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RESEARCH**

APPLICATION NUMBER:

21-150/S007

SUMMARY REVIEW

Addendum to Summary Basis for Regulatory Action

Date	November 8, 2007
From	Andrea Leonard-Segal, M.D. Director, Division of Nonprescription Clinical Evaluation
Subject	Division Director Summary Review
NDA/BLA #	NDA 21-150/SE6-007
Supp #	
Proprietary / Established (USAN) Names	Zyrtec-D (cetirizine HCl/pseudoephedrine HCl) McNeil Consumer Healthcare
Dosage Forms / Strength	Tablet Cetirizine HCl 5 mg/Pseudoephedrine HCl 120 mg
Proposed Indication(s)	<ul style="list-style-type: none"> • Temporarily relieves these symptoms due to hay fever or other upper respiratory allergies (runny nose; sneezing; itchy, watery eyes; itching of the nose or throat; nasal congestion) • Reduces swelling of nasal passages • Temporarily relieves sinus congestion and pressure • Temporarily restores freer breathing through the nose
Action:	Approval

This is an addendum to my memorandum dated November 7, 2007 on the above application. It will address three points.

As a point of clarification, this application did not trigger the Pediatric Research Equity Act (PREA). Although the sponsor requested a waiver for studies in children under the age of 12 years, the waiver request is not "relevant" because the application did not trigger PREA. Thus, the Agency does not respond to the waiver request.

Today, Dr. Sally Seymour completed her Division Director Memorandum of this application. I note that she expressed her view that _____ should not be an indication for this product. It is not an indication. All indications for this product are listed above. Note, the discussion of safety and efficacy in pediatric populations in her memorandum is not applicable to the Zyrtec-D switch application.

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/s/

Andrea Segal
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MEDICAL OFFICER

Summary Basis for Regulatory Action

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1. Introduction to Review

McNeil Consumer Healthcare submitted this 505(b)(1) application to switch Pfizer's Zyrtec-D (cetirizine HCl 5 mg/120 mg pseudoephedrine HCl) from prescription to nonprescription marketing. Since August 10, 2001, Zyrtec-D has been an approved combination prescription product for adults and children 12 years of age and older "for the relief of nasal and non-nasal symptoms associated with seasonal or perennial allergic rhinitis." The prescription label recommends one tablet twice daily (not to exceed two tablets in 24 hours) and the same daily dosing schedule is proposed for the OTC product. The indications for the OTC product are:

- Temporarily relieves symptoms due to hay fever or other respiratory allergies (runny nose; sneezing; itchy, watery eyes; itching of the nose or throat; nasal congestion)
- Reduces swelling of nasal passages
- Temporarily relieves sinus congestion and pressure
- Temporarily restores freer breathing through the nose

Cetirizine is an orally-active selective H₁-receptor antagonist and the principal human metabolite of hydroxyzine. Pseudoephedrine HCl (PSE) is an adrenergic nasal decongestant and is an OTC Monograph ingredient recognized as generally safe and effective in doses up to 240 mg daily for this indication (21 CFR 341.20).

Currently, cetirizine is also approved as a single ingredient prescription product in the following formulations:

- 5 mg and 10 mg strength tablets
- 5 mg and 10 mg chewable tablets

- 1 mg/1 mL syrup

The prescription indications for the single ingredient cetirizine products are:

- Relief of symptoms associated with seasonal allergic rhinitis in adults and children 2 years of age and older
- Relief of symptoms associated with perennial allergic rhinitis in adults and children 6 months of age and older.
- Treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 months of age and older.

The single-ingredient cetirizine formulations are also the subject of separate prescription to nonprescription switch applications. There is postmarketing data available on single-ingredient cetirizine since January 1, 1986.

At a meeting in May, 2001, the Joint Advisory Committees on Nonprescription Drug Products and Pulmonary-Allergy Drug Products concluded that cetirizine demonstrates a risk/benefit profile suitable for an OTC antihistamine. Cetirizine is currently available without a prescription in 46 countries.

No new preclinical, clinical pharmacology, clinical efficacy or clinical safety studies were submitted with this switch application because of the extensive data, including post-marketing safety data, already available on prescription Zyrtec-D that support the switch application.

2. CMC/Microbiology/Device

The chemistry reviewers recommend that, from the CMC standpoint, this supplement should be approved. There are no unresolved chemistry issues for this NDA.

3. Nonclinical Pharmacology/Toxicology

There was no new pharmacology/toxicology data provided or required for this OTC switch NDA supplement. The sponsor referenced the nonclinical pharmacology/toxicology data for the prescription NDA.

4. Clinical Pharmacology/Biopharmaceutics

There is no new clinical pharmacology data provided or required for this switch NDA. The applications referenced the data for the prescription NDA.

Refer to the clinical review by Dr. Susan Limb and to the pharmacokinetics (PK) data submitted with NDA 21-150, approved August 10, 2001. The pharmacokinetic studies did not demonstrate a food effect and therefore the prescription labeling for Zyrtec-D states that the time of administration may be varied to suit the patient's needs.

The approved product label for the prescription product states that following a single, 10-mg oral dose, the elimination half-life of cetirizine was prolonged by 50% and the apparent total body clearance was 40% lower in 16 geriatric subjects with a mean age of 77 years compared to 14 adult subjects with a mean age of 53 years. (The original geriatric pharmacokinetic (PK) study referenced in the prescription label included comparative data on two groups, those < 65

years old and those ≥ 65 years old.) The labeling states that the increased bioavailability of cetirizine may be related to a diminished renal function. Data demonstrated a 3-fold increase in half-life and a 70% decrease in clearance in patients with moderate renal function impairment (creatinine clearance 11 – 31 mL/min) compared to normal volunteers. The prescription label recommends a dose adjustment of 5 mg once daily for patients ≥ 77 years old. Patients with hepatic impairment also experienced a significant increase in half life and decrease in clearance when given 10 mg or 20 mg of cetirizine.

In the interest of safety, these data on drug clearance should translate into a warning on the OTC labeling for the full age range of those at possible risk for decreased clearance due to age-related renal insufficiency. Therefore the OTC label for Zyrtec-D should direct adults ≥ 65 years old to ask a doctor before use. These data should also translate into an OTC label warning about use in those with liver disease.

Pharmacokinetic interaction studies were conducted with pseudoephedrine, antipyrine, ketoconazole, erythromycin, and azithromycin and no interactions were observed. In a multiple dose study of theophylline and cetirizine, a 16% decrease in the clearance of cetirizine was observed but the disposition of theophylline was not altered. There is no contraindication for use with theophylline because the interaction is not clinically significant.

In four clinical studies in healthy adult males, no clinically significant mean increases in QTc were observed in cetirizine treated subjects. Nor were there significant drug interactions with ketoconazole or with azithromycin.

5. Clinical Microbiology (where relevant)

Not relevant to this application. There was no data submitted.

6. Clinical/Statistical

Efficacy

Refer to the clinical reviews by Dr. Susan Limb and Dr. Steven Osborne. No new efficacy data was provided to support the prescription to nonprescription switch of Zyrtec-D. The sponsor referenced data previously submitted for the approved prescription product.

Safety

Refer to the clinical reviews by Dr. Susan Limb and Dr. Steven Osborne. The safety of Zyrtec-D for OTC use is supported by the referenced studies from the original NDA and by extensive post-marketing worldwide data. An integrated review of safety was performed at the time of the Zyrtec-D approval in August, 2001 and was updated in 2004 when single ingredient cetirizine chewable tablets were approved for prescription use. The original assessment of safety was derived from clinical trials with the single ingredient cetirizine HCl, the OTC monograph for PSE, and three additional clinical trials with the cetirizine HCl-PSE combination product. For this OTC switch application, these safety data were considered, plus updated safety information from the following sources:

- Toxic Exposure Surveillance System (TESS) for cetirizine/pseudoephedrine products to May, 2006
- Update of the FDA Adverse Event Reporting System (AERS) to March, 2007

- World Health Organization's Drug Monitoring Program (WHO) (years 1978-2006)
- Drug Abuse Warning Network (DAWN) (years 2003-6)
- Literature update for cetirizine/pseudoephedrine through April, 2006
- Pfizer's Database of Adverse Events to May 10, 2006

There were no new safety signals identified upon review of these data, nor a suggestion of an increased incidence of serious adverse events. In the efficacy studies, there were no deaths in the Zyrtec-D arms, nor was a trend in serious adverse events identified. Commonly reported adverse events were insomnia, dry mouth, fatigue, somnolence, and headache.

Refer to section 7.1.1 of Dr. Osborne's review for an in depth discussion of the reported deaths in Pfizer's efficacy studies, postmarketing database and in AERS. A look at the 28 deaths, revealed that one patient was not taking Zyrtec-D and was shot and killed in his car (the one efficacy study case). For the other cases drug attribution could not be determined because of:

- Lack of temporal relationship
- An underlying medical condition responsible for death
- "Poly-pharmacy" confounding the reports
- Inadequate information in the report to draw a conclusion

It is important to note that the TESS data suggest that Zyrtec-D is not likely to lead to death in a typical overdose situation since there were no fatalities due to an overdose, whether intentional or unintentional. The DAWN data suggest that Zyrtec-D is not a drug of abuse. There is no history of a withdrawal syndrome for cetirizine, pseudoephedrine, or the combination.

To date, there have not been reports of Torsade de Pointes with cetirizine as the single suspect drug or with the cetirizine-PSE combination. This absence of reports is consistent with the QT data reviewed for the prescription approval for cetirizine HCl and briefly described in section 4 of this Division Director review. One patient in the WHO database had Torsade de Pointes; the reporting on this case is scanty but suggests that this 32-year-old man had asthma and a seizure disorder as co-morbid conditions since he was taking montelukast and levetiracetam. It is difficult to draw a relationship to Zyrtec-D based upon the data provided.

In section 7.1.2 of his review, Dr. Osborne provides an in depth discussion of the reported serious adverse events from clinical trials, none of which appear to have been related to Zyrtec-D. In his review of the post-marketing adverse event reports from all sources, Dr. Osborne did not describe new or unexpected adverse events and found that the adverse event profile reflected the known properties of the component drugs. He notes that the adverse event reports appear to be distributed over a broad range of conditions and that somnolence and fatigue are a recurring theme. It is appropriate that a drowsiness warning should appear on the OTC labeling.

The literature review did not raise new safety concerns, per se. However, Dr. Osborne does raise the issue that some of the literature shows that patients with asthma had symptoms of bronchospasm during the use of this combination product. While the events were not

significantly higher compared to a control or comparator drug in a study of asthma patients, asthma patients were at higher risk than those without asthma. Dr. Osborne comments that these data bear further watching and may generate the need for a warning in the labeling.

Considering the totality of the data, I agree with Drs. Osborne and Limb that the safety profile of Zyrtec-D suggests that this drug is safe enough to be a nonprescription medication for the indications sought.

7. Advisory Committee Meeting

At a meeting in May, 2001, the Joint Advisory Committees on Nonprescription Drug Products and Pulmonary-Allergy Drug Products concluded that cetirizine demonstrates a risk/benefit profile suitable for an OTC antihistamine. No additional advisory committee meeting was convened for this NDA. This prescription to OTC switch:

- is not a first in class switch,
- is for a well-recognized OTC indication,
- does not raise new safety issues
- does not require labeling language
- did not raise new consumer use issues

8. Other Regulatory Issues

The Division of Nonprescription Clinical Evaluation consulted the Pediatric and Maternal Health Staff for their recommendations on whether to grant a partial waiver under PREA to the sponsor. Refer to the consult by Drs. Felicia Collins and Lisa Mathis October 5, 2007 and the addendum to memorandum written by Dr. Mathis on November 6, 2007.

At the time Zyrtec-D was approved as a prescription product, a partial waiver for pediatric studies in those <12 years of age was granted because the dose of PSE in Zyrtec-D exceeded the recommended dosing for children < 12 years and because there were existing products for cetirizine and for PSE for children down to the age of 2 years. The sponsor requested a partial waiver for pediatric studies for children under the age of 12 years for the OTC switch application.

The sponsor should receive a partial waiver for pediatric studies for children under the age of 12 years for the OTC switch application.

To be clear, this is a full switch of prescription Zyrtec-D to nonprescription. There are no clinically meaningful changes in the indication or population. The OTC product indication is consistent with the accepted language for all OTC antihistamine products and it captures the scope of the prescription indication; the prescription and nonprescription indications are the same.

9. Labeling

The labeling needs to address the concerns regarding drug accumulation in the elderly population by recommending that those 65 years of age and older ask a doctor before use. The labeling will need to include a warning to ask a doctor if the consumer has kidney or liver disease. This product should have the drowsiness warning that is on the OTC labeling for other antihistamines that cause somnolence. There are no outstanding labeling issues to be resolved.

10. DSI Audits

There were no DSI audits needed for this NDA.

11. Conclusions and Recommendations

Zyrtec-D is a safe and effective drug for OTC availability in children 12 years and older and adults. The application should be approved. The sponsor should receive a partial waiver of pediatric studies for children under the age of 12 years.

Safety concerns to be followed postmarketing:

Adverse event reporting should be monitored to determine the appropriateness of adding an asthma warning to the labeling for Zyrtec-D.

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/s/

Andrea Segal
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