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Two less-sedating antihistamines previously approved in the US, terfenadine and astemizole, were withdrawn from the market due to their association with fatal cardiac arrhythmias.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.

. 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 enantiomer 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.

[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 cetiririzine and cetirizine/PSE. The CDER OTC Switch Review Team conducted a review of worldwide safety information to determine whether there were safety concerns that would prevent the use of cetirizine (as well as loratadine and fexofenadine) in the OTC setting. Results of this review were presented at a joint meeting of the Nonprescription and Pulmonary-Allergy Drug Products Advisory Committees on May 11, 2001. The Advisory Committee determined that cetirizine has a safety profile acceptable for OTC marketing [http://www.fda.gov/ohrms/dockets/ac/cder01.htm, Pulmonary-Allergy Drugs Advisory Committee]. PSE is an OTC monograph oral nasal decongestant, and is considered to be safe and effective in adults and children 12 years and older at 60 mg every four to six hours, not to exceed

240 mg per day. The total daily dose of PSE in the proposed product is the same as the OTC monograph dose.

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 5.53 billion total tablets, 5.28 billion mls, and 94,200 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 [redacted] 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 ——— 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 ——— upper respiratory allergies.
- Temporary relief of nasal congestion ——— 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
9/10/2007 11:24:14 AM
MEDICAL OFFICER

Sally Seymour
9/10/2007 11:49:07 AM
MEDICAL OFFICER
I concur.

NDA 74-Day Fileability Meeting Checklist

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

Product Name: **Zyrtec® (cetirizine hydrochloride)**
NDAs: **NDA 22-155 (Zyrtec® 1mg/ml syrup)**
sNDA 19-835 (Zyrtec® 5 & 10 mg tablets)
sNDA 21-621 (Zyrtec® 5 & 10 mg chewable tablets)
Sponsor: **Pfizer Consumer Healthcare**
Reviewer: **Lolita A. Lopez, M.D.**
Team Leader: **Daiva Shetty, M.D.**
Filing Meeting: **March 7, 2007**

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

13. Has the applicant presented the safety assessment based on all current world-wide knowledge regarding this product?	Ŏ	
14. Has the applicant submitted adequate and well-controlled actual usage trial(s) within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	**N/A**	
15. Has the applicant submitted adequate and well-controlled labeling comprehension trial(s) within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	**N/A**	
16. Has the applicant submitted draft labeling consistent with 201.5 and 201.56, current divisional policies, and the design of the development package?	Ŏ	
17. Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	Ŏ	
18. Has PREA been addressed?	Ŏ	
19. From a clinical perspective, is this NDA file-able? In no, please explain below.	Ŏ	

Reviewer Comments:

There are no clinical efficacy and safety studies submitted with these submissions. The sponsor relies on the clinical data submitted to approve prescription Zyrtec® formulations. Safety data was supported with postmarketing information.

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/s/

Lolita Lopez
3/19/2007 08:54:07 AM
MEDICAL OFFICER

Daiva Shetty
3/19/2007 10:17:47 AM
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