy studies for the original Zyrtec-D application, studies #A3771001, #A3771002, and #A3771007 evaluated a total of 2,311 subjects, in which 822 subjects received Zyrtec-D. There were no deaths in the Zyrtec-D arms. Overall, there were slightly more adverse events in the Zyrtec-D arms compared with placebo, but no trend in serious adverse events emerged. The most common adverse events from clinical trials and postmarketing data are insomnia, dry mouth, fatigue and somnolence. Through March 31, 2006 the Sponsor distributed [redacted] tablets worldwide. The adverse events are discussed further in section 7.

The Sponsor's 2005 Zyrtec-D product update, submitted December 15, 2006, did not show any new safety concerns during the period October 23, 2005-October 22, 2006. Postmarketing data submitted to the Sponsor or FDA, and a review of the literature, did not reveal any new safety concerns. In particular there were no cases of Torsade de Pointes, other severe cardiac arrhythmias, cytopenias, or male congenital hypospadias that could be clearly related to cetirizine/pseudoephedrine. An additional safety update from the Sponsor dated May 4, 2007, and covering the time period of May 11, 2006-January 16, 2007, did not reveal any safety concerns.

Of note, somnolence with the single-ingredient cetirizine was seen in up to 13.7% of patients (vs. 6.3% with placebo) age 12 and older in clinical trials, a higher incidence than with other "second generation" antihistamines (4-8% with loratadine, similar to placebo). Somnolence with the cetirizine-pseudoephedrine combination was lower than with the single-ingredient, 1.9% in clinical trials of 822 patients (with seasonal allergic rhinitis) vs. 0.1% with placebo. However, in a 2003 review, the Agency declined to remove a caution against use with activities that require mental alertness as the 1.9% incidence of somnolence was significantly higher than placebo. This caution will carry over to the OTC label under "when using this product" (see proposed label in section 9.4)

A review of the TESS, AERS, WHO, and DAWN databases did not reveal an increased incidence of serious AEs (or abuse). From the TESS database there were 2623 reports for cetirizine/pseudoephedrine with 1025 associated clinical effect (CE) terms. Of these cases, 59.0% (1547/2623) were in the pediatric age range (<17 years) and 36.6% (959/2623) were reports of adult exposures. A total of 1025 CEs were reported for 623 (23.8%, 623/2623) patients. Overall, the 4 most frequently reported clinical effects accounted for 53.2% (545/1025) of the total reported CEs. The 4 terms are: Drowsy Lethargy (17.8%, 182/1025), Tachycardia (13.9%, 142/1025), Other (12.1 %, 124/1 025) and Agitated Irritable (9.5%, 97/1025).

Comment:

1. The TESS data suggest that use of the cetirizine-pseudoephedrine product is not likely to lead to a death in a typical overdose situation, since there were no fatalities due to an overdose, whether intentional or unintentional.

A literature review also did not disclose any trends in serious AEs.

1.3.4 Dosing Regimen and Administration

The proposed dosing regimen for this oral combination tablet is one combination tablet every 12 hours for adults and children 12 years of age and older.

1.3.5 Drug-Drug Interactions

No drug-drug interactions were evaluated in the pivotal efficacy studies for Zyrtec-D (studies #A3771001, A3771002, or A3771007). The Sponsor provided data on any potential drug-drug

interactions from other published data on cetrizine-pseudoephedrine and noted two cases of suspected interaction. One case involved cetirizine/pseudoephedrine and Zithromax (azithromycin). The second case involved cetirizine/pseudoephedrine and Alesse (levonorgestrel/ethinyl estradiol). The Sponsor stated there were no trends of AEs or safety signal identified from these cases. There are no reported significant drug interactions between cetirizine/pseudoephedrine and low dose theophylline, azithromycin, ketoconazole, or erythromycin. The current Rx prescribing literature also notes that the drug should not be used with, or within 14 days, of using a MAO inhibitor due to a potential interaction with the pseudoephedrine component.

The OTC label will warn consumers to not use the product if they are taking a MAO inhibitor now or within the past 14 days. Since cetirizine is a metabolite of hydroxyzine, the label will also direct to avoid use for any consumer allergic to hydroxyzine.

1.3.6 Special Populations

The proposed labeling has all the appropriate warnings for consumers of certain age categories, with underlying medical conditions, and for those taking interacting medications.

2 INTRODUCTION AND BACKGROUND

Cetirizine is an orally-active, selective H_1-receptor antagonist and the principal human metabolite of hydroxyzine. Cetirizine is a racemic mixture currently available in the U.S. only as a prescription. Pseudoephedrine is an adrenergic agent commonly used as a nasal decongestant and for which it has an OTC monograph designation.

Zyrtec-D 12-Hour Extended Release Tablets (cetirizine hydrochloride 5 mg and pseudoephedrine hydrochloride 120 mg or cetirizine/pseudoephedrine 5 mg/120 mg or Zyrtec-D) are bilayer tablets containing 5 mg of cetirizine hydrochloride for immediate release and 120 mg of pseudoephedrine hydrochloride for extended release. Cetirizine hydrochloride is a selective H1 receptor antagonist, approved as a prescription drug in the United States for the symptomatic relief of seasonal allergic rhinitis (SAR) in patients 2 years of age and older, and for the symptomatic relief of perennial allergic rhinitis (PAR) and chronic idiopathic urticaria in patients 6 months of age and older. Pseudoephedrine HCl is an adrenergic receptor agonist and an over-the-counter (OTC) monograph ingredient in the United States for the treatment of nasal congestion. Under current labeling, Zyrtec-D is approved for the relief of nasal and non-nasal symptoms associated with seasonal or perennial allergic rhinitis in adults and children 12 years of age and older. The 120 mg of pseudoephedrine in Zyrtec-D exceeds the recommended dose for patients less than 12 years of age, thus this product is not recommended for patients less than 12 years of age.

The Sponsor proposes that over-the-counter indications include an indication for relief of nasal congestion [redacted] hay fever or other upper respiratory allergies. The Sponsor states that the [redacted] indication should be allowed since pseudoephedrine is generally recognized as safe and effective as an oral nasal decongestant under 21 CFR Part 341 (Cold,

Cough, Allergy, Bronchodilator, and Antihistaminic Drug Products for Over-The-Counter Human Use).

2.1 Product Information

McNeil Consumer Healthcare seeks approval to market a combination tablet containing cetirizine 5 mg/pseudoephedrine 120 mg for the indication of the temporary relief of symptoms of hay fever and other upper respiratory allergies and for relief of nasal congestion , hay fever, or other respiratory allergies in adults and children 12 years of age and older. The proposed dosing directions are:

- adults and children 12 years of age and older: one combination tablet every 12 hours; not more than 2 tablets in 24 hours
- children below 12 years of age: ask a doctor
- consumers with liver or kidney disease: ask a doctor

The Sponsor notes that the international birthdate of the cetirizine/pseudoephedrine combination product was 1999 in Italy. The Sponsor markets Zyrtec-D OTC overseas in 8 countries and as a prescription in 2 countries. Through March 31, 2006 the Sponsor distributed tablets worldwide.

2.2 Currently Available Treatment for Indications

Zyrtec is currently available as a single-ingredient 5 mg and 10 mg tablet, a 10 mg chewable tablet, and a syrup for the relief of upper respiratory allergy symptoms. The product is also available as Zyrtec-D, the combination of cetirizine and pseudoephedrine as noted above. The Sponsor has applied to switch all of the Zyrtec formulations to OTC. In addition, other antihistamines, both sedating and non-sedating, are available for the indication of the relief of SAR, PAR, and upper respiratory allergy symptoms in adults and children 12 years of age and older.

2.3 Availability of Proposed Active Ingredient in the United States

See section 2.1 and 2.2.

2.4 Important Issues With Pharmacologically Related Products

Two other non-sedating antihistamines, terfenadine and astemizole, have been removed from the market due to the occurrence of a cardiac arrhythmia (Torsade de Pointes) that can occur when the blood level of terfenadine or astemizole is elevated. The blood level can become elevated beyond the therapeutic range when the respective drug is co-administered with another drug such as ketoconazole or erythromycin. To date, there have not been reports of Torsade de Pointes cardiac arrhythmia with cetirizine as the single suspect drug or with the cetirizine-pseudoephedrine combination. See sections 7.2.9 and 8.6 for additional discussion on this topic.

A previous potential concern for congenital hypospadias, in male children of mothers with prenatal use of another drug of this class, loratadine, was not found with the combination cetirizine/pseudoephedrine.

The Rx label for Zyrtec-D warns consumers to avoid use if they are hypersensitive to any of the ingredients of the product or to hydroxyzine (an antihistamine structurally related to cetirizine). In addition, due to the pseudoephedrine component, consumers are warned to avoid use if they have narrow-angle glaucoma, urinary retention, are receiving MAO inhibitors, have severe hypertension or severe coronary artery disease. Those with liver or kidney disease are advised to take a lower dose.

2.5 Presubmission Regulatory Activity

The original NDA 19-835 for cetirizine (Zyrtec Tablets) was approved on April 12, 1995. Since then, NDAs have been approved for Zyrtec-D (cetirizine-pseudoephedrine), Zyrtec syrup, and Zyrtec Chewable Tablets. The Zyrtec-D approval in 2001 was based on two pharmacokinetic studies that demonstrated the bioequivalence between the Zyrtec-D formulation and the concomitant administration of Zyrtec (cetirizine hydrochloride) and Sudafed (pseudoephedrine). Subsequently, the Sponsor submitted additional safety and efficacy studies (#A3771001, #A3771002, and #A3771007) to support labeling changes (see comment below). Currently, the sponsor has applied to switch all single-ingredient Zyrtec products from prescription-to-over-the-counter (Rx-OTC). Table 1 below shows these Zyrtec products.

Comment:

1. The Sponsor submitted studies #A3771001 and #3771002 to show safety and efficacy in SAR and to request removal of the caution when engaged in activities requiring mental alertness. The request to remove the caution was denied in a 2003 review since the 1.9% incidence of somnolence was significantly higher than placebo (0.1%) and was considered clinically significant. Study #A3771007 showed safety and efficacy in asthmatics.

Table 1. Zyrtec product approvals

NDA #	Product Name	Year of Approval
19-835	Zyrtec Tablets 5 mg and 10 mg	1995
21-150	Zyrtec-D 12-Hour Tablets	2001
20-346	Zyrtec Syrup 1mg/ml	1996
21-621	Zyrtec Chewable Tablets 5 mg and 10 mg	2004

The Sponsor and FDA discussed the content of this NDA at a pre-NDA meeting. No issues were identified.

2.6 Other Relevant Background Information

None.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Not applicable.

3.2 Animal Pharmacology/Toxicology

No new animal data or toxicology data were submitted. Nonclinical pharmacology and toxicology information for cetirizine/pseudoephedrine was filed with the original NDA 21-150 approved August 10, 2001.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The Sponsor provided results of three cetirizine/pseudoephedrine efficacy trials, safety data regarding single-ingredient cetirizine, single-ingredient pseudoephedrine, and the combination product cetirizine/pseudoephedrine, and the proposed OTC labeling of the combination product, all of which are considered in this review. The Sponsor referenced data from the original NDA and subsequent products as noted below.

Reference is made to the following NDAs and their respective supplements:

- The Original New Drug Application NDA 19-835 for Zyrtec Tablets approved December 8, 1995.
- The Original New Drug Application NDA 20-346 in its entirety for Zyrtec syrup, approved September 27, 1996.
- The Original New Drug Application NDA 21-150 in its entirety for Zyrtec-D 12-Hour Extended Release Tablets approved August 10, 2001.
- The Original New Drug Application NDA 21-621 in its entirety for Zyrtec chewable tablet approved March 16, 2004.

4.2 Tables of Clinical Studies

Table 2 below shows the three pivotal studies conducted for the Zyrtec-D Rx approval and supplements.

Table 2. Pivotal studies conducted with Zyrtec-D for the Rx approval and supplements.

Trial Number/ Population	No. of Centers Country	Start and Completion Dates	Treatment Duration	Treatment Arms	Number of ITT Subjects	Age (yr.) mean ± S.D.	Race (%) Whites/Non-whites	Sex (%) Males/Females
A3771001 Adults	36 Centers in U.S.	MAY 00 through JUL 00	2 weeks	Cetirizine/ pseudoephedrine 5 mg/120 mg BID	353	31.6 ± 13.5	85.0/15.0	41.9/58.1
				Loratadine/ pseudoephedrine 5 mg/120 mg BID	348	31.5 ± 12.9	85.3/14.7	41.7/58.3
				Placebo	352	31.7 ± 12.6	83.8/16.2	38.1/61.9
A3771002 Adults	36 Centers in U.S.	MAY 00 through AUG 00	2 weeks	Cetirizine/ pseudoephedrine 5 mg/120 mg BID	330	30.3 ± 11.8	83.3/16.7	41.2/58.8
				Fexofenadine/ pseudoephedrine 60 mg/120 mg BID	324	31.1 ± 12.3	84.3/15.7	42.9/57.1
				Placebo	331	30.8 ± 12.6	86.4/13.6	40.5/59.5
A3771007 Adults	36 Centers in U.S.	FEB 02 through JUL 02	4 weeks	Cetirizine/ pseudoephedrine 5 mg/120 mg BID	139	29.9 ± 13.2	87.8/12.2	44.6/55.4
				Placebo	134	28.7 ± 13.1	84.3/15.7	47.8/52.2

4.3 Review Strategy

This review will focus on the safety update. The pulmonary division reviewer will evaluate efficacy data.

4.4 Data Quality and Integrity

Not applicable. There were no DSI audits conducted for the study site or data analyses.

4.5 Compliance with Good Clinical Practices

Not applicable to this review.

4.6 Financial Disclosures

For the original NDA approval (and supplements) for Zyrtec-D, the Sponsor conducted three studies, Studies #A3771001, A3771002, and A3771007, each involving 36 clinical sites and multiple investigators. The Sponsor previously submitted financial disclosure information regarding Studies #A3771001 and A3771002. For study #A3771007 the Sponsor notes that 10 of the 176 investigators had a financial interest which the Sponsor has disclosed on Form 3455. There were no financial disclosures that would cast doubt on the findings.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

There is no new human pharmacokinetic or bioavailability information contained in this application. Human pharmacokinetic and bioavailability information for cetirizine-pseudoephedrine may be found in the original NDA 21-150 approved August 10, 2001.

5.2 Pharmacodynamics

No new pharmacodynamic data were submitted with this application.

5.3 Exposure-Response Relationships

No new exposure-response relationship data were submitted with this application.

6 INTEGRATED REVIEW OF EFFICACY

Efficacy of the product is extrapolated based on two pharmacokinetic (PK) studies submitted with the original NDA, approved in 2001, and the subsequent safety and efficacy studies submitted in an attempt to support a removal of a drowsiness (caution against use with activities requiring mental alertness) warning from the label. Studies #A3771001, A3771002, and A3771007 have been previously reviewed but are described for completeness. The pulmonary division reviewer will review the efficacy of the product for OTC use.

6.1 Indication

The proposed indication for Zyrtec-D is the temporary relief of symptoms of hay fever and other upper respiratory allergies and for relief of nasal congestion [redacted] hay fever, or other respiratory allergies in adults and children 12 years of age and older.

6.1.4 Efficacy Findings

The three pivotal clinical trials, Studies #A3771001, #A3771002 and #A3771007 have a similar trial design in that they were multicenter, randomized, double-blind, placebo-controlled, parallel, outpatient trials of subjects with at least moderate SAR symptoms due to hypersensitivity to outdoor allergy triggers such as ragweed, grass and tree pollen.

Study #A3771001:
This was a randomized, double-blind, parallel group, 2-week, placebo controlled, multicenter study of the efficacy and safety of cetirizine-pseudoephedrine vs. loratadine-pseudoephedrine (Claritin-D 12 Hour) and vs. placebo in 1094 subjects twelve years of age and older with seasonal allergic rhinitis. A total of 1094 subjects were randomized and received treatment

medication twice daily for two weeks. The primary efficacy endpoint was the absolute change from baseline in total symptom severity complex (TSSC) score. This score was the sum of seven individual symptoms (sneezing, runny nose, itchy nose, itchy eyes, watery eyes, postnasal drip, and nasal congestion). Secondary efficacy measures were the percent change from baseline in subject's total symptom score, change from baseline in seven individual symptom scores, change from baseline in the investigator's total symptom score, responder classification for total symptom scores, subject global evaluations of treatment effectiveness and treatment satisfaction, and investigator global evaluation. Results of this study showed that both cetirizine/pseudoephedrine 5 mg/120 mg (TSSC -4.74 change from baseline, $p<0.01$ vs placebo) and the active comparator loratadine/pseudoephedrine 5 mg/120 mg (TSSC -4.59 change from baseline) were significantly better at reducing symptoms associated with SAR compared to placebo (TSSC -2.89 change from baseline). There was no significant difference between the cetirizine/pseudoephedrine 5 mg/120 mg and loratadine/pseudoephedrine 5 mg/120 mg treatment groups. The results of all other secondary analyses were consistent with these primary results for all time points and for the efficacy analyzable and completer samples.

Study #A3771002:
This was a randomized, double-blind, parallel group, 2-week, placebo controlled, multicenter study of the efficacy and safety of cetirizine- pseudoephedrine vs. fexofenadine-pseudoephedrine (Allegra-D) and placebo in 1000 subjects twelve years of age and older with seasonal allergic rhinitis. This trial was conducted in 36 centers on subjects with a documented history of a prevalent allergen (tree or grass)-related SAR (verified by either RAST or skin testing). Subjects completed symptom diary cards on a daily basis. The TSSC scale was used to rate symptom severity (0=none; l=mild; 2=moderate; 3=severe). At the end of week 2, each subject also made a global assessment of the effect of therapy. The investigator evaluated symptom severity prior to therapy and at the end of weeks 1 and 2 using the same rating sale as the subjects. All reported results of this study show that cetirizine/pseudoephedrine 5 mg/120 mg was not statistically significantly different from fexofenadine/pseudoephedrine 60 mg/120 mg at reducing symptoms associated with SAR. However, subjects within both the cetirizine/pseudoephedrine 5 mg/120 mg and fexofenadine/pseudoephedrine 60 mg/120 mg of the ITT sample experienced significant improvement in total symptom scores compared to placebo ($p<0.01$). The results of both primary and secondary analyses were consistent for all time points and for each of the analysis samples. The results of this study demonstrated that both cetirizine/pseudoephedrine 5 mg/120 mg and fexofenadine/pseudoephedrine 60 mg/120 mg provided effective symptomatic relief in adults with SAR. The traditional measure of efficacy used in this study, total symptom score, showed that cetirizine/pseudoephedrine produced greater improvements in symptoms of SAR than placebo, though the improvements were not statistically significantly different from the fexofenadine/pseudoephedrine group. Subjects treated with either cetirizine/pseudoephedrine or fexofenadine/pseudoephedrine reported significant improvement in individual symptoms compared to those treated with placebo throughout the treatment period ($P<0.01$). These effects were consistent across the ITT, efficacy analyzable, and completer samples.

Study #A3771007:
This was a multicenter, randomized, double-blind, 5-week, placebo controlled study of the efficacy and safety of Zyrtec-D 12 Hour (Cetirizine HCl/Pseudoephedrine HCl) versus placebo

in 274 patients twelve years of age and older with seasonal allergic rhinitis and concomitant mild to moderate asthma. After one week of screening subjects were followed for four weeks of treatment with a clinical follow-up every two weeks. The median duration of therapy for subjects in this study was 28 days. Subjects were required to do home monitoring of peak expiratory flow rate (PEFR) and maintain diaries of allergic rhinitis and asthma symptoms as well as beta-agonist usage. Clinical evaluations also consisted of laboratory testing at visit 1, administration of the Asthma Quality of Life Questionnaires (AQLQ) at visits 2, 3, and 4, and routine spirometry at all visits. The primary efficacy parameter was the subject's total symptom score. Other efficacy variables for this study included investigator's total symptom score, pulmonary function testing, AQLQ, subject's and the investigator's global evaluation of effectiveness, and a rating of the willingness of the subject to take the study medication again. The mean total symptom score for cetirizine/pseudoephedrine 5 mg/120 mg showed a statistically significant greater improvement than placebo of 18.7% ($P< 0.001$). Statistically significant differences between the cetirizine/pseudoephedrine 5 mg/120 mg and placebo groups were observed for each of the individual symptom measurements (sneezing, runny nose, itchy nose, postnasal drip, and nasal congestion). Reductions in asthma symptom severity combined scores in the cetirizine/pseudoephedrine 5 mg/120 mg group were also statistically significant in comparison with the placebo group in the change from baseline to Week 2 in morning scores ($P = 0.002$) and in the change from baseline to Week 2 and Week 4 in evening scores ($P< 0.001$ and $P = 0.007$, respectively). The percentage of subjects in the cetirizine/pseudoephedrine 5 mg/l20 mg group reporting satisfaction with the treatment of SAR symptoms was statistically significantly higher than in the placebo group (68.1 % vs 37.7%, $p < 0.001$). The percentage of subjects in the cetirizine/pseudoephedrine 5 mg/120 mg group reporting satisfaction with the treatment of asthma symptoms was statistically significantly higher than in the placebo group (61.5% vs 45.0%, $p < 0.001$) was observed. In each AQLQ domain measure, the increases from baseline to both post-baseline time points were statistically significantly larger in the cetirizine-pseudoephedrine 5 mg/120 mg group than in the placebo group, and, with one exception (emotional function at Week 4).

Comments:

1. The pulmonary division reviewer will assess the adequacy of these studies as support for OTC use of the product for the requested claims.

7 INTEGRATED REVIEW OF SAFETY

The Sponsor referenced its prior submissions (see table 3 below) for each of the following NDA applications in the current Integrated Summary of Safety:

Table 3. List of NDAs referenced by Sponsor for this application.

NDA No.	Zyrtec Formulation	Approval Date
21-150	Zyrtec-D 12-Hour	8/10/2001
19-835	Zyrtec tablet	12/08/1995
20-346	Zyrtec syrup	09/27/1996
21-621	Zyrtec chewable tablet	03/16/2004

An integrated review of safety was conducted at the time of the approval of Zyrtec-D for seasonal allergic rhinitis (SAR) on August 10, 2001, and was updated at the time of approval for Zyrtec chewable tablets in 2004. The original assessment of safety was based on clinical trials with the single ingredient cetirizine, the monograph data for pseudoephedrine and the 3 clinical trials with the cetirizine-pseudoephedrine combination product, Studies #A3771001, 3771002, and 3771007. With this submission the following sections of the Integrated Summary of Safety (ISS) are being updated:

- Sponsor-received global post-marketing safety data for the period September 21, 1999-May 10, 2006
- Drug Abuse Warning Network (Substance Abuse and Mental Health Services Administration, Department of Health and Human Services)
- Update of the Toxic Exposure Surveillance System (TESS) database from the American Association of Poison Control Centers for cetirizine/pseudoephedrine products from December 1, 2005-May 31, 2006
- World Health Organization (WHO) database from 1978-June 30, 2006
- Update of the FDA Adverse Event Reporting System (AERS) database for the period February 1, 2006-August 1, 2006.
- Literature update for cetirizine/pseudoephedrine for the period October 1, 2005-April 30, 2006.

7.1 Methods and Findings

The Sponsor defined an adverse event (AE) as any untoward medical occurrence or unfavorable and unintended sign in a subject administered a pharmaceutical product, whether or not considered related to the use of that product. This included the onset of new illness and the exacerbation of pre-existing conditions. A serious adverse event (SAE) was any adverse drug experience occurring at any dose that resulted in any of the following outcomes:

- death
- life-threatening AE (i.e., one that placed the subject, in the view of the initial reporter, at immediate risk of death from the AE as it occurred)
- persistent or significant disability/incapacity
- required in-patient hospitalization, or prolonged hospitalization

- congenital anomaly or birth defect

All subjects who received at least one dose of study drug were included in the safety analyses. In the three pivotal trials there was just one reported serious adverse event, which occurred in Study# A3771007 in a placebo subject.

A summary of SAEs reported from company-sponsored clinical trials covering the entire span of the drug's clinical development (1986 to May 10, 2006) identified only 5 SAEs including 1 death, which involved a patient who was shot and killed while in his car. In 2 of the SAE cases the patient was receiving placebo. An analysis of these events revealed no potential safety concerns and no reporting trends were noted in the data.

An assessment of the human exposure data for cetirizine/pseudoephedrine in the TESS database showed that across pediatric and adult age categories there were 10 cases with major effects (0.4% of all cases) and no deaths. The large majority of cases (92.6%, 2428/2623) resulted in no effects, minor effects, or other possible minimal effects. Based on the data assembled in this report, cetirizine/pseudoephedrine exposure, regardless of age group involved, does not appear to represent a significant toxicologic risk.

A special safety review of cytopenias, arrhythmias and somnolence indicated that, based on US sales, cetirizine does not pose a risk of thrombocytopenia or arrhythmias. It does have reported rates of somnolence that are increased compared fexofenadine and loratadine.

7.1.1 Deaths

There was one reported death in the three pivotal efficacy studies. This subject had received the comparator drug fexofenadine/pseudoephedrine in Study #A377002. Nine days after discontinuing the study drug he was reported to have been shot and killed while in his car. According to the police report, the patient was murdered. This death was not related to the study drug.

In the Sponsor's postmarketing database there were 22 reported deaths of which 20 were from the "Pfizer Zyrtec Management Program". In 18 of the 20 cases a clear temporal relationship between cetirizine or cetirizine/pseudoephedrine use and death could not be determined. Typically, a patient/consumer had used cetirizine at an unknown time and was deceased at the time of the report. In the two cases (out of the 20 cases) where clearer information was provided, the cause of death was reported to be due to an underlying medical condition: lung cancer in one case and an intracerebral hemorrhage in the other case.

In one of the two cases outside the Pfizer Zyrtec Management Program, a consumer reported that an 18-year-old female died of cardiac arrest. She had a medical history of QT prolongation, mitral valve prolapse, Gittleman's syndrome, and bronchitis, and was concomitantly taking magnesium and potassium supplements, and Ortho Tri-cyclen, then took cetirizine / pseudoephedrine, azithromycin, ciprofloxacin, and ipratropium/albuterol.

In the Sponsor's search of the AERS database for the period November 1, 1997-March 31, 2006, there were 2 reported deaths for the cetirizine-pseudoephedrine combination product. One of these patients is the 18-year-old female noted above, while the other is a 57-year-old male. The case descriptions are noted below:

- FDA ISR# 4115415 was an 18-year-old female who died [redacted]. Her concomitant medications included Zithromax, Zyrtec-D 12 Hour, salbutamol, magnesium potassium, ethynylestradiol, norgestimate. Bronchitis and an "ill-defined disorder" were the listed indications for the medications she was taking. The AE terms were: Cardiac arrest, Torsade de pointes, Ventricular tachycardia, Disease recurrence, Bronchitis and Medication error. A consumer reported the case.

- FDA ISR# 4249433 was a 57-year-old male with a reported event date of August 28, 2003. No concomitant medications were listed for the report. The indication for his treatment was listed as "hypersensitivity". The AE terms were: Dyspnea and Insomnia. Both a health professional and a consumer reported the case.

Comment:

1. The case of the 18- year- old female is the same as the death reported from the Sponsor's database above. This is the only instance where a torsade de pointes cardiac arrhythmia is noted in a case report in this review. The terms disease recurrence, bronchitis, and medication error confound any attempt to link the arrhythmia to Zyrtec-D. Separately, the case of the 57-year old male has insufficient detail to attribute causality to Zyrtec-D. In neither case was the dose of Zyrtec-D reported.

Worldwide, in this reviewer's query of AERS DataMart there were apparently four deaths listed under a Zyrtec-D search during the period April 1, 2001-March 31, 2007. Two of these deaths were domestic and two were reported from overseas. However, case summaries were not available for any of the four cases.

Comment;

1. Since case summaries were not available for any of the four deaths from this reviewer's AERS DataMart search, no conclusions can be drawn as to whether Zyrtec-D use was related to the deaths or not.

As discussed in sections 7.1.16 and 7.1.17 of this review, there were no fatalities associated with intentional overdose or abuses of the combination product, cetirizine/pseudoephedrine.

7.1.2 Other Serious Adverse Events

The Sponsor notes that it searched Pfizer's corporate safety database, (called the "ARISg" database), for serious AE cases from Company-sponsored cetirizine/pseudoephedrine clinical

trials received by Pfizer and entered into the database between January 1, 1986 and May 10, 2006. All subjects who received at least one dose of study drug were included in the safety analyses. Five reports of non-fatal serious adverse events were found.

Two reports were from the same clinical trial, Study #A3771002. The remaining three were from three different clinical trials: Study #A3771007, RPCE91D1201 (A179) and A158. The five SAEs consisted of three males and two females, mean age 29.2 years. One patient was in the 12- to 17-year age group, the remaining four were from the 18- to 64-year age group. Four patients recovered; one died. The one death is listed in section 7.1.1 (involved a patient who was shot and killed while in his car). The other four cases are listed below:

In case 9933759, a 32-year-old female, with a history of abortions, was enrolled in a clinical trial, Study #A158, and received drug #1 (cetirizine capsule) for allergic rhinitis with total daily dose of 10mg for 10 days. She also received drug #2 (pseudoephedrine capsule) for allergic rhinitis with total daily dose of 240mg for 10 days. A diagnosis of pregnancy was made 16 days after the study started. The study drug was stopped four days later and a spontaneous abortion occurred four days after discontinuation of the study drug, at 12 weeks' gestation. The spontaneous abortion was due to placental insufficiency, which had also been the cause of her previous abortions. The investigator assessment was unknown while the Sponsor's causality assessment was not related.

In case 9501377, a 22-year-old female with an 18-year history of asthma was treated with inhaled salbutamol. She began taking inhaled beclomethasone for worsening asthma, and approximately two weeks later, enrolled in a clinical trial, Study #RPCE91D1201 (AI79), receiving one capsule twice daily of 5 mg cetirizine/120 mg pseudoephedrine for treatment of perennial allergic rhinitis. One week later, she was admitted to the hospital with a severe asthma attack, noted to be the first "bad" attack in her life. This event was reported as "associated with the development of a small pneumomediastinum with some surgical emphysema in the neck." Study medication was discontinued. Treatment with intravenous hydrocortisone, oral prednisolone, nebulized salbutamol, inhaled beclomethasone and erythromycin resulted in a rapid and complete recovery. The investigator assessed the event as unlikely related to study drug, with probable cause as exacerbation of an underlying condition, possibly precipitated by stress.

In case A026142, a 41-year-old male with a history of groin strain enrolled in a clinical trial, Study #A3771002, and started taking study drug via blinded therapy. Approximately one week later, he underwent an elective hernia repair. Although the procedure was scheduled as outpatient surgery, his physician was not able to discharge him by the end of the day (reason unspecified), and the subject was admitted overnight. The investigator assessed that the hernia repair was unrelated to the study drug, but was related to a history of groin strain. The patient had been randomized to placebo.

In case 2002000454, a 14-year-old male with a history of sinus headaches enrolled in a clinical trial, Study #A3771007, and began blinded therapy. Four days later the patient had a headache and began vomiting. He went to the emergency room, was admitted and was diagnosed with

meningitis. He was treated with vancomycin, ceftriaxone, and albuterol and he recovered. According to the investigator, the drug was permanently discontinued due to the meningitis - and while the cause of meningitis was unknown, it was not related to the study drug since the patient had been randomized to placebo.

Comment:

1. These 4 cases from the Sponsor's clinical trials illustrate SAEs that are either unrelated to Zyrtec-D use, since the subjects were randomized to placebo, or not clearly related to Zyrtec-D use, since the subjects had a concomitant illness or used additional medications.

An assessment of the human exposure data for cetirizine/pseudoephedrine in the TESS database showed that across pediatric and adult age categories there were 10 cases with major effects (0.4% of all cases) and no deaths. The large majority of cases (92.6%, 2428/2623) resulted in no effects, minor effects, or other possible minimal effects. Based on the data assembled in this report, cetirizine/pseudoephedrine exposure, regardless of age group involved, does not appear to represent a significant toxicologic risk.

7.1.3 Dropouts and Other Significant Adverse Events

The Sponsor reported these data for Studies #A3771001 and A3771002 with the original NDA 21-150 approved August 10, 2001. In Study #A3771007 thirty-nine (of 274) subjects dropped out of the study due to treatment-emergent AEs. Of these, nine were in the cetirizine-pseudoephedrine group, but only four of the AEs were considered related to the study drug. None of the AEs were considered serious in the dropouts.

7.1.3.1 Overall profile of dropouts

The Sponsor reported this data in the original Zyrtec-D NDA application and supplements.

7.1.3.2 Adverse events associated with dropouts

The Sponsor noted that the individual subjects and AEs were described in the original Zyrtec-D NDA application and supplements, thus they did not repeat those findings in the current application.

7.1.3.3 Other significant adverse events

Not applicable.

7.1.4 Other Search Strategies

Not applicable.

7.1.5 Common Adverse Events

Historically, common (>1%) drug-related adverse events in patients 12 years of age and older associated with use of the combination of cetirizine-pseudoephedrine include the following reactions:

- Insomnia
- Dry mouth
- Fatigue
- Somnolence
- Pharyngitis
- Epistaxis
- Accidental injury
- Dizziness
- Sinusitis

From clinical trials the most common AEs reported with the use of the cetirizine-pseudoephedrine combination are headache, somnolence, fatigue, and dry mouth. The exacerbation of asthma was a common AE in Study#3771007, which enrolled subjects with asthma. Other AEs reported with the use of Zyrtec-D are insomnia, nervousness, dizziness, dyspepsia, nausea, pharyngitis, anorexia, and thirst. The occurrence of these of these and other events was recorded in the subject's medical records and on the CRF, regardless of causality. All AEs were followed to satisfactory resolution or stabilization of the event(s).

Comment:

1. All of the common adverse events occurred at numerically higher rates than placebo in clinical trials involving 822 patients with SAR who took Zyrtec-D (vs. 817 in the placebo group). Insomnia was the most common and occurred in 4.3% of patients (vs. 0.6% with placebo). Somnolence occurred in 1.9% of patients (vs. 0.1% with placebo). In other studies involving the single ingredient cetirizine the rate of somnolence is higher, up to 13.7%.

7.1.5.1 Eliciting adverse events data in the development program

Safety was assessed through the monitoring of adverse events (AEs), vital signs, clinical laboratory evaluations, physical examinations, and 12-lead electrocardiograms. Subjects were questioned or examined by the investigator for evidence of AEs.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The adverse event categorization and preferred terms were appropriate. MedDRA terminology was used.

7.1.5.3 Incidence of common adverse events

Adverse events that occurred during the three clinical studies are consistent with the known adverse event profile for the cetirizine-pseudoephedrine combination, except for the exacerbation of asthma seen in 14.4% of the subjects in the cetirizine-pseudoephedrine group vs. 10.4% in the placebo group in Study #A3771007. Headache was noted to be 3% in Study #A3771002 and somnolence was noted to be 5.8% in Study #A3771007.

7.1.5.4 Common adverse event tables

The original NDA application for Zyrtec-D listed adverse events in the clinical trials as noted below in Table 4.

Table 4. Adverse events in clinical trials enrolling 1397 patients

Adverse Experience	Zyrtec-D (n=701)	Placebo (n=696)
Insomnia	4.0	0.6
Dry mouth	3.6	0.4
Fatigue	2.4	0.9
Somnolence	1.9	0.1
Pharyngitis	1.7	1.1
Epistaxis	1.1	0.9
Accidental Injury	1.1	0.4
Dizziness	1.1	0.1
Sinusitis	1.0	0.6

7.1.5.5 Identifying common and drug-related adverse events

Headache was considered treatment-related, while exacerbation of asthma is not clearly linked to cetirizine-pseudoephedrine. None of the serious AEs reported in the clinical trials were related to cetirizine/pseudoephedrine.

7.1.5.6 Additional analyses and explorations

Not applicable.

7.1.6 Less Common Adverse Events

The population and number of adverse events in the three clinical studies were too small to assess the incidence of less common adverse events.

7.1.7 Laboratory Findings

The Sponsor reported these data for cetirizine/pseudoephedrine with the original NDA 21-150 approved August 10, 2001. In the current submission the Sponsor discusses cytopenia data, comparing reports of overall cytopenias, thrombocytopenias, and eosinophilia using cetirizine versus fexofenadine or loratadine. The Sponsor notes an overall very low rate of cytopenias, slightly higher than with fexofenadine and slightly lower than with loratadine. The Sponsor notes 7 domestic reports of thrombocytopenia per 100 million exposures of cetirizine.

Comment:

1. Apparently, there was once a concern that use of the second generation antihistamines could lead to a cytopenia. The Sponsor's data does not indicate a safety concern with cetirizine.

7.1.7.1 Overview of laboratory testing in the development program

The laboratory testing measures used in Studies #A3771001, A3771002, and A3771007 are standard for clinical trials.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The Sponsor reported these data for cetirizine/pseudoephedrine with the original NDA 21-150 approved August 10, 2001. There is no additional information in the current submission.

7.1.7.3 Standard analyses and explorations of laboratory data

The Sponsor reported these data for cetirizine/pseudoephedrine with the original NDA 21-150 approved August 10, 2001. There is no additional information in the current submission.

7.1.7.4 Analyses focused on measures of central tendency

Not applicable.

7.1.7.5 Analyses focused on outliers or shifts from normal to abnormal

Not applicable.

7.1.7.6 Marked outliers and dropouts for laboratory abnormalities

None.

7.1.7.7 Additional analyses and explorations

There were no additional analyses or explorations in the current submission.

7.1.7.8 Special assessments

Not applicable.

7.1.8 Vital Signs

The Sponsor reported these data for cetirizine/pseudoephedrine with the original NDA 21-150 approved August 10, 2001. There is no additional information in the current submission.

7.1.8.1 Overview of vital signs testing in the development program

Not applicable.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable.

7.1.8.3 Standard analyses and explorations of vital signs data

Not applicable.

7.1.8.3.1 Analyses focused on measures of central tendencies

Not applicable.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Not applicable.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

The Sponsor reported these data for cetirizine/pseudoephedrine with the original NDA 21-150 approved August 10, 2001. There is no additional information in the current submission.

7.1.8.4 Additional analyses and explorations

Not applicable.

7.1.9 Electrocardiograms (ECGs)

In the Sponsor's clinical trials, Studies #A3771001, A3771002, A3771007, tachycardia was seen in less than 1% of subjects in the Zyrtec-D arms. No serious arrhythmias were noted in these trials. See section 7.1.17 for data from post-marketing experience.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECG testing looked for abnormalities in cardiac rhythm, such as Torsade de Pointes, or in cardiac intervals, such as the QT interval. No clinically significant electrocardiogram findings were reported in studies #A3771001, A3771002, A3771007.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable.

7.1.9.3 Standard analyses and explorations of ECG data

Not applicable.

7.1.9.3.1 Analyses focused on measures of central tendency

Not applicable.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Not applicable.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Not applicable.

7.1.9.4 Additional analyses and explorations

Not applicable.

7.1.10 Immunogenicity

No immunogenicity studies were performed for this submission. There are no known immunogenicity issues related to cetirizine or pseudoephedrine.

7.1.11 Human Carcinogenicity

There are no known carcinogenicity issues related to cetirizine or pseudoephedrine.

7.1.12 Special Safety Studies

There were no special safety studies requested or performed for this application.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no history of a withdrawal syndrome for cetirizine, pseudoephedrine, or the combination cetirizine-pseudoephedrine.

To evaluate a drug abuse potential the Sponsor submitted data from the Drug Abuse Warning Network (DAWN). This is a public health surveillance system that monitors drug-related visits to hospital emergency departments and drug-related deaths in the United States. The new DAWN summary reports are available for 2003 and 2004. The 2004 report provided national estimates of 1.3 million drug abuse-related visits and 442 drug abuse-related visits per 100,000 population per year. From 2003 to September 2006, emergency departments at DAWN sample hospitals reported 10,802 cases for upper-respiratory combinations. On a population basis, national estimates for upper-respiratory combinations were 9,431 upper-respiratory combination-related episodes and 3 upper-respiratory combination-related episodes per 100,000 population. No mention of cetirizine-pseudoephedrine was found in the 2003 DAWN mortality data report.

Comment:

The DAWN data suggest that the cetirizine-pseudoephedrine combination product is not a drug of abuse or misuse.

7.1.14 Human Reproduction and Pregnancy Data

No human reproduction or pregnancy studies were performed for this submission.

7.1.15 Assessment of Effect on Growth

There were no data submitted on effects on growth.

7.1.16 Overdose Experience

To evaluate overdose experience the Sponsor submitted data from the TESS database of the American Association of Poison Control Centers (AAPCC). This report tabulates information on all cases reported to a participating poison control center (PCC) in the United States involving a human exposure to cetirizine/pseudoephedrine from 2001 to 2005.

There were 2623 reports for cetirizine/pseudoephedrine with 1025 associated clinical effect (CE) terms. Of these cases, 59.0% (1547/2623) were in the pediatric age range (<17 years) and 36.6% (959/2623) were reports of adult exposures. A total of 4.5% (117/2623) of the reports had no age data. The mean age was 19.1 years; the median age was 14 years and the age distribution revealed that a disproportionately large fraction of the cases was in the age range <2 years old (19.0%, 498/2623).

All the reported cases involved ingestion as a route of exposure (ROE) but more than one ROE could be recorded for a given case and there were 9 reports of inhalation, 1 report each of dermal and rectal exposure and 2 reports of unknown ROE.

A total of 1942 (74.0%, 1942/2623) reports were of single substance exposures, 16.4% (429/2623) involved 2 substances and 9.6% (252/2623) involved 3 or more substances.

The proportion of male patients ranged from 53.2% (823/1547) in the pediatric cases to 34.6% (332/959) among the adult cases. In the group of cases without age data, the proportion of males was 27.4% (32/1 17). Overall, men comprised 45.3% (1187/2623) of the reports and women 54.6% (1432/2623). Only 0.2% (4/2623) of the reports had no reported gender.

Overall, unintentional exposures accounted 85.6% (2244/2623) of the reported cases. Not unexpectedly, this proportion was higher among pediatric cases (91.0%, 1407/1547) than among reports for adults and reports with no age data (77.8%, 837/1076).

There were relatively more Intentional-suspected suicide reports in the adult category (12.5%,120/959) compared to the pediatric (6.5%, 101/1547) and relatively more reports of Adverse reaction-drug (6.6%,63/959) among adults compared to the pediatric reports (1.0%, 15/1547).

There were no reported deaths. Ten cases (3 pediatric and 7 adult) were reported with major effects (0.4%, 10/2623). Moderate effects were reported in 3.4% (88/2623) of cases and were more frequent among adults (5.7%, 55/959) compared to pediatric cases (2.1%, 32/1547). The 5 categories of medical outcome identifying minimal clinical effects, no effects, minor effects, nontoxic exposures and unrelated effects accounted for 92.6% (2428/2623) of all reports.

Table 5 below provides a complete listing of the reported CEs for each of the age categories. The TESS clinical effects vocabulary has been retained and more than 1 CE can be reported for a single case. The listed terms are those used in the TESS system and have been reproduced without change except to separate the organ system from the complete term.

A total of 1025 CEs were reported for 623 (23.8%, 623/2623) patients. Overall, the 4 most frequently reported clinical effects accounted for 53.2% (545/1025) of the total reported CEs. The 4 terms are: Drowsy Lethargy (17.8%, 182/1025), Tachycardia (13.9%, 142/1025), Other (12.1 %, 124/1 025) and Agitated Irritable (9.5%, 97/1025). There were no important differences between the age categories, although for 2 CEs the reported frequencies were somewhat higher in adults than in pediatric reports. These were: Agitated Irritable (adult: 11.4%, 41/359 versus pediatric: 8.6%, 53/614) and Nausea (adult: 7.2%, 26/359 versus pediatric: 4.4%, 27/614).

There were 2080 therapies or treatments reported for 1426 cases. It should be noted that since 26% of the reported exposures involved more than a single substance, the reported treatments may have been undertaken for clinical effects not attributable to cetirizine/pseudoephedrine. Overall, 3 of the treatments accounted for 72.6% (1510/2080) of the total. They were: Dilute Irrigate Wash 43.8% (910/2080), Food Snack 15.1% (314/2080), Charcoal Single 13.8% (286/2080).

Table 5. Clinical Effect Terms for Cetirizine/Pseudoephedrine Exposure by Age Category in Descending Order of Total Frequency within Organ System [Number (%)].

Organ System	Clinical Effect Term	Pediatric (≤ 17 years)	Adult (≥ 18 years)	No Age Data	Overall Total
Cardio	Tachycardia	90 (14.7)	45 (12.5)	7 (13.5)	142 (13.9)
Cardio	Hypertension	16 (2.6)	7 (1.9)	1 (1.9)	24 (2.3)
Cardio	Chest Pain	4 (0.7)	4 (1.1)	1 (1.9)	9 (0.9)
Cardio	Hypotension	4 (0.7)	1 (0.3)		5 (0.5)
Cardio	Conduction Disturbance	3 (0.5)	1 (0.3)		4 (0.4)
Cardio	Bradycardia		3 (0.8)		3 (0.3)
Cardio	Dysrhythmia Other	1 (0.2)	1 (0.3)		2 (0.2)
Cardio	Dysrhythmia VTach		1 (0.3)		1 (0.1)
Dermal	Erythema Flushed	9 (1.5)	6 (1.7)		15 (1.5)
Dermal	Pruritus	3 (0.5)	5 (1.4)		8 (0.8)
Dermal	Rash	3 (0.5)	3 (0.8)	1 (1.9)	7 (0.7)
Dermal	Edema	5 (0.8)			5 (0.5)
Dermal	Hives Welts	1 (0.2)	3 (0.8)	1 (1.9)	5 (0.5)
Dermal	Ecchymosis		1 (0.3)		1 (0.1)
Dermal	Irritation Pain	1 (0.2)			1 (0.1)
Dermal	Pallor	1 (0.2)			1 (0.1)
Gastro	Vomiting	37 (6.0)	19 (5.3)	4 (7.7)	60 (5.9)
Gastro	Nausea	27 (4.4)	26 (7.2)	3 (5.8)	56 (5.5)
Gastro	Abdominal Pain	7 (1.1)	5 (1.4)	2 (3.8)	14 (1.4)
Gastro	Diarrhea	7 (1.1)		3 (5.8)	10 (1.0)
Gastro	Throat Irritation	3 (0.5)		1 (1.9)	4 (0.4)
Gastro	Anorexia	1 (0.2)	1 (0.3)		2 (0.2)
Gastro	Hematemesis		1 (0.3)		1 (0.1)
Gastro	Oral Irritation	1 (0.2)			1 (0.1)
HemeHep	AST ALT Low	1 (0.2)			1 (0.1)
Misc	Other	78 (12.7)	42 (11.7)	4 (7.7)	124 (12.1)
Misc	Diaphoresis	4 (0.7)	3 (0.8)		7 (0.7)
Misc	Adverse Reaction To Treatment	1 (0.2)	5 (1.4)		6 (0.6)
Misc	Electrolyte Abnormality	2 (0.3)	3 (0.8)		5 (0.5)
Misc	Fever Hyperthermia	3 (0.5)	2 (0.6)		5 (0.5)
Misc	Acidosis	3 (0.5)			3 (0.3)
Misc	Bleeding Other	1 (0.2)	1 (0.3)		2 (0.2)
Misc	CPK Elevated	2 (0.3)			2 (0.2)
Misc	Hyperglycemia	2 (0.3)			2 (0.2)
Misc	Pain Not Dermal GI Ocular	1 (0.2)	1 (0.3)		2 (0.2)
Misc	Alkalosis		1 (0.3)		1 (0.1)
Misc	Rhabdomyolysis	1 (0.2)			1 (0.1)

Organ System	Clinical Effect Term	Pediatric (≤ 17 years)	Adult (≥ 18 years)	No Age Data	Overall Total
Neuro	Drowsy Lethargy	111 (18.1)	62 (17.3)	9 (17.3)	182 (17.8)
Neuro	Agitated Irritable	53 (8.6)	41 (11.4)	3 (5.8)	97 (9.5)
Neuro	Dizziness Vertigo	35 (5.7)	21 (5.8)	3 (5.8)	59 (5.8)
Neuro	Headache	12 (2.0)	5 (1.4)	2 (3.8)	19 (1.9)
Neuro	Tremor	11 (1.8)	2 (0.6)		13 (1.3)
Neuro	Slurred Speech	8 (1.3)	2 (0.6)	1 (1.9)	11 (1.1)
Neuro	Hallucination Delusions	6 (1.0)	4 (1.1)		10 (1.0)
Neuro	Coma	3 (0.5)	4 (1.1)	1 (1.9)	8 (0.8)
Neuro	Confusion	4 (0.7)	4 (1.1)		8 (0.8)
Neuro	Ataxia	4 (0.7)	1 (0.3)	1 (1.9)	6 (0.6)
Neuro	Numbness	2 (0.3)	2 (0.6)		4 (0.4)
Neuro	Tinnitus	2 (0.3)	1 (0.3)		3 (0.3)
Neuro	Seizure Multiple	2 (0.3)			2 (0.2)
Neuro	Seizure Single	1 (0.2)	1 (0.3)		2 (0.2)
Neuro	Syncope	1 (0.2)	1 (0.3)		2 (0.2)
Neuro	Fasciculations	1 (0.2)			1 (0.1)
Neuro	Muscle Weak		1 (0.3)		1 (0.1)
Ocular	Mydriasis	11 (1.8)	5 (1.4)	2 (3.8)	18 (1.8)
Ocular	Blurred Vision	1 (0.2)	1 (0.3)	1 (1.9)	3 (0.3)
Ocular	Irritation Pain	1 (0.2)	1 (0.3)		2 (0.2)
Ocular	Nystagmus	1 (0.2)	1 (0.3)		2 (0.2)
Ocular	Pupil Nonreactive	1 (0.2)	1 (0.3)		2 (0.2)
Ocular	Miosis		1 (0.3)		1 (0.1)
Renal	Urinary Retention	1 (0.2)	1 (0.3)		2 (0.2)
Resp	Hyperventilation Tachypnea	7 (1.1)	2 (0.6)		9 (0.9)
Resp	Dyspnea	5 (0.8)	3 (0.8)		8 (0.8)
Resp	Respiratory Depression	4 (0.7)			4 (0.4)
Resp	Cough Choke	2 (0.3)			2 (0.2)
Resp	Bronchospasm	1 (0.2)			1 (0.1)
Resp	X-Ray Findings			1 (1.9)	1 (0.1)
	Total CE terms	614 (100)	359 (100)	52 (100)	1025 (100)
	Cases with CE term(s) (row %)	298 (47.8)	296 (47.5)	29 (4.7)	623 (100)
	Total cases (row %)	1547 (59.0)	959 (36.6)	117 (4.5)	2623 (100)
	% Total cases with CE term(s)	19.3	30.9	24.8	23.8

a Unless otherwise indicated, all percents are calculated based on the total number of clinical effect terms for each age category.

The Sponsor also tabulated all the reported circumstances (such as dosing error, access stored unlocked, access from suitcase) that led to reported overdoses and termed these circumstances as exposure scenarios. Overall, there were 1502 exposure scenarios reported for 1424 cases. There were 736 scenarios involving 687 pediatric cases and 683 scenarios involving 659 reports of adult exposures. A larger proportion of the adult cases had reported scenarios (68.7%, 659/959) than did the pediatric cases (44.4%, 687/1547).

The 8 most frequently reported exposure scenarios all involved a dosing error of one form or other. Together these exposure scenarios accounted for 90.9% (1366/1502) of all the reported scenarios. The largest difference between the age categories was for the most frequently reported scenario - Dose Inadvertently Twice (adult: 52.1 %, 356/683; pediatric: 39.7%, 292/736).

Comment:

1. The TESS data suggest that use of the cetirizine-pseudoephedrine product is not likely to lead to a death in a typical overdose situation, since there were no fatalities due to an overdose, whether intentional or unintentional.

7.1.17 Postmarketing Experience

Postmarketing experience data submitted to this NDA comes from three different sources: the Sponsor's database, the Sponsor's search of the FDA's SRS and AERS database and this FDA reviewer's search of the AERS database. Included in the Sponsor's database are AE reports it has received from since the 1999 approval of Zyrtec-D. These reports include those of UCB Pharma, which sponsors cetirizine/pseudoephedrine approvals and submissions in more than 70 countries, and those of Pfizer, which markets in 10 countries (including OTC marketing in 8 countries).

The Sponsor submitted 382 abstracts or summaries of nonclinical and clinical studies from a MEDLINE search (1966-mid-July 2006) in which the combination cetirizine-pseudoephedrine was discussed. See section 8.6, the Literature Review, for comments regarding these references.

Sponsor's Database of AEs received by Pfizer from September 21, 1999-May 10, 2006

The Sponsor's database is that of Pfizer (including UCB Pharma, the overseas marketer of Pfizer's cetirizine/pseudoephedrine product). Between September 21, 1999 and May 10, 2006, Pfizer received 635 cases from sources other than clinical trials. These cases comprise 1,497 AE terms. Of these 635 cases, 82.05% (521 cases) were non-serious, 14.49% (92 cases) were serious and 3.46% were reported deaths (22 cases).

Almost all cases (93.54%) were spontaneous reports from either patients/consumers (56.38%) or healthcare professionals (33.70%). Other cases derived from other sources, including: solicited (5.67%), sales representatives (2.20%), health authorities (1.26%), attorneys (0.47%) and spontaneous (0.31%).

More than half of all cases reported were for females (62.52%), almost one-third were male (30.24%), and gender was unknown for the remainder (7.24%). For cases where age was reported, mean age was 40.43 years (range: <6 months to 90 years). Age was unknown in 237 reports (37.32%).

For age-designated cases, 1 (0.16%) AE report was in an infant <6 months, 2 (.31%) in children 2 to <6 years, 11 (1.73%) in children 6 to <12 years, and 26 (4.09%) children of 12 to < 18 years. In adults, 317 reports (49.92%) were for 18 to <65 years, 26 (4.09%) for 65 to <77 years, and 15 (2.36%) for >77 years.

Outcome was unknown for 50.24% of all cetirizine/pseudoephedrine cases. In 25.51% of all cetirizine/pseudoephedrine cases, an outcome of recovered, recovering, or recovering with sequelae was reported. In 20.79% of all cases, an outcome of not recovered was reported. Death was identified as an outcome for 3.46% of cases including both spontaneous and solicited reports. Most of death reports (20/22; 90.91%) were received through solicited sources from Pfizer marketing programs. Two death reports (9.09%) were received from a source other than solicited.

Among all 1,497 AE terms associated with all 635 cases under review for the combination cetirizine/pseudoephedrine, the most commonly reported AE terms were identified within the nine SOC terms shown below in Table 6:

Table 6. Most commonly reported SOC terms for 1497 AEs in 635 patients in Sponsor's internal database during the period September 21, 1999 and May 10, 2006.

SOC Classification	Symptom	No. of cases	Percentage of total terms (n=1497)
General disorders and administration-site conditions	drug ineffective	121	8.08
Nervous-system disorders	somnolence	54	3.61
Psychiatric disorders	insomnia	46	3.07
Gastrointestinal disorders	dry mouth	28	1.87
Skin and subcutaneous disorders	rash	28	1.87
Immune system disorders	hypersensitivity	28	1.87
Cardiac disorders	tachycardia	27	1.80
Vascular disorders	hypertension	20	1.34
Respiratory, thoracic and mediastinal disorders	nasal congestion	18	1.20

The 22 deaths were previously discussed in section 7.1.1. The remaining 92 serious AEs are shown in Table 7 below. Of note, there were 6 convulsions, 2 suicides, 2 thrombocytopenic events, 2 drug interactions, 1 ventricular arrhythmia, and 1 spontaneous abortion.

Table 7: Adverse Event Terms (n=359) Associated with the Reported Nonfatal Serious Cases (n=92) for Cetirizine/Pseudoephedrine, From Sponsor's Database, Outside of Clinical Trials

MedDRA SOC/ Preferred Term	Ceterizine/Pseudoephedrine Count (%)[a]
Nervous System Disorders	**62 (17.27)**
Loss Of Consciousness[b]	7 (1.95)
Convulsion[b]	6 (1.67)
Memory Impairment	5 (1.39)
Somnolence[b]	5 (1.39)
Cerebrovascular Accident[b]	3 (0.84)
Dizziness[b]	3 (0.84)
Headache	3 (0.84)
Ageusia	2 (0.56)
Disturbance in Attention	2 (0.56)
Transient Ischaemic Attack	2 (0.56)
Anosmia	2 (0.56)
Tremor	2 (0.56)
Paraesthesia	2 (0.56)
General Disorders And Administration Site Conditions	**39 (10.86)**
Drug Ineffective[b]	5 (1.39)
Fatigue	5 (1.39)
Pain	5 (1.39)
Unevaluable Event[b]	5 (1.39)
Chest Pain	3 (0.84)
Asthenia	3 (0.84)
Drug Interaction	2 (0.56)
Malaise	2 (0.56)
Respiratory, Thoracic And Mediastinal Disorders	**34 (9.47)**
Dyspnoea[b]	5 (1.39)
Sinus Disorder	4 (1.11)
Throat Tightness	3 (0.84)
Asthma	3 (0.84)
Respiratory Disorder	2 (0.56)
Cough	2 (0.56)
Emphysema	2 (0.56)
Investigations	**31 (8.64)**
Blood Glucose Increased	3 (0.84)
Amphetamines Positive	2 (0.56)
Heart Rate Irregular	2 (0.56)
Gastrointestinal Disorders	**25 (6.96)**
Diarrhoea	3 (0.84)
Dry Mouth	2 (0.56)
Nausea	2 (0.56)
Dysphagia	2 (0.56)
Constipation	2 (0.56)
Vomiting	2 (0.56)
Psychiatric Disorders	**20 (5.57)**
Anxiety	3 (0.84)
Insomnia	2 (0.56)
Depression	2 (0.56)

Table 7 (Continued)

MedDRA SOC/ Preferred Term	Ceterizine/Pseudophedrine Count (%)[a]
Cardiac Disorders	**16 (4.46)**
Tachycardia[b]	5 (1.39)
Palpitations	2 (0.56)
Cyanosis	2 (0.56)
Myocardial Infarction	2 (0.56)
Tachycardia Paroxysmal	2 (0.56)
Atrial Fibrillation	2 (0.56)
Infections and Infestations	**15 (4.18)**
Sinusitis	3 (0.84)
Pneumonia	2 (0.56)
Fungal Infection	2 (0.56)
Musculoskeletal and Connective Tissue Disorders	**13 (3.62)**
Arthritis	4 (1.11)
Injury, Poisoning and Procedural	**12 (3.34)**
Injury	2 (0.56)
Back Injury	2 (0.56)
Skin and Subcutaneous Tissue Disorders	**12 (3.34)**
Rash[b]	4 (1.11)
Pruritis	2 (0.56)
Surgical and Medical Procedures	**12 (3.34)**
Surgery	4 (1.11)
Sinus Operation	2 (0.56)
Immune System Disorders	**11 (3.06)**
Hypersensitivity	7 (1.95)
Multiple Allergies	2 (0.56)
Eye Disorders	**11 (3.06)**
Blindness	2 (0.56)
Eye Disorder	2 (0.56)
Vascular Disorders	**9 (2.51)**
Hypertension[b]	5 (1.39)
Flushing	2 (0.56)
Hypotension	2 (0.56)
Neoplasms Benign, Malignant and Unspecified	**8 (2.23)**
Prostate Cancer	2 (0.56)
Renal and Urinary Disorders	**8 (2.23)**
Urinary Incontinence	2 (0.56)
Social Circumstances	**5 (1.39)**
Disability	5 (1.39)
Ear and Labyrinth Disorder	**5 (1.39)**
Hypoacusis	2 (0.56)
Reproductive System and Breast Disorders	**4 (1.11)**
Ovarian Cyst	2 (0.56)
Total No. of AE Terms Reported in Serious Cases	**359**
Total No. of Serious Cases	**92**
Total No. of AE Terms / Total No. of Cases	**3.90**

Sponsor's AERS DataMart Postmarketing Evaluation:

The Sponsor states it queried the AERS Database for FDA individual safety reports (ISRs, MedWatch forms) describing all serious adverse events worldwide, expected and unexpected, involving the cetirizine-pseudoephedrine 5 mg/120 mg combination from the period November 1, 1997-March 31, 2006. Cases were identified by using an extensive list of synonyms and tradenames for cetirizine/pseudoephedrine-containing products with appropriate wildcard searching techniques. Only cases involving cetirizine/pseudoephedrine as a suspect agent were included in the analysis. Categorization of the cases based on seriousness was based on reported outcomes in accordance with FDA definitions. All AE terminology was standardized to MedDRA 9.1.

Comment:

1. It is not clear from the Sponsor's "Methods" description exactly what terms they used for all of the selectable categories in the AERS database search. In particular the AERS DataMart database does not have Zyrtec-D listed as a single ingredient NDA product. Thus, some modification of the search terms is needed to produce results for cetirizine/pseudoephedrine (see search terms for FDA reviewer's AERS search in Appendix 1).

On March 19, 2007 FDA requested clarification of the Sponsor's AERS database search terms. On April 27, 2007 the Sponsor responded that the search criteria were contained in the Methods Section (Section 2) of the submission. They also noted that only the AERS database was searched for the combination cetirizine/pseudoephedrine (and not the SRS database) since the product was approved in 2001 and the AERS database "covers the period November 1, 1997 to the present. The database used for the ISS presentation was current through March 31, 2006."

Table 8 below shows the demographics of the 93 total case reports. About half of the cases involved adults (49.5%), 10.8% involved children (age≤17), and 39.8% had no reported age data. The two deaths were in adults.

Table 8. Demographic Characteristics and Case Report Data for Adverse Event Reports Associated with Cetirizine/Pseudoephedrine: FDA AERS Database, November 1, 1997-March 31, 2006, Number (%).

Category[a]		Pediatric (≤ 17)	Adult (≥ 18)	No Age Data	Overall Total
Total case reports	N (row %)	10 (10.8)	46 (49.5)	37 (39.8)	93 (100)
Total AE terms	N (row %)	35 (8.7)	225 (56.0)	142 (35.3)	402 (100)
AE terms/case		3.5	4.9	3.8	4.3
Gender (N, %)	Female	4 (40.0)	28 (60.9)	26 (70.3)	58 (62.4)
	Male	6 (60.0)	18 (39.1)	2 (5.4)	26 (28.0)
	No gender data			9 (24.3)	9 (9.7)
Age	N (%)	10 (100)	46 (100)		56 (60.2)
	Mean (yr)	13.7	44.5		39.0
	StdDev (yr)	2.9	16.2		18.9
	Min (yr)	7	18		7
	Max (yr)	17	75		75
Age Group	7-11	1 (10.0)			1 (1.1)
	12-17	9 (90.0)			9 (9.7)
	18-40		19 (41.3)		19 (20.4)
	41-65		22 (47.8)		22 (23.7)
	66-77		5 (10.9)		5 (5.4)
	ND			37 (100)	37 (39.8)
Seriousness (N,%)	Non-serious	5 (50.0)	29 (63.0)	22 (59.5)	56 (60.2)
	Serious[b]	3 (30.0)	13 (28.3)	14 (37.8)	30 (32.3)
	Deaths		2 (4.3)		2 (2.2)
	No outcome data	2 (20.0)	2 (4.3)	1 (2.7)	5 (5.4)
Report Type (N, %)	Direct	2 (20.0)	3 (6.5)	2 (5.4)	7 (7.5)
	Expedited	7 (70.0)	38 (82.6)	27 (73.0)	72 (77.4)
	Periodic	1 (10.0)	5 (10.9)	8 (21.6)	14 (15.1)
Outcome (N, %)	Death		2 (4.3)		2 (2.2)
	Disability	2 (20.0)	2 (4.3)	2 (5.4)	6 (6.5)
	Hospitalization	2 (20.0)	10 (21.7)	9 (24.3)	21 (22.6)
	Life-threatening		1 (2.2)		1 (1.1)
	Other	7 (70.0)	36 (78.3)	30 (81.1)	73 (78.5)
	Required intervention	1 (10.0)	2 (4.3)	4 (10.8)	7 (7.5)
Report Source (N, %)	Company representative		1 (2.2)	15 (40.5)	16 (17.2)
	Consumer	2 (20.0)	27 (58.7)	18 (48.6)	47 (50.5)
	Foreign	4 (40.0)	9 (19.6)	1 (2.7)	14 (15.1)
	Health professional	6 (60.0)	22 (47.8)	19 (51.4)	47 (50.5)
	Literature		1 (2.2)		1 (1.1)

a All percents are calculated based on the total number of case reports for each column. For Outcome and Report source more than one entry was permissible, so the percentages total to more than 100%.
b Serious cases and deaths were identified by the reported outcome. Deaths are not included in the counts for the serious cases.

Table 9 below shows 93 total cases with 402 associated AE terms. Of these, 60.2% (56/93) were not serious, 32.3% (30/93) were serious and 2.2% (2/93) were deaths. Five cases (5.4%, 5/93) had no outcome data. Seriousness was determined by reported outcome for the case.

The AE terms were broadly distributed across the SOCs (system, organ, class). The three SOCs with the highest reporting rates: Nervous system disorders ("Nerv", 17.7%, 71/402), General disorders and administration site conditions ("Genrl", 10.7%, 43/402) and Investigations ("Inv", 9.5%, 38/402).

The Cardiac Disorders SOC had a higher reporting rate for serious cases than for not serious cases (11.9%, 19/159 versus 2.6%, 6/229) and the Psychiatric Disorders SOC had a higher rate of reports for serious cases than for not serious cases (10.1 %, 16/159 versus 6.1%, 14/229).

Table 9. Adverse Event Reporting Rates for Cetirizine/Pseudoephedrine, by SOC and Seriousness: FDA AERS Database, November 1, 1997-March 31, 2006, Number (%).

SOC Abbr[b]	Not serious	Serious	Death	No outcome data	Overall total
Blood	1 (0.4)				1 (0.2)
Card	6 (2.6)	19 (11.9)	3 (37.5)		28 (7.0)
Ear	4 (1.7)	1 (0.6)			5 (1.2)
Eye	9 (3.9)				9 (2.2)
Gastr	19 (8.3)	7 (4.4)			26 (6.5)
Genrl	25 (10.9)	15 (9.4)	1 (12.5)	2 (33.3)	43 (10.7)
Hepat	3 (1.3)				3 (0.7)
Immun	5 (2.2)	5 (3.1)			10 (2.5)
Infec	4 (1.7)	9 (5.7)	1 (12.5)		14 (3.5)
Inj&P	6 (2.6)	7 (4.4)	1 (12.5)	2 (33.3)	16 (4.0)
Inv	24 (10.5)	14 (8.8)			38 (9.5)
Metab	4 (1.7)	1 (0.6)			5 (1.2)
Musc	10 (4.4)	4 (2.5)			14 (3.5)
Neopl	3 (1.3)	3 (1.9)			6 (1.5)
Nerv	47 (20.5)	23 (14.5)		1 (16.7)	71 (17.7)
Preg		1 (0.6)			1 (0.2)
Psych	14 (6.1)	16 (10.1)	1 (12.5)		31 (7.7)
Renal	7 (3.1)	4 (2.5)			11 (2.7)
Repro	2 (0.9)	1 (0.6)			3 (0.7)
Resp	15 (6.6)	14 (8.8)	1 (12.5)		30 (7.5)
Skin	6 (2.6)	5 (3.1)		1 (16.7)	12 (3.0)
SocCi	3 (1.3)	4 (2.5)			7 (1.7)
Surg	5 (2.2)	1 (0.6)			6 (1.5)
Vasc	7 (3.1)	5 (3.1)			12 (3.0)
Total AE terms (col %)	229 (100)	159 (100)	8 (100)	6 (100)	402 (100)
Total AE terms (row %)	229 (57.0)	159 (39.6)	8 (2.0)	6 (1.5)	402 (100)
Total cases (row %)	56 (60.2)	30 (32.3)	2 (2.2)	5 (5.4)	93 (100)
Terms/case	4.1	5.3	4.0	1.2	4.3

a Unless otherwise indicated, the percent basis is the total number of terms in each seriousness category.

The Sponsor further analyzed the serious reports from Table 9 above and noted that there were too few reports of individual terms to make meaningful comparisons. The terms associated with serious reports were distributed over a broad range, with only 2 terms having more than 2.0% of the total. These were: Dyspnea (2.5%, 4/159) and Memory impairment (2.5, 4/159).

There were two reports of death in Table 9 above (these are the same cases as in section 7.1.1) . The amount of Zyrtec-D ingested was not reported for either death. One was an 18 year old female taking Zithromax, Zyrtec-D 12 Hour, salbutamol, magnesium potassium and ethynylestradiol, norgestimate. Bronchitis and "ill-defined disorder" were the listed indications for the medications. The AE terms reported for the case were: Cardiac arrest, Torsade de pointes, Ventricular tachycardia, Disease recurrence, Bronchitis and Medication error. A consumer reported the case.

The second death was a 57 year old male with no listed concomitant medications. The indication for his treatment was listed as "hypersensitivity" and the AE terms reported were: Dyspnea and Insomnia. Both a health professional and a consumer reported the case.

Table 10 below shows the most frequent AE terms sorted by age category. The ranking was based on the overall occurrence rate. The Sponsor notes that, as a single SOC, only drug ineffective had an overall rate over 2%. Table 11 below shows deaths listed by MedDRA terms.

Table 10. Most Frequent Adverse Event Terms for Cetirizine/Pseudoephedrine, Reports by MedDRA Term and Age Category (Frequency ≥3), FDA AERS Database, November 1, 1997-March 31, 2006, Number (%).

SOC Abbr[b]	MedDRA Preferred Term	Pediatric (≤ 17)	Adult (≥ 18)	No age data	Overall total
Genrl	Drug ineffective		6 (2.7)	3 (2.1)	9 (2.2)
Resp	Dyspnoea	1 (2.9)	3 (1.3)	3 (2.1)	7 (1.7)
Genrl	Condition aggravated		4 (1.8)	1 (0.7)	5 (1.2)
Nerv	Convulsion	2 (5.7)		3 (2.1)	5 (1.2)
Nerv	Dizziness		4 (1.8)	1 (0.7)	5 (1.2)
Nerv	Somnolence	1 (2.9)	3 (1.3)	1 (0.7)	5 (1.2)
Psych	Anxiety	1 (2.9)	2 (0.9)	1 (0.7)	4 (1.0)
Resp	Asthma		2 (0.9)	2 (1.4)	4 (1.0)
Genrl	Fatigue	1 (2.9)	1 (0.4)	2 (1.4)	4 (1.0)
Nerv	Headache	1 (2.9)	3 (1.3)		4 (1.0)
Psych	Insomnia		2 (0.9)	2 (1.4)	4 (1.0)
Nerv	Loss of consciousness	2 (5.7)	1 (0.4)	1 (0.7)	4 (1.0)
Nerv	Memory impairment		2 (0.9)	2 (1.4)	4 (1.0)
Card	Palpitations	1 (2.9)	3 (1.3)		4 (1.0)
Resp	Sinus disorder		2 (0.9)	2 (1.4)	4 (1.0)
Gastr	Abdominal pain			3 (2.1)	3 (0.7)
Nerv	Ageusia		1 (0.4)	2 (1.4)	3 (0.7)
Nerv	Anosmia		1 (0.4)	2 (1.4)	3 (0.7)
Inv	Blood glucose increased		3 (1.3)		3 (0.7)
Gastr	Diarrhoea		3 (1.3)		3 (0.7)
Inv	Heart rate increased	1 (2.9)	2 (0.9)		3 (0.7)
Vasc	Hypertension		2 (0.9)	1 (0.7)	3 (0.7)
Ear	Hypoacusis		1 (0.4)	2 (1.4)	3 (0.7)
Vasc	Hypotension	1 (2.9)	1 (0.4)	1 (0.7)	3 (0.7)
Inj&P	Medication error	2 (5.7)	1 (0.4)		3 (0.7)
Immun	Multiple allergies		2 (0.9)	1 (0.7)	3 (0.7)
Genrl	Pain	1 (2.9)		2 (1.4)	3 (0.7)
Genrl	Pyrexia		3 (1.3)		3 (0.7)
Inj&P	Treatment noncompliance		3 (1.3)		3 (0.7)
Renal	Urinary retention			3 (2.1)	3 (0.7)
	Total AE terms (col %)	35 (100)	225 (100)	142 (100)	402 (100)
	Total AE terms (row %)	35 (8.7)	225 (56.0)	142 (35.3)	402 (100)
	Total cases (row %)	10 (10.8)	46 (49.5)	37 (39.8)	93 (100)
	Terms/case	3.5	4.9	3.8	4.3

Comment:

1. In Table 10 above the vertical sum of the entries in the columns (pediatric, adult, no age data, and overall total, does not appear to equal the total AE terms in each column respectively (35, 225, 142, 402) since there are many SOC terms not listed for which the frequency was less than 3 occurrences for that term.

Table 11. Adverse Event Terms for Cetirizine/Pseudoephedrine, Death by MedDRA Term and Age Group, FDA AERS Database, November 1, 1997-March 31, 2006, Number (%).

SOC Abbr[b]	MedDRA Preferred Term	18-40	41-65	Overall Total
Card	Cardiac arrest	1 (16.7)		1 (12.5)
Card	Torsade de pointes	1 (16.7)		1 (12.5)
Card	Ventricular tachycardia	1 (16.7)		1 (12.5)
Genrl	Disease recurrence	1 (16.7)		1 (12.5)
Infec	Bronchitis	1 (16.7)		1 (12.5)
Inj&P	Medication error	1 (16.7)		1 (12.5)
Psych	Insomnia		1 (50.0)	1 (12.5)
Resp	Dyspnoea		1 (50.0)	1 (12.5)
	Total terms (col %)	6 (100)	2 (100)	8 (100)
	Total terms (row %)	6 (75.0)	2 (25.0)	8 (100)
	Total cases (row %)	1 (50.0)	1 (50.0)	2 (100)
	Terms/case	6.0	2.0	4.0

a Unless otherwise indicated, the percent basis is the total number of terms in each age group.

Summary of the Sponsor's AERS data

An analysis of the AEs reported for cetirizine/pseudoephedrine revealed 93 cases involving 402 AE terms. Among the reports for cetirizine/pseudoephedrine, there were 30 serious cases (32.3% of total reports), including 159 associated AE terms and 2 deaths (2.2% of total reports). Considered overall, the gender distribution of the patients reported was 62.4% (58/93) women and 28.0% men (26/93). A total of 9.7% (9/93) of the reports had no reported gender. The mean age of the 60.2% of reports with age information was 39.0 years. A total of 10.8% (10/93) of the reports involved patients <17 years old. The three SOCs with the highest reporting rates accounted for 37.8% (152/402) of all the reported terms. These were: Nervous system disorders (17.7%, 71/402), General disorders and administration site conditions (10.7%, 43/402) and Investigations (9.5%, 38/402). With respect to individual AE terms, only Drug ineffective (2.2%, 9/402) had a reporting rate exceeding 2% of the overall total number of terms. Across the age groups, only two SOCs, both in the 12-17 age group, had a notably higher reporting rate. These were: Nervous system disorders (30.3%, 10/33 versus 17.7%, 71/402) and Psychiatric disorders (18.2%, 6/33 versus 7.7%, 31/402).

For the reports categorized as serious based on outcome data, the three SOCs with the highest proportion of reported terms were: Nervous system disorders (14.5%, 23/159), Cardiology disorders (11.9%, 19/159) and Psychiatric disorders (10.1 %, 16/159). In the 18-40 age group, the Cardiac disorders SOC accounted for 31.3% (10/32) of the terms reported for the age group compared to 11.9% (19/159) observed overall. Among the reports in the 41-65 age group, the Nervous system disorders SOC had somewhat higher reporting rate than the overall rate (27.3%,9/33 versus 14.5%,23/159).

FDA Reviewer's AERS DataMart Evaluation:

To supplement the Sponsor's adverse event report, this reviewer queried the AERS DataMart database for the combination of cetirizine and pseudoephedrine as a primary drug suspect covering the time period of April 1, 2006-March 31, 2007. The combination product is apparently not listed in the database as a single-ingredient product (e.g.NDA 21-150). However, when cetirizine and pseudoephedrine are listed as primary ingredients the search yielded 39 serious adverse events, including 4 deaths. The complete search criteria employed are listed in Appendix 1.

FDA - AERS DataMart
Cases By Gender And Age Group
April 2006 to March 2007

Gender	Age Group	Total	Death	Serious	Hospitalized	Disabled	Congenital Anomalies	Life Threatening	Required Intervention
Female	Null	3	1	3	0	2	0	0	0
	Neonate	0	0	0	0	0	0	0	0
	Infant	0	0	0	0	0	0	0	0
	Child	0	0	0	0	0	0	0	0
	Adolescent	0	0	0	0	0	0	0	0
	Adult	14	1	14	10	4	0	2	0
	Elderly	7	0	7	6	1	0	0	0
	Gender Total:	24	2	24	16	7	0	2	0
Male	Null	2	0	2	0	0	2	0	0
	Neonate	1	0	1	0	0	1	0	0
	Infant	2	0	2	2	0	2	0	0
	Child	0	0	0	0	0	0	0	0
	Adolescent	2	2	2	1	0	0	0	0
	Adult	6	0	6	4	1	0	1	0
	Elderly	2	0	2	1	1	0	0	0
	Gender Total:	15	2	15	8	2	5	1	0
Not Specified	Null	0	0	0	0	0	0	0	0
	Neonate	0	0	0	0	0	0	0	0
	Infant	0	0	0	0	0	0	0	0
	Child	0	0	0	0	0	0	0	0
	Adolescent	0	0	0	0	0	0	0	0
	Adult	0	0	0	0	0	0	0	0
	Elderly	0	0	0	0	0	0	0	0
	Gender Total:	0	0	0	0	0	0	0	0

As noted in the table of cases by ISR type below, 14 of 39 cases are domestic and 25 of 39 cases are foreign.

FDA - AERS DataMart
Cases By ISR Type
April 2006 to March 2007

ISR Type	Total	Death	Serious	Hospitalized	Disabled	Congenital Anomalies	Life Threatening	Required Intervention
Expedited (15-Day)	39	4	39	24	9	5	3	0
Domestic	14	2	14	8	5	1	0	0
Foreign	25	2	25	16	4	4	3	0
	39	4	39	24	9	5	3	0

When analyzed by time, as shown in Cases by Year and Quarter, the listing below shows a slightly lower trending, with 6 cases in the first quarter of 2007.

FDA - AERS DataMart
Cases By Year and Quarter
April 2006 to March 2007

Year	Quarter	Total	Death	Serious	Hospitalized	Disabled	Congenital Anomalies	Life Threatening	Required Intervention
2006	2	14	0	14	7	5	4	0	0
	3	12	3	12	7	4	0	1	0
	4	7	0	7	5	0	1	2	0
	Yearly Totals:	33	3	33	19	9	5	3	0
2007	1	6	1	6	5	0	0	0	0
	Yearly Totals:	6	1	6	5	0	0	0	0
	Grand Totals:	39	4	39	24	9	5	3	0

Of note, individual case reports were available only for 11 of the 39 total cases. None of the 11 available reports included the deaths. In addition, the primary drug was Zyrtec (not Zyrtec-D) in 2 of the 11 reports and Sudafed 12 Hour, pseudoephedrine, or Actifed was the primary drug in the other 9 reports. Zyrtec-D was listed as a secondary drug in 1 of the 11 reports.

Comment:

1. The Sponsor's AERS DataMart search disclosed 93 total cases from November 1997-March 2005, of which 30 cases were serious, including two deaths. The effective time frame for the Sponsor's search may have been shorter than the listed time period, since Zyrtec-D was approved in August 2001 in the U.S. (with the first approval in 1999 in Italy). While it is not clear how many doses of Zyrtec-D were distributed (or consumed) over the time frames of the Sponsor's search vs. the FDA reviewer's search, there is no evidence that serious adverse events due to use of Zyrtec-D are increasing over time.

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

Reports of AEs associated with cetirizine as a suspect medication were obtained from the WHO drug safety database maintained in Uppsala, Sweden from 1978-June 30, 2006. The first case was dated February 7, 2004 and the most recent was May 2, 2006.

There were a total of 5 cases, 2 from Italy and 3 from the US. The 2 from Italy were not categorized as serious; 2 from the US were serious and 1 from the US was not classified.

One of the cases from Italy involved an acute allergic reaction and the other involved nausea, vomiting, tremor and vertigo. Two of the 3 cases from the US involved cardiac events. *One was a serious case in a 32 year old male who experienced cardiac arrest, cardiac failure in conjunction with QT prolongation and Torsade de pointes* and the other was a case of supraventricular tachycardia, of unclassified serious/not serious. The third case from the US was

a serious case involving pain, an intervertebral disc disorder and drug abuse. The case details are shown below:

WHO ID Number: 8582474
Date of case entry to database: 11/2312004
61 year-old male patient reported from Italy.
Concomitant medications: Ascriptin.
WHOART Preferred terms: Urticaria, lip disorder
Seriousness: not serious.
Outcome: recovered; drug withdrawn, reaction abated.

WHO ID Number: 9010848
Date of case entry to database: 09/2212005
16 year-old male patient reported by a general practitioner from Italy.
Concomitant medications: none reported.
WHOART Preferred terms: Tremor, vertigo, vomiting, nausea
Seriousness: not serious.
Outcome: recovered; drug withdrawn, reaction abated.

WHO ID Number: 8368455
Date of case entry to database: 02/07/2004
Female patient, age not given, reported by a physician from the US.
Concomitant medications: none reported.
WHOART Preferred terms: Supraventricular tachycardia.
Seriousness: not reported
Outcome: not reported

WHO ID Number: 8582474
Date of case entry to database: 11/02/2005
Female patient, age not given, reported by a physician from the US.
Concomitant medications: Nicotinic acid, Escitalopram, Buspirone, Cyclobenzaprine, Paracetamol/Hydrocodone bitartrate, Omeprazole, Ascorbic acid, Gabapentin, Sumatriptan, Triamcinolone and Salbutamol.
WHOART Preferred terms: Pain, Intervertebral disc disorder, drug abuse.
Seriousness: serious
Reason: other.
Outcome: not reported

WHO ID Number: 9262018
Date of case entry to database: 05/02/2006
32 year-old male patient reported by a physician from the US.
Concomitant medications: Montelukast, Levetiracetam.
WHOART Preferred terms: Cardiac arrest, cardiac failure, cardiac failure, cardiomyopathy, creatine phosphokinase decreased, fibrillation ventricular, hypokinesia, myocardial ischaemia, QT prolonged, T wave inversion and Torsade de pointes.

Seriousness: serious;
Reason: Caused/ prolonged hospitalization.
Outcome: not reported.

Comment:

1. The two serious cases reported to the WHO database provide scant data and are confounded by apparent concomitant illness and concomitant medications. The female patient of unstated age (WHO case 8582474) had an intervetebral disc disorder and used 11 concomitant medications. The 32-year old male patient (WHO case 9262018) is the only patient in this review with Torsade de Pointes. However, he may have had asthma (used montelukast) and a seizure disorder (used levetiracetam) as co-morbid conditions.

2. Summarizing the Postmarketing Data on cetirizine/pseudoephedrine, the side effect profile reflects the known pharmacologic properties of the component drugs. No previously unrecognized adverse events of significant frequency were identified. In general, the reported AEs appear to be distributed over a broad range of conditions, though somnolence and fatigue are a recurring theme. Based on these data the product is acceptable for OTC use.

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 822 subjects 12 years and older were exposed to Zyrtec-D in 3 clinical trials. The safety database in the three pivotal trials comprised 353 subjects in the Zyrtec-D arm in Study #A3771001, in which ten subjects reported severe treatment-emergent adverse events, 330 subjects in the Zyrtec-D arm in study #A3771002 in which 11 subjects reported 16 severe treatment-emergent adverse events, and 139 subjects in the Zyrtec-D arm of Study #A3771007 in which no serious adverse events were recorded in this arm, although 9 subjects discontinued due to exacerbation of asthma and somnolence. In all three studies the subjects were age 12 or older and had SAR or PAR, while subjects in Study #A3771007 also had asthma.

7.2.1.1 Study type and design/patient enumeration

The Sponsor submitted three studies, Study# A3771001, Study #A3771002 and Study# A3771007, to support the application. All three studies were randomized, blinded and multiple-dose. Laboratory personnel were blinded.

Study #A3771001
Safety was assessed by summarizing the incidence of treatment-emergent adverse events, measurement of vital signs, physical examination findings, and concomitant medications. A total of 351 treatment-emergent (all causalities) adverse events were reported by 256 (23.6%) subjects during the study. The incidence of treatment-emergent adverse events was slightly higher in

subjects receiving active drug, with 88 (24.0%) cetirizine/pseudoephedrine 5 mg/120 mg- treated subjects and 96 (26.72%) loratadine/pseudoephedrine 5 mg/120 mg-treated subjects reporting adverse events compared with 72 (19.9%) placebo-treated subjects. Although the majority of treatment-emergent adverse events were mild or moderate in severity, 10 (2.7%) subjects in the cetirizine/pseudoephedrine 5 mg/120 mg group, 18 (5.0%) subjects in the loratadine/pseudoephedrine 5 mg/120 mg group, and 11 (3.0%) subjects in the placebo group reported severe treatment-emergent adverse events. Headache was the most frequently reported treatment-emergent adverse event reported by 6 (1.6%) subjects in the cetirizine/pseudoephedrine 5 mg/120 mg group, 16 (4.5%) subjects in the loratadine/pseudoephedrine 5 mg/120 mg group, and 11 (3.0%) of subjects in the placebo treatment group. There were no serious adverse events or deaths reported or entered into Pfizer's early alert safety database during the study. A clinical review of vital sign and of physical examination data showed no clinically meaningful changes during the study.

Study #A3771002

Safety was assessed by summarizing the incidence of treatment-emergent adverse events, measurement of vital signs, physical examination findings, and concomitant medications. A total of 317 treatment-emergent (all causalities) adverse events were reported by 233 (23.3%) subjects during the double-blind treatment phase of the study. The incidence of treatment-emergent adverse events was similar between treatment groups, with 84 (25.1 %) of the cetirizine/pseudoephedrine subjects, and 83 (25.2%) of the fexofenadine/pseudoephedrine subjects, and 66 (19.8%) of the placebo subjects reporting adverse events. Twenty-five serious adverse events were reported, with 16 occurring in 11 (3.3%) subjects in the cetirizine/pseudoephedrine group, 5 occurring in 5 (1.5%) subjects in the fexofenadine/pseudoephedrine group, and 4 occurring in 3 (0.9%) subjects in the placebo group. The most frequently reported treatment-emergent adverse event was headache, which occurred in 10 (3.0%) subjects in the cetirizine/pseudoephedrine group, 17 (5.2%) subjects in the fexofenadine/pseudoephedrine group, and 14 (4.2%) subjects in the placebo group. There were no clinically significant vital signs or physical examination abnormalities during this study.

Study #A3771007

Safety was assessed by summarizing the incidence of treatment-emergent adverse events, measurement of vital signs, physical examination findings, and concomitant medications. There was one serious adverse event, viral meningitis, in a placebo subject. A total of 235 subjects completed the study. Thirty-nine subjects discontinued from the study due to treatment-emergent adverse events: of these, 9 in the cetirizine/pseudoephedrine 5 mg/120 mg group and 8 in the placebo group discontinued due to treatment-emergent adverse events. Four subjects in the cetirizine/pseudoephedrine 5 mg/120 mg group and no subjects in the placebo group discontinued due to adverse events considered to be related to study drug. The majority of adverse events were mild or moderate in severity. The most commonly occurring adverse events were exacerbation of asthma (20 cetirizine/pseudoephedrine 5 mg/120 mg subjects, 14.4%; 14 placebo subjects, 10.4%) and somnolence (8 cetirizine/pseudoephedrine subjects, 5.8%; 1 placebo subject, 0.7%). Changes in vital signs, physical examinations, and laboratory results (collected on limited basis) were minor.

7.2.1.2 Demographics

The Sponsor reported these data for cetirizine/pseudoephedrine with the original NDA 21-150 approved August 10, 2001. There is no new information in the current submission.

7.2.1.3 Extent of exposure (dose/duration)

In the three clinical trials for the original NDA 21-150 cetirizine/pseudoephedrine was dosed 5 mg/120 mg twice daily for 2 weeks in Studies # A3771001 and #A3771002 and for 4 weeks in Study #A3771007. There is no new information in the current submission.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Data from the Sponsor's safety update is discussed in section 7.1.17 and data from the AERS Database is discussed in section 7.2.9. Safety data from the literature is discussed in section 8.2 of this review.

7.2.3 Adequacy of Overall Clinical Experience

This is a supplemental application. The original submission of this NDA contained full safety data for the ingredients, cetirizine-pseudoephedrine. No safety issues were identified at the time of the original application. The safety data appears adequate for the switch from prescription to OTC use.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Animal or in vitro data were not provided in this application.

7.2.5 Adequacy of Routine Clinical Testing

Not applicable for this supplemental safety data submission.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The Sponsor provided sufficient data to characterize the pharmacological profile of the cetirizine/pseudoephedrine during the original submission of the NDA. The prescription label notes a 70% decrease in renal clearance of cetirizine in renal impaired patients and a 50% increase in the half life of cetirizine in patients with chronic liver disease. In the proposed OTC label patients with liver or kidney disease are warned to ask a doctor before use.

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

From a clinical safety perspective there are no recommendations for further studies.

7.2.8 Assessment of Quality and Completeness of Data

From a clinical safety perspective, this application is adequate and complete.

7.2.9 Additional Submissions, Including Safety Update

The Sponsor's additional literature review is discussed in section 8.6. On May 4, 2007 the Sponsor submitted a 4-month safety update for the period May 11, 2006 to January 16, 2007 for Zyrtec-D. The report contained a total of 80 adverse events, of which 16 were serious and 64 were nonserious. There were no deaths. There was no serious adverse event term reported more than twice. In particular, there were no reports of thrombocytopenia, seizures, tachycardia, or ventricular arrhythmia. There were no new or unexpected findings.

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

Drug ineffective, insomnia, somnolence, and possibly tachycardia are the notable drug-related adverse events. Any of these AEs could be expected to occur in patients with allergic rhinitis who take an antihistamine-decongestant. The product has been used over a sufficient period of time (since 1999 in Italy and 2001 in the U.S.) and in an adequate number of doses worldwide (858,605,084 tablets distributed) to ensure that most AEs that will be seen OTC have probably already been seen in the Rx market.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

The Sponsor submitted three clinical trials, studies #A3771001, A3771002, and A3771007, with adverse event data for the original Rx Zyrtec-D NDA and its supplements. A total of 822 subjects were exposed to Zyrtec-D in these three studies. The Sponsor referenced three other NDAs for Zyrtec products in the current submission: NDAs for Zyrtec Tablets, Zyrtec Syrup, and Zyrtec Chewable Tablets. Safety data were evaluated in the medical reviews for the approval of the original Zyrtec-D NDA and the referenced NDAs.

7.4.1.1 Pooled data vs. individual study data

Adverse events in the three clinical trials, Studies # A3771001, A3771002, and A3771007 were similar. In study #A3771007 subjects had an additional adverse event due to enrolling asthma patients, worsening of asthma, which was not statistically higher than placebo.

7.4.1.2 Combining data

Not applicable.

7.4.2 Explorations for Predictive Factors

There was no analysis based upon dose, duration of use, or concomitant medication with the three clinical trials.

7.4.2.1 Explorations for dose dependency for adverse findings

There was no evaluation for dose dependency for adverse finding in this application.

7.4.2.2 Explorations for time dependency for adverse findings

There was no evaluation for time dependency for adverse finding in this application.

7.4.2.3 Explorations for drug-demographic interactions

The prescription label notes that the cetirizine elimination half-life was prolonged by 50% and the apparent total body clearance was lower by 40% in 16 geriatric subjects with a mean age of 77 years. The label notes these effects are probably due to decreased renal function (age-related). As with other antihistamines or antihistamine-decongestant combinations, younger subjects might be more likely to experience nervousness or hyperkinesis while older subjects might be more likely to experience sedation with cetirizine/pseudoephedrine compared to placebo.

Comment:

1. Since the Zyrtec-D combination contains only 5 mg of cetirizine and is dosed at 12-hour intervals, the likelihood of drug accumulation is of less concern than with the single-ingredient products that might contain 10 mg of cetirizine. A caution against use by geriatric patients is not included in the prescription label and is not needed in the OTC label.

7.4.2.4 Explorations for drug-disease interactions

The Sponsor has not conducted any study exploring drug-disease interactions for this product. The current product label does not indicate any known drug-disease interactions; however, those with trouble urinating due to an enlarged prostate gland, or with high blood pressure or heart, liver, kidney, or thyroid disease are advised to ask a doctor before use.

7.4.2.5 Explorations for drug-drug interactions

Pharmakokinetic interaction trials were done in adults with cetirizine and pseudoephedrine, antipyrine, ketoconazole, erythromycin, and azithromycin. No interactions were observed.

In Pfizer's corporate safety database a total of 11 cases involved the AE term *drug interaction* from January 1, 1986-May 10, 2006. Of these, 2 (18.18%) were classified as serious and no cases reported an outcome of death. The two serious cases reporting a drug interaction were medically confirmed. One case involved a suspected interaction between cetirizine-

pseudoephedrine and Zithromax (azithromycin). The second case involved as suspected interaction between cetirizine/pseudoephedrine and Alesse (levonorgestrel/ethinyl estradiol). Only one ingredient (alcohol) was identified more than once and it was identified as a co-suspect drug in two consumer cases. The Sponsor stated there were no trends of AEs or safety signals identified from these cases.

Comments:

1. The current Rx prescribing literature notes that no clinically significant drug interaction have been found between cetirizine and low dose theophylline, azithromycin, ketoconazole, or erythromycin. However, the case of the interaction with azithromycin is noted above, though no further details are provided.

2. The current Rx prescribing literature also notes that the drug should not be used with, or within 14 days, of using a MAO inhibitor due to a potential interaction with the pseudoephedrine component.

7.4.3 Causality Determination

The Sponsor did not perform special causality assessments.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

For adults and children 12 years and over, one tablet every 12 hours; not more than 2 tablets in 24 hours.

8.2 Drug-Drug Interactions

See section 7.4.2.5.

8.3 Special Populations

The current label advises those who have ever had an allergic reaction to the product or any of its ingredients, or who have heart disease, high blood pressure, thyroid disease, diabetes, liver or kidney disease, or have trouble urinating due to an enlarged prostate gland or any of its ingredients, to not use the product.

8.4 Pediatrics

The Sponsor requests a full waiver for submission of pediatric use information because Zyrtec-D 12 Hour Tablets are not likely to be used in a substantial number of pediatric patients. Zyrtec-D 12 Hour Tablets, NDA 21-150 were approved on August 10, 2001 for the relief of nasal and non-

nasal symptoms associated with seasonal or perennial allergic rhinitis in adults and children 12 years of age and older. The extended release dose of pseudoephedrine HCl in this product (120 mg) exceeds the dose approved for use in children less than 12 years of age. The Sponsor has not studied Zyrtec-D in the pediatric population.

Comment:

1. The Pediatric Research Equity Act (PREA) requires the study of potentially useful drugs in the pediatric population. The Sponsor is requesting a waiver since they do not plan to market the product in children less than 12 years of age. However, this age group does suffer from SAR and PAR and might benefit from the product. The Sponsor might have to develop a different formulation since not all children less than 12 years of age can swallow a pill. The FDA Pediatric and Maternal Health Staff will help determine whether a waiver should be granted or the Sponsor should be required to study the product in children less than 12 years old. Of note, another antihistamine/decongestant product containing bromopheniramine and pseudoephedrine is available OTC for hay fever and other respiratory allergies in children ages 6 to under 12 years (labeled as "ask a doctor" for children under 6 years old).

2. The monograph does not allow consumer labeling for antihistamines for children <6 years old. For children ages 2-<6 years old antihistamines may be used through professional labeling. Pseudoephedrine is labeled down to 2 years of age in the monograph.

8.5 Advisory Committee Meeting

No advisory committee meetings addressed this application.

8.6 Literature Review

The Sponsor reviewed the worldwide literature relevant to the efficacy and safety of cetirizine using the MEDLINE database from 1966 to mid-July 2006. The Sponsor states that it did not review safety of pseudoephedrine as a single ingredient since it is a monograph drug and has been used in the OTC population for years and has a well-characterized safety profile. For efficacy of cetirizine they provided 145 articles or studies that looked at SAR and PAR (a few references discussed use for idiopathic urticaria). These references supported the efficacy of cetirizine for SAR and PAR.

For safety the Sponsor searched under the headings of adverse effects, clinical trials, and reviews and identified 382 citations. The Sponsor divided these safety citations into clinical trials, case reports or case series, and review articles. Most of the references focused on cetirizine as a single ingredient, while a few focused on the combination product.

Clinical Trials:
The Sponsor identified 35 clinical trials discussing safety of cetirizine. Of these, 16 evaluated cetirizine in patients with SAR or PAR, or they specifically evaluated the sedative effects of cetirizine. Only three of the 15 studied the cetirizine-pseudoephedrine combination (see below).

The remaining 18 studies discussed cetirizine pharmacokinetics or use in urticaria, asthma, or COPD, or they focused on laboratory markers of allergic responses (skin wheal and flare responses). A general theme in these studies was an incidence of headache and sedation from cetirizine in the range of 2-10%. In the 15 pertinent studies no serious adverse events were mentioned.

Zieglmayer et al. (2005, reference 1) performed a randomized, crossover study comparing a cetirizine/pseudoephedrine combination vs. nasal budesonide (a corticosteroid) in a 4-day treatment of 36 subjects with allergic rhinitis from dust mites. Subjects were given the study drug than exposed to dust mite allergen. Both treatments were effective in reducing nasal congestion. Seven cetirizine/pseudoephedrine and 3 budesonide participants reported adverse events, but the investigators assessed all the events to be related to dust mite allergy and not the study drugs.

Horak et al. (1998, reference 2) studied efficacy and safety of the combination of cetirizine 5 mg /pseudoephedrine 120 mg vs. placebo in the treatment of PAR due to dust mite allergy in 24 patients over 7 days. The combination was more effective than placebo. No serious AEs occurred. Thirteen patients in the cetirizine-pseudoephedrine group and 16 patients in the placebo group reported symptoms, all mild to moderate in severity. Bronchospasm was reported by 10 patients, though it was not clear which treatment group these patients were in. Other AEs in the active group were dry mouth, agitation, anxiety, nervousness, and tiredness.

Stubner et al. (2001, reference 3) studied the efficacy and safety of the combination of cetirizine 5 mg -pseudoephedrine 120 mg vs. xylometazoline (each drug given twice daily) in the treatment of PAR due to dust mite allergy in 36 patients over 4 days. Both drugs were effective as decongestants, though the combination led to fewer nasal secretions. Twenty AEs were noted, 5 in the cetirizine-pseudoephedrine group (1 "lost power", 1 respiratory difficulty, 2 bronchospasm, 1 cough). Bronchospasm was also noted by 7 of the 15 subjects reporting AEs in the xylomatazoline group.

Day et al. (2005, reference 4) studied cetirizine 10 mg vs. fexofenadine 180 mg in 599 patients with SAR who were exposed to ragweed pollen. In the cetirizine group 18 subjects of 299 reported headache (7.2%). Asthenia was noted in 5 subjects (2.0%) and somnolence in 2 subjects (0.8%). No SAEs were noted.

Gong et al. (2005 reference 5) performed a crossover study of cetirizine 5 mg, 10 mg, 20 mg vs. albuterol in 16 subjects with mild, stable asthma. Subjects were given an inhaled allergen after drug treatment. Cetirizine failed to decrease bronchial sensitivity to inhaled allergen in 8 of the 10 subjects. One subject developed moderate drowsiness after cetirizine 20 mg and one subject in the cetrizine 20 mg group developed persistent asthma symptoms and dropped out. Overall, the investigators found no serious AEs in either group.

Marinez-Cocera et al. (2005, reference 6) studied a new antihistamine, rupatadine 10 mg daily, vs. cetirizine 10 mg daily (no placebo group) in a 14-day treatment of 249 patients with SAR. Both drugs had similar efficacy. Adverse events were similar in both groups. The most frequent

AEs with cetirizine were headache (19.7%), fatigue/asthenia (6.8%), and somnolence (8.5%). No serious AEs were reported.

Sienra-Monge et al. (1999, reference 7) discussed safety of cetirizine (0.2 mg/kg) vs. loratadine in 80 children 2 to 6 years of age with PAR (due to dust mites or pollen) over 28 days of use. There were no significant laboratory abnormalities with either drug. Two adverse events were reported, both in the cetirizine group. One case was somnolence and irritability and the other was a generalized rash. Both patients were discontinued from the study and their symptoms resolved.

Case Reports or Series:
The Sponsor identified 115 references they define as case reports or series discussing safety of cetirizine. However, none of these reports or series discussed use of the combination cetirizine/pseudoephedrine. The majority of the references were single case reports of symptoms from use of cetirizine including:

- dystonia
- oculogyric crisis
- drug eruption
- cold urticaria
- solar urticaria
- acute hepatitis
- recurrent acute hepatitis
- gynecomastia (2 children age 5 and 6 years old)
- torsade de pointes (with an overdose of cetirizine)

One small series in the elderly is pertinent:

Simons et al. (1999, reference 8) assessed the central nervous system effects of cetrizine 10 mg in a 5-way crossover study in 15 elderly subjects (mean age 71 years old) compared with loratadine, diphenhydramine, chlorpheniramine, or placebo. The investigators assessed cognitive processing, somnolence (subjective assessment using a visual analogue scale), and histamine skin tests to document H1 blockade. They found loratadine and cetirizine less likely to cause CNS adverse events than the active comparators. No serious AEs were reported.

Review Articles:
The Sponsor identified 115 references they define as review articles discussing safety of cetirizine. Of these, the Sponsor highlighted 24 articles. One of these discussed the combination of cetirizine-pseudoephedrine, while the remainder spoke more broadly of cetirizine. The cardiac safety of cetirizine was noted in several, including the Paakari article (below).

Paakari (2002, reference 9) analyzed the literature on the cardiotoxicity of new antihistamines and cisapride. The author found that preclinical, animal, and human data substantiated the absence of any clinically important effect of cetirizine on cardiac function or cardiac conduction. Specifically, no effects were found on the QT interval and experiments with potassium channel conduction in two different cell systems indicated no effect would be expected.

Wellington and Jarvis (2001, reference 10) reviewed the combination of cetirizine 5 mg – pseudoephedrine 120 mg. The onset of action of the combination is about 30 minutes. The combination is more effective for SAR or PAR symptoms than either ingredient alone. The most common AEs are dry mouth, insomnia, headache, somnolence, asthenia, and nervousness. They note one trial of 210 patients had a discontinuation rate due to AEs of 5.7% for the combination, 2.9% for cetirizine, and 12.9% for pseudoephedrine. Cetirizine alone has a higher frequency of somnolence (7%) and asthenia (4%) than does the combination.

The remaining review articles do not raise a significant safety concern for the combination product.

Comments:

1. The literature review has only a few examples of studies of the cetririzine-pseudoephedrine combination. The literature clearly supports the efficacy of cetirizine for treatment of SAR and PAR. The two clinical trials of the combination product show efficacy in the treatment of PAR due to dust mite allergies. It is likely these data can be extrapolated to treatment of SAR due to pollen as the hypersensitivity response is similar.

2. There was no data to raise a concern about serious AEs due to labeled use of the single ingredient cetirizine or the combination product cetirizine-pseudoephedrine. However, the study groups used sample sizes of a dozen to a few hundred subjects per arm. It is possible that rare AEs could be seen with wider use in the OTC population.

3. It is not definitive that the cetirizine single ingredient or combination product is safe in the population with asthma. Asthma symptoms are not always predictable, especially when asthma patients are exposed to dust mites or pollen. However, the few reports of bronchospasm while using the cetirizine single ingredient product or the combination might suggest this group of patients should consult with their physician before use.

8.7 Postmarketing Risk Management Plan

There is no postmarketing risk management plan.

8.8 Other Relevant Materials

There were no more relevant materials submitted.

9 OVERALL ASSESSMENT

9.1 Conclusions

For the original NDA approval in 2001 (and subsequent supplements), the Sponsor conducted three studies of the efficacy and safety of the Zyrtec-D combination product containing cetirizine

5 mg/ pseudoephedrine 120 mg. These studies documented safety and efficacy in adult subjects with symptoms of seasonal allergic rhinitis and perennial allergic rhinitis. There were no serious adverse events that could be attributed to the combination product in these trials.

The Sponsor's internal AE reports, TESS database search, DAWN database search, WHO database search, the Sponsor's literature search and this reviewer's literature search did not reveal any new or worrisome information about the combination product. In particular, there were no unconfounded cases of Torsade de Pointes. The Sponsor's search of the FDA AERS Database showed 30 serious AEs from November 1997-March 2006. This reviewer's FDA AERS Database search from April 2006-March 2007 did not provide any data indicating a safety concern. None of these searches revealed any new or worrisome information about the combination product cetirizine/pseudoephedrine.

However, some of the literature showed that patients with asthma had symptoms of bronchospasm during use of cetirizine/pseudoephedrine. While this adverse event was not significantly higher compared to a control or comparator drug in a study of asthma patients, asthma patients are at higher risk than patients without asthma. These data bear further watching and we should consider labeling advising patients with asthma to consult their physician before use.

9.2 Recommendation on Regulatory Action

The proposed sNDA 21-150 Zyrtec-D 12 Hour Tablets (cetirizine HCl 5 mg / pseudoephedrine HCl 120 mg) for the OTC marketing of this tablet for the indication of the temporary relief of symptoms of hay fever and other upper respiratory allergies and for relief of nasal congestion due to hay fever or other upper respiratory allergies in adults and children 12 years of age and older has an acceptable safety profile for OTC marketing. Therefore, this application is approvable from the safety standpoint. Final approvability depends on the efficacy assessment by the pulmonary division reviewer. The drug should be labeled such that patients with asthma should consult with their physician before use. The Sponsor's request for a pediatric waiver will be addressed through a consult from the Office of Pediatric and Maternal Health.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No special postmarketing risk management activities are recommended.

9.3.2 Required Phase 4 Commitments

No special Phase 4 commitments are recommended.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

The proposed label is presented on the next page. An interdisciplinary scientist in the Office of Nonprescription Products is reviewing the proposed label. The Sponsor incorporated most of the important warnings for cetrizine and pseudoephedrine. The label is acceptable from a clinical point of review after the following adjustments are made:

In the section "ask a doctor before use if you have" a bullet should be added for

- asthma
- glaucoma
- if you are taking a sedative or tranquilizer

The Sponsor also provided a Consumer Package Insert which the interdisciplinary scientist in the Office of Nonprescription Products is reviewing.

3 Page(s) Withheld

_____ Trade Secret / Confidential

6 Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical-_____

Appendix 1

Search Criteria for 39 cases in the FDA Reviewer's query of AERS DataMart for cetirizine/pseudoephedrine for the period April 1, 2006-March 31, 2007.

Criteria: PRIMARY DRUG, PRIMARY INGREDIENT, MANU, FDA Received Date, OUTCOME, REPORT TYPE, DRUG ROLE, BEST REPRESENTATIVE, INTERACTING INGREDIENT

PRIMARY DRUG
N019835 / ZYRTEC

PRIMARY INGREDIENT
PSEUDOEPHEDRINE HYDROCHLORIDE,
CETIRIZINE HYDROCHLORIDE

MANU
PFIZER CONSUMER HEALTHCARE,
PFIZER CONSUMER HEALTHCARE DIV WARNER LAMBERT CO,
PFIZER GLOBAL RESEARCH AND DEVELOPMENT,
PFIZER GLOBAL RESEARCH DEVELOPMENT,
PFIZER INC,
PFIZER INC,
PFIZER INC,
PFIZER IRELAND PHARMACEUTICALS,
PFIZER IRELAND PHARMACEUTICALS TABLET PLANT,
PFIZER LABORATORIES DIV PFIZER INC,
PFIZER MEDICINAL PRODUCT RESEARCH AND DEVELOPMENT,
PFIZER PHARMACEUTICALS CORP,
PFIZER PHARMACEUTICALS DIV PFIZER INC,
PFIZER PHARMACEUTICALS INC,
PFIZER PHARMACEUTICALS LTD,
PFIZER PHARMACEUTICALS PRODUCTION CORP LTD

FDA Received Date
2006APR-2007MAR

OUTCOME
Death, Life-Threatening, Hospitalization - Initial or Prolonged, Disability, Congenital Anomaly, Required Intervention to Prevent Permanent Impairment/Damage

REPORT TYPE
Domestic 5 Day, Foreign 5 Day, Unknown 5 Day, Domestic 10 Day, Foreign 10 Day, Unknown 10 Day, Domestic Expedited (15-Day), Foreign Expedited (15-Day), Unknown Expedited (15-Day)

DRUG ROLE
PRIMARY

BEST REPRESENTATIVE
TRUE

INTERACTING INGREDIENT
PSEUDOEPHEDRINE HYDROCHLORIDE

SEARCH PERFORMED: April 24, 2007

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