CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-150

MEDICAL REVIEW(S)

MEDICAL REVIEW # 1

January 2001

MEDICAL OFFICER REVIEW

Division of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION #:NDA	21, 150	APPLICATION TYPE:	Original NDA
SPONSOR:	Pfizer	PRODUCT/PROPRIETARY NAME:	Zyrtec-D
		USAN Established Name:	Ceterizine/ Pseudoephedrine
CATEGORY OF DRUG:	Antihistamine/ Decongestant	ROUTE OF ADMINISTRATION:	Extended release tablet
MEDICAL REVIEWER:	Nicklas	REVIEW DATE:	2 January 2001

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
18 January 2000	19 January 2000	Original NDA	see overview below

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:

Overview of Application/Review: Two pivotal PK studies were submitted by the sponsor, along with 2 other studies that utilized the bilayer tablet formulation. In addition, the results of 20 studies using other formulations of the combination of cetirizine and pseudoephedrine were submitted as part of the safety database for this combination product. No severe or serious adverse events were reported. The type of adverse events reported were those generally associated with administration of either cetirizine or pseudoephedrine. No clinically significant changes in vital signs, ECGs or laboratory values were noted associated with the bilayer formulation of cetirizine and pseudoephedrine. Based on the PK data provided by the sponsor, bioequivalence between the bilayer tablet and concomitant administration of cetiriizine and pseudoephedrine was demonstrated (see Biopharm Review). Some labeling changes are recommended (see discussion below)

Outstanding Issues: labeling changes need to be made as indicated below.

Recommended Regulatory Action: This NDA is approvable.

N drive location:

New Clinical Studies: _____ Clinical Hold _____ Study May Proceed

NDAs:

Efficacy / Label Supp...: ___x___ Approvable _____ Not Approvable

Signed: Medical Reviewer: /S/ Date: 1/3/2001

Medical Team Leader: /S/ Date: 1/3/01

NDA 21, 150
Zyrtec-D
Cetirizine/pseudoephedrine extended release tablet

I. Background: Zyrtec tablets and syrup are approved for seasonal allergic rhinitis, perennial allergic rhinitis and chronic urticaria in patients 2 years of age and older at a dosage of 5-10 mg per day (as a 5 or 10 mg tablet once a day) in patients 12 years of age and older; 5-10 mg per day (as 1-2 teaspoonfuls once a day) in patients 6-11 years of age; and 2.5-5 mg per day (1/2-1 teaspoonful once a day or ½ teaspoonful bid in patients 2-5 years of age). The recommended dose for patients with hepatic or renal impairment is 5 mg per day. With hepatic impairment, there is a 50% decrease in half life and a 40% decrease in clearance after 10-20 mg of Zyrtec.

No effect of Zyrtec on the QTc interval was seen at a dose of 60 mg for one week, or at a dose of 20 mg in conjunction with erythromycin. When Zyrtec was given at a dose of 20 mg in conjunction with ketoconazole, there was a mean QTc increase of 17.4 msec compared to an increase of 9.1 msec when Zyrtec was given alone. The effect of doses higher than 10 mg has not been evaluated in children less than 12 years of age and there has been no evaluation of effect on QTc interval in children less than 6 years of age.

Zyrtec-D bilayer tablet contains 5 mg of ceterizine, an H-1 receptor antagonist and 120 mg of pseudoephedrine (PSE) a sympathomimetic. The ceterizine is in an immediate release form and the PSE is in a sustained release form. This

bilayer tablet is proposed for bid administration, giving a total daily dose of 10 mg of Zyrtec and 240 mg of PSE.

The bilayer tablet consists of two distinct layers. The PSE layer is composed of a matrix of PSE in the release-controlling polymer hydroxpropylmethylcellulose (HPMC). PSE is released by diffusion from and erosion of the HPMC matrix. The immediate release layer contains cetirizine and lactose, croscarmellose sodium, microcrystalline cellulose, colloidal silicon dioxide and magnesium stearate excipients.

Immediate release PSE is usually given in a dose

II. Clinical: There were two pivotal PK studies done. Study 006 was a single dose bioavailability study under fasting and fed conditions and study 007 was a single and multiple dose PK study comparing Zyrtec-D with the concomitant administration of each of the components of this product. Two other PK studies (9817 and 9831) were done with the same formulation but are considered supportive because they did not contain a reference product that was approved for use in the U.S. The results of 20 other studies are submitted that used formulations other than the bilayer formulation. In summary, safety data submitted in this NDA include: 1) 4 studies conducted with the bilayer tablet formulation; 2)

studies conducted with other combination formulations (e.g.

and 3) studies in which cetirizine and PSE were administered concomitantly. This included 2161 patients, 9 years of age and older, from 24 studies, who were either normal healthy volunteers or had allergic rhinitis. In many cases, the clinical information in this NDA is derived from the package inserts for Zyrtec, PSE and PSE with other antihistamines.

☛ Study 007 entitled, "A comparative single and multiple dose bioavailability study of cetirizine (5 mg)/pseudoephedrine (120 mg) bilayer tablet bid versus co-administration of ceterizine (5 mg) and pseudoephedrine (120 mg) bid"

☛ study objective: "to assess the comparative bioavailability of cetirizine and pseudoephderine in a bilayere tablet dosage form with the concomitant administration of a reference standard, a commercial dosage form of cetirizine and pseudoephedrine, after a single dose and at steady-state after multiple dose administration to healthy subjects"

☛ study characteristics:

1. number of patients: 24 entered; 24 completed
2. age range: 20-41 years of age
3. patient population: healthy volunteers
4. study design: open, randomized, single and multiple dose, two-way crossover pharmacokinetic study

5. drug administration: 5 mg ceterizine/120 mg pseudoephedrine bilayer tablet (ceterizine immediate release) (pseudoephedrine sustained release formulation) with a polymer matrix vs 5 mg ceterizine (Zyrtec) and 120 mg pseudoephrine (Sudafed LA) given concomitantly for 7 days
6. periods of study: 7 days of treatment with each of the two treatment arms separated by a washout period of at least 7 days
7. parameters evaluated: blood drawn for Cmax, Tmax, AUC and half-life for up to 48 hours after the first dose and up to 12 hours after the last dose; safety parameters included blood pressure, pulse rate, and 12 lead ECGs done PRN and AEs

☛ Study results:

1. For cetirizine, the geometric mean ratios and 90% confidence intervals for AUC and Cmax following single dose administration of the bilayer tablet vs single dose concomitant administration of Zyrtec and Sudafed were 96% (—— o) and 102% (——— , respectively.
2. For pseudoephedrine, the geometric mean ratios and 90% confidence intervals for AUC and Cmax following single dose administration of the bilayer tablet vs single dose concomitant administration of Zyrtec and Sudafed were 104% ——) and 106% —— , respectively.

3. For ceterizine, the geometric mean ratios and 90% confidence intervals for AUC, Cmax and Cmin following multiple dose administration of the bilayer tablet vs concomitant administration of Zyrtec and Sudafed were 97% ( ), 92% ( ) and 102% ( ), respectively.
4. For pseudoephedrine, the geometric mean ratios and 90% confidence intervals for AUC, Cmax and Cmin following multiple dose administration of the bilayer tablet vs concomitant administration of Zyrtec and Sudafed were 105% ( ), 109% ( ) and 101% ( ) respectively.
5. Individual results for cetirizine following single dose administration showed that the Cmax ranged from ng/ml after administration of the bilayer tablet compared to ng/ml after concomitant administration of Zyrtec and Sudafed. AUC ranged from hr.ng/ml after administration of the bilayer tablet and hr.ng/ml after concomitant administration of Zyrtec and Sudafed. The half-life varied between hrs for the bilayer formulation and hrs after concomitant administration of Zyrtec and Sudafed. Tmax was hours after administration of the bilayer tablet and hours after the concomitant administration of Zyrtec and Sudafed.
6. Individual results for PSE following single dose administration showed that the Cmax ranged from

— ng/ml after administration of the bilayer tablet compared to —— ng/ml after concomitant administration of Zyrtec and Sudafed. AUC ranged from —— hr.ng/ml after administration of the bilayer tablet and —— hr.ng/ml after concomitant administration of Zyrtec and Sudafed. The half-life varied between —— hrs for the bilayer formulation and —— hrs after concomitant administration of Zyrtec and Sudafed. Tmax was ~ hours after both treatments.

7. Individual results for cetirizine following multiple dose administration showed that the Cmax ranged from —— ng/ml after administration of the bilayer tablet compared to —— ng/ml after concomitant administration of Zyrtec and Sudafed. AUC ranged from —— hr.ng/ml after administration of the bilayer tablet and —— hr.ng/ml after concomitant administration of Zyrtec and Sudafed. The Cmin varied between —— ng/ml after administration of the bilayer tablet and —— ng/ml after concomitant administration of Zyrtec and Sudafed. Tmax was —— hours with both treatments.

8. Individual results for PSE following multiple dose administration showed that the Cmax ranged from —— ng/ml after administration of the bilayer tablet compared to —— after concomitant administration of Zyrted and Sudafed. AUC ranged from —— hr.ng/ml after administration of the bilayer tablet and —— hr.ng/ml after concomitant administration of

Zyrtec and Sudafed. The Cmin varied between — ng/ml after administration of the bilayer tablet and — ng/ml after concomitant administration of Zyrtec and Sudafed. Tmax was — hours after the bilayer tablet and — hours after concomitant administration of the components. There was more bioavailabiility of PSE when given as the bilayer tablet than when the same dose was given alone.

9. Adverse events were reported by 7 (29%) of patients after administration of the bilayer tablet (15 AEs) and by 9 (38%) of patients after concomitant administration of the two drugs (27 AEs). The AEs reported by patients after receiving the bilayer tablet were blepharitis, headache (3), nightmares, insomnia, dyspepsia (2), nausea and vomiting (2), pharyngitis, asthenia, tachycardia, feeling hot, and blurred vision. Headache, asthenia, nausea, insomnia, and pharyngitis were reported more frequently after receiving cetirizine plus PSE than after receiving the bilayer combination formulation. There were no reports of severe, serious or unexpected AEs. There was no clinically significant difference between the incidence or type of AEs noted after administration of the bilayer tablet and the concomitant administration of Zyrtec and Sudafed.

☛ Study 006, entitled, "a comparative single dose bioavailability study of cetirizine (5 mgt)/pseudoephedrine (120 mg) bilayer tablet under fed and fasting conditions"

☛ **study objective: "to assess the effect of a high fat meal on the bioavailability of cetirizine and pseudoephedrine in a bilayer tablet dosage form afte a single dose administration to healthy subjects"**

☛ **study characteristics:**

1. **number of patients: 24 patients**
2. **age range: 18-45 years**
3. **patient population: healthy adults**
4. **study design: open, single dose, tow-way crossover study**
5. **drug administration: 5 mg cetirizine and 120 mg PSE in sustained release oral formulation**
6. **periods of study: 7 day washout between treatment periods**
7. **parameters evaluated: PK of cetirizine and pseudoephedrine up to 48 hours after drug administration; Cmax, Tmax, AUC and half-life determined**

☛ **study results:**

1. **No patient discontinued the study due to safety related reasons. Two patients reported 3 AEs when they received the study drug under fed condition. Moderate vomiting in a 42 year old white female was considered to be treatment-related. One episode of**

syncope (vasovagal reaction associated with drawing blood) occurred in a 25 year old African-American woman after fed administration was not considered treatment-related. The third AE was conjunctivitis due to contact lens irritation.

2. Food had no significant effect on cetirizine absorption (AUC) or half-life but Tmax was delayed by 1.8 hours and Cmax was decreased by 30% after a high fat meal. Food had no effect on any PK parameters of PSE

☛ non-US clinical studies:

1. Study 9817: open, crossover, single and multiple dose study in 16 normal volunteers who received 5 mg cetirizine and 120 mg PSE in the bilayer tablet and the ⟵ capsule. Patients after receiving the bilayer tablet had 67 AEs considered possibly or probably due to the drug, while patients had 62 AEs possibly or probably related to drug administration after receiving the ⟵ capsule. All AEs were mild except for 4 patients who received the bilayer formulation who developed moderate headache ~~(1)~~, dizziness (1), nausea (1), and vomiting (1). Fatigue, dry mouth and headache were the most common AEs. For the most part, there were no significant differences between the type, severity or frequency of AEs in the two treatment groups, although there was more fatigue (6 vs 3 and insomnia (4 vs 1) reported in the ⟵ group and more hyperkinesia (5 vs 3), rhinitis (5 vs 2) and nausea (4 vs 1)

reported in the bilayer group. There were 7 patients who reported rhinitis or pharyngitis after receiving the bilayer tablet compared with 2 patients after receiving the —— capsule. No AEs were considered serious. There was no significant change in vital signs, ECGs or laboratory tests after administration of either drug.

2. Study 9831: open, crossover, single dose study in 16 normal volunteers who received 5 mg cetirizine and 120 mg PSE in the bilayer tablet formulation and the —— capsule formulation. There were 9 AEs possibly or probably related to the bilayer tablet and 11 AEs possibly or probably related to the —— capsule. The most frequent AEs were fatigue and dry mouth and there were no serious AEs and there was no clinically significant difference between the number of specific AEs reported after administration of the —— and the bilayer formulation. There was no significant change in vital signs, ECGs or laboratory tests after administration of either formulation.

3. Study A220: No serious AEs were reported in this study and no patients discontinued treatment because of AEs.

☛ Overall safety data:

☛ The integrated summary of safety includes data from 2161 patients in 24 studies conducted in the US and Europe. Studies included in the ISS were studies 006, 007, 9817, 9831, A220, 143-003, 143-004, 90CK16-0476, 93CK16-0645, 96 CK16-0678, 96CK16-1679, 89CK16-

0465, A179, A180, A181, A182, 9608, 9609, 9511, 89CK16-0405, 89CK16-0458, A149, A150 and A158. Studies with the bilayer formulation including cetirizine and PSE were studies 006, 007, 9817, and 9831.

- There were no severe or serious adverse events in studies using the bilayer formulation involving 80 patients who received this formulation. Of this patient population, 45% were females and 55% were males. In the two pivotal studies, 54% were white and 46% were non-white. There were 3 serious AEs reported. One was a patient who developed hallucinations after receiving 120 mg of PSE; another was a pregnant patient who received 5 mg cetirizine and 120 mg PSE and developed a spontaneous abortion; and the third was a patient who was hospitalized with severe asthma who had received the —— capsule with 5 mg cetirizine and 120 mg of PSE.

- There were 84 patients who discontinued treatment for medical reasons but none of these were patients that received the bilayer formulation. The AEs that precipitated discontinuation with other formulations were either unlikely to be related to the study drugs or typical AEs seen after administration of cetirizine or PSE (e.g. dry mouth, insomnia).

- **In individual studies, adverse events occurring with an incidence of 4% or greater in patients who received the bilayer formulation were 1) fatigue; 2) dry mouth; 3) headache; 4) hyperkinesia; 5) rhinitis; 6) nausea; 7) somnolence; 8) apathy; 9) abdominal pain; 10) insomnia; 11) dizziness; and 12) dyspepsia.**

- **There were no clinically significant findings on laboratory testing, measurement of vital signs or ECGs. This included two patients who received a non-bilayer formulation of cetirizine and PSE who had a mild elevation in SGPT considered related to the study drug that resolved 13 days after discontinuing the study drug, as well as one patient who had a mild elevation in SGOT that resolved 41 days after discontinuing the study drug.**

III. Labeling:

A. Description section: acceptable as currently written.

B. Clinical Pharmacology: Mechanism of Action section: acceptable as written.

C. Clinical Pharmacology: Pharmacokinetics section: acceptable as written since the data is consistent with the data generated in the studies with drug product and with the labeling for cetirizine.

D. Interaction studies section: acceptable as written and consistent with the labeling for cetirizine.

E. Special Populations section: acceptable as written and where reference is made to cetirizine, it is compatible with the current labeling for this drug product.

F. Pharmacodynamics section: acceptable as written and consistent with the labeling for cetirizine.

G. Clinical Studies section: The second paragraph dealing with onset of action is not present in the labeling for cetirizine. Since this data was not reviewed in this NDA, this paragraph should be deleted from the labeling.

H. Indications and usage section: acceptable as written

I. Contraindications section: acceptable as written.

J. Warnings section: acceptable as written.

K. Precautions section: acceptable as written

L. Carcinogenesis, mutagenesis, and impairment of fertility as well as pregnancy category B and Nursing Mothers sections: for pharmacology review.

M. Geriatric use section: acceptable as written and consistent with the labeling for cetirizine, except that at the end of this statement the sponsor should reference the Geriatric Patients subsection of the CLINICAL PHARMACOLOGY section. This section is consistent with the CFR (21CFR Part 201, page 45325) and the ~~MOR of~~ 21 February 2000 for NDAs 19,835 and 20,346.

N. Pediatric use section: acceptable as written.

O. Adverse Reactions section: acceptable as written and consistent with the labeling for cetirizine.

P. Drug Abuse and Dependence section: acceptable.
Q. Overdosage section: acceptable as written and consistent with the labeling for cetirizine.
R. Dosage and Administration section: acceptable as written
S. How Supplied section: acceptable as written
T. Carton Covers: The sponsor proposes to label this

[redacted]e

IV. DSI Consult: The memo of 18 August 2000 from DSI to this Division, recommended that study 007 not be accepted for review, since they felt that the PK data from that study were questionable. This conclusion was based on the fact that the sponsor had selected samples for re-assay without establishing re-assay criteria a priori, thereby biasing the study results. Suspicion was heightened by the fact that there was no analytical or clinical reason to suggest that the original data were inaccurate. DSI recommended that the sponsor re-analyze the data from this study; 1) using only the original data; and 2) using only re-assay data for all patients (for resolution of this issue see V below).

V. Data Analysis Issues Related to Study 007: The sponsor stated in the NDA submission that, "Following the initial assay of the samples from this study (143-007) Pfizer personnel noted some apparent anomalies in the plasma

concentration versus time profiles. In an effort to corroborate these findings, ——— was instructed to reassay a subset of samples in duplicate. These reanalyses brought into question the reliability of the data generated by one of the two analysts assigned to this project. Upon being informed of this, Pfizer requested a complete reanalysis, in duplicate, of all samples." Therefore, the raw data sheets submitted by the sponsor had a column of original assay data and two columns of reanalyzed assay data. The data used in the final analysis appeared to be in some cases data from analysis of the original assay, in some cases an average of two reanalyzed assay values and in other cases the average of a value from the original assay data and one from the reanalyzed assay data.

The sponsor was asked to submit a final determination based on analysis of the original assay data. Review of this data by Biopharm showed that this drug product produced a pharmacokinetic effect bioequivalent to concomitant administration of 10 mg of cetirizine and 120 mg of pseudoephedrine, as claimed by the sponsor.

VI. Financial Disclosure: One investigator did not respond to requests from the sponsor to provide a financial disclosure. In regard to the other investigators, the sponsor reviewed their financial data and determined that there was no significant information to report.

VII. Pediatric Waiver: A Pediatric Waiver for patients under 12 years of age was requested by the sponsor and considered acceptable by the Division, based on the fact that the concentration of pseudoephedrine in this drug product is higher than the recommended dose for patients less than 12 years of age and the fact that approved products containing pseudoephedrine or cetirizine are adequately labeled and available for patients 2-11 years of age.

APPEARS THIS WAY
ON ORIGINAL

MEDICAL OFFICER REVIEW

Division of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION #:NDA	21,150	APPLICATION TYPE:	Amendment
SPONSOR:	Pfizer	PRODUCT/PROPRIETARY NAME:	Zyrtec-D
		USAN Established Name:	Cetirizine
CATEGORY OF DRUG:	Antihistamine	ROUTE OF ADMINISTRATION:	Oral tablet
MEDICAL REVIEWER:	Nicklas	REVIEW DATE:	21 May 2001

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
28 March 2001	29 March 2001	Safety update	see overview below

Overview of Application/Review: This submission contains a review of the sponsor's database and the medical literature for cetirizine and pseudoephedrine for the period from 25 May 1999 (the cut off time for the original NDA) to 28 February 2001. The sponsor reports two serious adverse events, neither of which was related to this drug product. Other than this, there is no new safety data submitted by the sponsor.

Outstanding Issues: none

Recommended Regulatory Action: The drug product remains approvable from a clinical standpoint.

N drive location:

NDAs:

Efficacy / Label Supp.: ___x___ Approvable _____ Not Approvable

Signed: **Medical Reviewer:** _____ **Date:** _____

Medical Team Leader: _____ **Date:** _____

APPEARS THIS WAY
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/s/

Richard Nicklas
5/25/01 03:51:59 PM
MEDICAL OFFICER

Badrul Chowdhury
5/30/01 04:24:01 PM
MEDICAL OFFICER
I concur

APPEARS THIS WAY
ON ORIGINAL