CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-155

SUMMARY REVIEW

Summary Basis for Regulatory Action

Date	November 12, 2007
From	Andrea Leonard-Segal, M.D. Director, Division of Nonprescription Clinical Evaluation
Subject	Division Director Summary Review
NDA/BLA # **Supp #**	NDA 19-835/S-022 (Zyrtec tablets) NDA 21-621/S005 (Zyrtec Chewable Tablets) NDA 22-155 (Zyrtec Syrup)
Proprietary / Established (USAN) Names	Zyrtec (cetirizine HCl) McNeil Consumer Healthcare
Dosage Forms / Strength	Tablet Cetirizine HCl 10 mg and Tablet Cetirizine HCl 5 mg Chewable Tablets 10 mg and Chewable Tablets 5 mg Syrup 1 mg/ml
Proposed Indication(s)	• Temporarily relieves these symptoms due to hay fever and other upper respiratory allergies (runny nose; sneezing; itchy, watery eyes; itching of nose or throat) • Relief of itching due to hives (urticaria)
Action:	Approval

1. Introduction to Review

McNeil Consumer Healthcare submitted these three NDAs to switch Pfizer's Zyrtec (cetirizine HCl) from prescription to nonprescription marketing. In 1995, cetirizine was first approved as a prescription drug to treat seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adults and children ≥ 12 years old. In 1996 it was approved to treat SAR and PAR in children ages 6-11 years and, in 1998, in children 2-5 years of age. Cetirizine is currently approved and marketed by prescription for the following indications: SAR in adults and children ≥ 2 years old, PAR in adults and children ≥ 6 months old, and chronic idiopathic urticaria (CIU) in adults and children ≥ 6 months old. The proposed switch formulations include tablets (5 mg and 10 mg), chewable tablets (5 mg and 10 mg), and syrup (1 mg/ml). The syrup formulation is proposed as a partial switch since it would remain available for prescription use under NDA 20-346 (approved in 1996) for children ages 6 months to < 2 years of age to treat allergic rhinitis and 6 months to < 6 years of age to treat hives.

The indications for OTC Zyrtec are:

- Temporarily relieves these symptoms due to hay fever and other upper respiratory allergies (runny nose; sneezing; itchy, watery eyes; itching of nose or throat)
  The allergic rhinitis indication is for adults and children ≥ 2 years old.

- Relieves itching due to hives (urticaria). This product will not prevent hives or an allergic skin reaction from occurring.
  The itching due to hives indication is for adults and children ≥ 6 years of age.

Cetirizine is an orally-active selective H_1-receptor antagonist and the principal human metabolite of hydroxyzine. 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, that support the switch application.

2. CMC/Microbiology/Device

The chemistry reviewers recommend that, from the CMC standpoint, these three NDAs should be approved. There are no unresolved chemistry issues. See the review by Dr. Yubing Tang for the syrup formulation and the review by Dr. Stuart Zimmerman for the tablet and chewable tablet formulations.

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 NDAs. Cetirizine is a pregnancy Category B drug.

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.

Pharmacokinetic studies did not demonstrate a food effect and therefore the prescription labeling for Zyrtec states that the time of administration may be varied to suit the patient's needs.

The approved product labeling for prescription cetirizine 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 and for patients with renal impairment. 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.

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 should direct adults ≥ 65 years old to ask a

doctor before use. These data on drug clearance should also translate into a warning about use in those with liver disease and kidney 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. This decrease in clearance was 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
Not relevant to this application.

6. Clinical/Statistical
Efficacy
Refer to the clinical reviews by Dr. Susan Limb and Lolita Lopez. No new efficacy data was provided to support the prescription to nonprescription switch of Zyrtec; the sponsor referenced data previously submitted for the approved prescription product. Consistent with Agency policy, the efficacy of prescription Zyrtec in children to treat SAR, PAR and CIU, was extrapolated, based upon PK studies. Refer to the November 8, 2007 Division Director Memorandum by Dr. Sally Seymour that describes the thinking behind the longstanding Agency approach to establishing the efficacy of drugs in children to treat SAR, PAR, and CIU and the consistency of that approach with the 1994 Final Pediatric Labeling Rule.

Safety
Refer to the clinical reviews by Dr. Susan Limb and Dr. Lolita Lopez for a detailed analysis of the safety data. The safety of Zyrtec for OTC use is supported by the referenced studies from the original NDA and by extensive worldwide post-marketing data for adults and children. An integrated review of safety was performed at the time of the Zyrtec approval and was most recently updated in 2004 when single ingredient cetirizine chewable tablets were approved for prescription use. For this OTC switch application, safety data included:

- Summaries of serious adverse events from clinical trials previously submitted and evaluated to support the prescription approval of the single-ingredient applications
- Toxic Exposure Surveillance System (TESS) (1995 - 2005)
- Update of the FDA Adverse Event Reporting System (AERS) (1969 - 2006)
- A report summarizing adverse event reporting to the World Health Organization's Drug Monitoring Program (WHO)
- Drug Abuse Warning Network (DAWN) (1995 - 2006)
- Literature update for cetirizine (1966 - 2006)
- Pfizer's Database of Adverse Events (1986 - 2007)

There has been an extensive time and extent of use of cetirizine. There were no new safety signals identified upon review of the data, nor a suggestion of an increased incidence of

serious adverse events. Commonly reported adverse events were somnolence, fatigue, dry mouth and dizziness. The most common treatment related adverse events in children were abdominal pain and somnolence. The TESS, AERS, WHO and DAWN databases did not reveal any new safety signals, or specific trends. There is no evidence that cetirizine is a drug of abuse or misuse. There is no history of a withdrawal syndrome for cetirizine. The TESS data does not suggest that cetirizine is a significant toxicologic risk.

There was no conclusive evidence of a causal relationship between the use of cetirizine and deaths reported in the postmarketing data because the reports did not establish a clear temporal relationship, limited information was provided about the patient, and there were underlying confounding medical conditions and medications. There were no new safety concerns identified in the adverse event reports or in the literature review. Dr. Lopez carefully reviewed the safety data for concerns related to seizures or cardiac safety that could preclude the switch of these cetirizine applications and found none. She also compared the adverse event reporting patterns and the nature of the reported adverse events in the United States (prescription only) and Canada (general sales) markets and found the data similar.

I agree with Drs. Lopez, Limb, and Seymour that the safety profile of Zyrtec suggests that this drug is safe enough to be a nonprescription medication for the indications sought. There is nothing in the safety review that would cause me to part from the conclusion of the 2001 Joint Advisory Committee on Nonprescription Drug Products and Pulmonary-Allergy Drug Products that cetirizine demonstrates a risk/benefit profile suitable for an OTC antihistamine.

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 new labeling language
- did not raise new consumer use issues

8. Other Regulatory Issues

On October 18-19, 2007, a joint meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee met to discuss the safety and efficacy of nonprescription cough and cold products marketed for pediatric use. At that meeting the joint committees voted that it was not appropriate to extrapolate efficacy data from adults to children < 2 years of age or 2 to <12 years of age to treat common cold symptoms, including cough. The committee unanimously voted that clinical studies in children < 12 years old, with clinical endpoints, would be necessary to support efficacy in children < 12 years old. Although there were some presentations at the meeting that discussed the extrapolation of efficacy for allergic rhinitis, the committee's recommendations did not address issues related to allergic rhinitis.

Since the advisory committee meeting, there have been many internal agency discussions about the recommendations that emerged. At the present time, just 2 -3 weeks following the advisory committee meeting, it is not clear what the agency position will be on pediatric efficacy standards for cough/cold products. It is also not clear what impact the advisory committee recommendations might have on approvals for the allergic rhinitis and hives indications in the pediatric population or, for that matter, on other pediatric drug indications. Until there is an Agency position, for these Zyrtec NDA switch applications, it is appropriate to be consistent with the approach taken for the approval of other nonprescription switch NDAs for allergic rhinitis and for the relief of itching due to hives. Thus, I recommend that the efficacy standard that led to the approval of pediatric labeling for prescription antihistamine products is also appropriate for pediatric labeling for the OTC products subject to the switch.

These NDAs for the syrup, chewable tablet and the tablet formulations do not trigger the Pediatric Research Equity Act (PREA).

9. Labeling

The labeling needs to address the concerns of drug accumulation in the elderly population by recommending that those 65 years of age and older ask a doctor. The labeling will need to include a warning to ask a doctor if the consumer has kidney or liver disease. This product needs to have the drowsiness warning that is on the OTC labeling for other antihistamines that cause somnolence. At the time of this Division Director review, there are outstanding labeling issues and the final labeling review from Cazemiro Martin is pending. For approval, the sponsor will need to comply with all labeling requests in a timeframe that allows for review prior to the PDUFA date. Since cetirizine is excreted in breast milk, as in the Zyrtec-D label, the labels for these Zyrtec products should state that use of this product by women who are breast-feeding is not recommended.

The syrup formulation for allergic rhinitis will be marketed with a dosing cup that is appropriately marked to enable measurement of the correct medication doses for treating allergic rhinitis in adults and children; likewise, the syrup formulation for the hives indication will be marketed with a dosing cup that is appropriately marked.

10. DSI Audits

There were no DSI audits needed for this NDA.

11. Conclusions and Recommendations

Zyrtec is a safe and effective drug for the target pediatric and adult populations to use for the sought indications.

The three NDA switch applications should be approved.

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/s/

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