CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-150

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW # 2

July 2001

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	NDA 21-150
Drug Substance	Cetrizine HCl / pseudoephedrine HCl
Drug Product(s)	Zyrtec-D 12 Hour extended release tablets (Cetrizine HCl 5 mg / pseudoephedrine HCl 120 mg)
Sponsor	Pfizer Inc.
Type of submission	Response to the Agency's comments in the approvable letter
Date of submission	2/12/2001
Reviewer	Young Moon Choi, Ph.D.
Team Leader	Emmanuel Fadiran, Ph.D. OCPB/DPE-2

1. SYNOPSIS

On 1/18/2000, the sponsor submitted the original NDA 21-150 for approval of Zyrtec-D12. Zyrtec-D 12 Hour is a film-coated bilayer tablet, containing 5 mg of immediate-release cetirizine HCl, an antihistamine, and 120 mg of extended-release pseudoephedrine HCl, a sympathomimetic amine with decongestant action, per tablet. The proposed indication is seasonal and perennial allergic rhinitis with nasal congestion, in patients 12 years and older. The proposed dosing regimen is 1 tablet every 12 h. The recommended doses for Zyrtec-D do not exceed the recommended daily doses for currently approved cetirizine or pseudoephedrine products.

The combination of these two active ingredients has not previously been approved. Also, BID dosing of cetirizine HCl is currently only approved for Zyrtec Syrup (5 mg cetirizine HCl/5 ml), 2.5 mg BID for use in children, age 2-5 years.

Originally, the sponsor submitted two *in vivo* pharmacokinetic studies addressing the issues of a possible interaction of the bilayer tablet with food, and the comparative bioavailability between the proposed combination product and the co-administration of the individual active ingredients, respectively. No safety and efficacy studies were submitted.

The Agency has completed the review of the application [Refer to the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) review by Dr. Wakelkamp on 1/10/2001], and an approvable letter has been sent to the sponsor on 1/17/2001 with 32 comments that should be addressed by the sponsor.

The present submission dated 2/12/2001 includes the sponsor's responses to the Agency's comments in the approvable letter of 1/17/2001. Among those responses, the current OCPB review addresses the sponsor's response #27, that is, the proposed labeling change of 'Distribution' and 'Metabolism' of pseudoephedrine under the Pharmacokinetics section based on literature search (Refer to the following page 2).

The proposed labeling needs to be revised as in the "Labeling Comments".

The Agency's Comment #27

Investigate the distribution and metabolism characteristics of pseudoephedrine to the extent possible, from the public domain. Include any information found to be adequate in the "Distribution" and "Metabolism" subsections of the PHARMACOKINETICS section of the package insert. Alternatively, if the information in the public domain is found to be inadequate, insert a statement in these subsections reflective of such a fact.

Pfizer's Response to the Comment #27

In order to evaluate the pharmacokinetic distribution and metabolism of pseudoephedrine, a search of the medical literature was conducted. The databases consulted were Medline (1966-December, 2000) and [redacted] 1974-January, 2001). The search terms used were "ephedrine", "pseudoephedrine", "pharmacokinetics", "metabolism", "drug distribution", "protein binding", "drug tissue level", and "human". The literature citations resulting from this search were evaluated for their relevance to the topic. Based upon this examination of the scientific literature, Pfizer proposes the following additional wording for the Package Insert:

Distribution:

The apparent volume of distribution/(V/F) of pseudoephedrine has been reported to be approximately 2.6-3.3 L/kg [1, 2, 3] indicating extensive distribution into extravascular sites. Approximately 0.4-0 7% of the pseudoephedrine dose was excreted in the breast milk over 24 hours after a single dose [4]. The pattern of the relative milk/plasma drug concentration profile showed that pseudoephedrine concentrations in milk were 2 to 3 fold higher than those in plasma. Although no plasma protein binding data in humans are available, the milk/plasma drug concentration profile suggests low plasma protein binding.

Metabolism:

One to seven per cent of pseudoephedrine is metabolized to the active metabolite norpseudoephedrine by N-demethylation. [5]

References

1. Dickerson, J., Perrier, D., Mayersohn, M., Bressler, R.: Dose tolerance and pharmacokinetic studies of L(+) pseudoephedrine capsules in man. Europ. J. Clin. Pharmacol. 14, 253-259 (1978)
2. Kuntzman, R., Tsai, I., Brand, L, Mark, L.C: The influence of urinary pH on the plasma half-life of pseudoephedrine in man and dog and a sensitive assay for its determination in human plasma. Clin. Pharmacol. Ther. 12, 62-67 (1970)
3. Williams, B.O., Liao, S.H.T., Lai, A.A, Arnold, J.D., Perkins, J.G., Blum, M.R., Findlay, J.WA.: Bioavailability of pseudoephedrine and triprolidine from combination and single-ingredient products. Clin Pharmacy 3, 638-643 (1984)
4. Findlay, J.W.A., Butz., R.F., Sailstad, JM., Warren, J.T., Welch, R.M.: Pseudoephedrine and triprolidine in plasma and breast milk of nursing mothers. Br. J. Clin. Pharmac. 18, 901-906 (1984)
5. Delbeke, F.T., Debackere, M.: The influence of diuretics on the excretion and metabolism of doping agents: part VI. pseudoephedrine. Biopharm. Drug Disposit. 12, 37-48 (1991)

[redacted]

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2. REVIEWER'S COMMENTS

2-1. Distribution

The value of apparent volume of distribution is dependent on bioavailability after oral administration. Therefore, this reviewer recommends that the statement, "- indicating extensive distribution into extravascular sites", be removed.

Furthermore, this reviewer is of the opinion that the proposed statement about excretion of pseudoephedrine in breast milk should appear under the section of Elimination after revision as follows:

> "It was reported that 0.4-0 7% of the pseudoephedrine dose was estimated to be excreted in the breast milk over 24 hours after a single dose. The pattern of the relative milk/plasma drug concentration profile showed that pseudoephedrine concentrations in milk were 2 to 3 fold higher than those in plasma."

The statement, "Although no plasma protein binding data in humans are available, the milk/plasma drug concentration profile suggests low plasma protein binding", should be removed since the low protein binding of pseudoephedrine is not based on a solid evidence.

2-2. Metabolism

Metabolism section needs minor change:

> "One to seven per cent of pseudoephedrine dose appeared to be metabolized to norpseudoephedrine by N-demethylation after single dose. [5]"

3. LABELING COMMENTS

The labeling should be read as follows:

> **Distribution:**
> The apparent volume of distribution/(V/F) of pseudoephedrine has been reported to be 2.6-3.3 L/kg. No plasma protein binding data of psuedoephedrine in humans are available.
>
> **Metabolism:**
> One to seven per cent of pseudoephedrine dose appeared to be metabolized to norpseudoephedrine by N-demethylation after single dose.
>
> **Elimination:**
> It was reported that 0.4-0 7% of the pseudoephedrine dose was estimated to be excreted in the breast milk over 24 hours after a single dose. The pattern of the relative milk/plasma drug concentration profile showed that pseudoephedrine concentrations in milk were 2 to 3 fold higher than those in plasma.

[redacted]

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4. RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II has reviewed the NDA 21-150 dated on 2/12/2001. It has been found that the submission is acceptable from a clinical pharmacology and biopharmaceutical perspective, provided the labeling change as recommended in the "Labeling Comments"

Young Moon Choi, Ph.D.
Pharmacokineticist
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Office of Clinical Pharmacology and Biopharmaceutics

Concurrence

Emmanuel Fadiran, Ph.D.
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cc NDA 21-150: Division File
HFD-870: Young Moon Choi, Emmanuel Fadiran, Henry Malinowski
HFD-570: Craig Ostroff

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/s/

Young-Moon Choi
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Emmanuel Fadiran
6/1/01 09:37:00 AM
BIOPHARMACEUTICS

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CLINICAL PHARMACOLOGY REVIEW # 1

January 2001

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-150/N-000

Generic name, dose and formulation:	cetirizine HCl 5 mg/pseudoephedrine HCl 120 mg tablets
Trade name:	Zyrtec-D™ 12 Hour
Sponsor:	Pfizer, Inc.
Type of submission:	Original NDA, Category 4S
Dates of submission:	01/18/2000, 04/07/2000, 08/04/2000, 09/29/2000, 11/29/2000 and 12/12/2000
Reviewer:	Monique Wakelkamp-Barnes, M.D., Ph.D.

I SYNOPSIS

Zyrtec-D 12 Hour contains cetirizine HCl, an antihistamine and pseudoephedrine HCl, an adrenergic agent with decongestant action. Zyrtec-D 12 Hour is a film-coated bilayered tablet, containing 5 mg of immediate-release cetirizine HCl and 120 mg of extended-release pseudoephedrine HCl per tablet. The proposed indication is seasonal and perennial allergic rhinitis with nasal congestion, in patients 12 years and older. The proposed dosing regimen is 1 tablet every 12 h. The recommended doses for Zyrtec-D do not exceed the recommended daily doses for currently approved cetirizine or pseudoephedrine products. However, the combination of these two active ingredients has not previously been approved. Also, BID dosing of cetirizine HCl is currently only approved for Zyrtec® Syrup (5 mg cetirizine HCl/5 ml), 2.5 mg BID for use in children, age 2-5 years.

The sponsor submitted two *in vivo* pharmacokinetic studies, 143-006 and 143-007, addressing the issues of a possible interaction of the bilayer tablet with food, and the comparative bioavailability between the proposed combination product and the co-administration of the individual active ingredients, respectively. No safety and efficacy studies were submitted. The possibility of a drug interaction between cetirizine and pseudoephedrine has been studied previously and information on this issue is contained in the package insert for Zyrtec® (cetirizine HCl) Immediate Release Tablets. No clinically significant drug interactions between cetirizine and pseudoephedrine have been observed.

Study 143-006 was a comparative single-dose BA study of the proposed cetirizine HCl 5 mg/pseudoephedrine HCl 120 mg bilayer tablet under fed and fasting conditions and included 24 healthy subjects. The study had an open, single-dose, two-way cross-over design, with a 7-day wash-out period between the two treatments. After intake of a high-fat meal, no significant effect on the cetirizine AUC was found, but C_{max} was significantly decreased, by 30%, and T_{max} was significantly prolonged, by 1.8 h. These findings are consistent with earlier observations of food

interaction with regular Zyrtec® (cetirizine HCl) tablets. There was no significant food-effect on the AUC, C_{max} and T_{max} values of pseudoephedrine HCl.

Study 143-007 was a comparative single and multiple dose bioavailability study of the proposed bilayer tablet vs. co-administration of cetirizine 5 mg and pseudoephedrine 120 mg. Twenty-four healthy subjects were given either a single dose of a cetirizine 5 mg/pseudoephedrine 120 mg bilayer tablet, followed by BID dosing for 6.5 days or a single dose of a 5 mg Zyrtec® (cetirizine HCl) tablet, together with a single dose of a 120 mg pseudoephedrine caplet (Sudafed® LA 120 mg), followed by BID dosing for 6.5 days. After a wash-out period, the subjects crossed over to the alternative treatment. In connection with apparent analytical problems during the assay of the study samples, the reportable cetirizine and pseudoephedrine concentrations that were submitted by the sponsor consisted of a mixture of original assay values and the mean values of a duplicate re-assay. Upon inspection by the Division of Scientific Investigations, it was concluded that there were no analytical or clinical reasons to suggest that the original data were inaccurate and the submitted data were considered unacceptable by the Agency. The sponsor agreed to re-analyze the data for estimation of the pharmacokinetic parameters of cetirizine and pseudoephedrine and determination of bioequivalence using a) the original assay results only and b) the mean values of the repeats only. In both cases, the cetirizine/pseudoephedrine bilayer tablet was found to be bioequivalent to the co-administration of a cetirizine tablet and a pseudoephedrine caplet, after single-dose administration and at steady-state.

Importantly, the pharmacokinetic investigations were not conducted under strict fasting conditions, which is usually recommended from a study design perspective. Instead, the morning doses were taken at about 1-1.5 h after intake of a standardized breakfast, which influenced the pharmacokinetics of cetirizine. However, in comparing the study results with data from study 143-006 and with historical data, it can be concluded that the cetirizine plasma concentration profiles for both the bilayer tablet and the Zyrtec tablet formulations were influenced equally by the food intake and thus, the comparison between the formulations remains acceptable.

Based on the submitted exposure data and comparison with historical data for the 10 mg Zyrtec® (cetirizine HCl) tablet, BID dosing of 5 mg cetirizine in adults is expected to be as safe and efficacious as is QD dosing of 10 mg cetirizine.

Dissolution tests were performed on cetirizine HCl/pseudoephedrine HCl bilayer tablets from lot 8107 used in studies 143-006 and 143-007.
The dissolution specifications proposed by the sponsor are as follows:
Selected medium: 0.1 N HCl
USP I (basket), ——— n
Cetirizine: Q = 75% at 60 min
Pseudoephedrine: ——— dissolved at 1 h, ——— at 4 h and ——— at 12 h

The proposed dissolution specification for cetirizine was not adequate. For pseudoephedrine, the second and third time points (4 h and 12 h) were selected too late, since about ——— or more of the drug is already dissolved at 4 h. Therefore, a revision of the proposed dissolution specifications of Zyrtec-D is warranted.

Conclusions

- The Zyrtec-D 12 Hour Tablet is bioequivalent to the co-administration of the separate active ingredients with regard to both cetirizine HCl and pseudoephedrine HCl.

- BID dosing of 5 mg cetirizine in adults is expected to be as safe and efficacious as is QD dosing of 10 mg cetirizine.

- Regular Zyrtec® (cetirizine HCl) Tablets are labeled to be taken either with or without food. Based on the similarity in food effect on cetirizine bioavailability between Zyrtec® (cetirizine HCl) Tablets and the proposed Zyrtec-D 12 Hour Tablet and the lack of food effect on pseudoephedrine HCl bioavailability, Zyrtec-D 12 Hour Tablets may also be administered either with or without food.

- The *in vitro* dissolution specifications for the proposed method should be revised to:
  Cetirizine HCl: Q = — at 30 min
  Pseudoephedrine HCl: —— dissolved at 1 h, —— dissolved at 2 h,
  —— % at 6 h

- Some revisions in the proposed labeling are recommended, which are outlined in the labeling section of this review.

Reviewer comments to the sponsor:

1) Based on the submitted dissolution data, generated for the batch that was used in studies 143-006 and 143-007, as well as stability data, the *in vitro* dissolution specifications for the proposed dissolution method should be revised to:
Cetirizine HCl: Q = — at 30 min
Pseudoephedrine HCl: —— dissolved at 1 h, —— dissolved at 2 h, —— at 6 h

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II RECOMMENDATION

The Human Pharmacokinetics and Bioavailability section of NDA 21-150/N-000 is acceptable to support the Bioavailability and Bioequivalence regulation covered by 21 CFR part 320, provided that comment 1 and the recommended labeling revisions are adequately addressed by the sponsor. Comment 1 and the recommended labeling revisions should be appropriately conveyed to the sponsor.

Reviewer Date

/S/ 01/09/2001

Monique Wakelkamp-Barnes, M.D., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Final version signed by Young Moon Choi, Ph.D., Acting Teamleader /S/ 01-09-01

cc NDA 21-150/N-000:

	Division File
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HFD-570:	Young Moon Choi
	Monique Wakelkamp-Barnes
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III BACKGROUND

Q. What is Zyrtec-D 12 Hour?

Zyrtec-D 12 Hour contains cetirizine HCl, an antihistamine and pseudoephedrine HCl, an adrenergic agent with decongestant action. Zyrtec-D 12 Hour is a film-coated bilayered tablet, containing 5 mg of cetirizine HCl and 120 mg of pseudoephedrine HCl per tablet for BID dosing. The immediate release cetirizine HCl layer is composed of cetirizine HCl and tablet excipients. The extended release pseudoephedrine HCl layer is composed of pseudoephedrine HCl in a release-controlling polymer matrix containing hydroxypropyl methylcellulose (HPMC). The proposed indication is seasonal and perennial allergic rhinitis with nasal congestion, in patients, 12 years and older. The proposed dosing regimen is 1 tablet every 12 h.

It should be noted that the combination of these two active ingredients has not previously been approved. The present submission is therefore a type 4 NDA (new combination). Also, BID dosing of cetirizine HCl is currently only approved for Zyrtec Syrup (5 mg cetirizine HCl/5 ml), 2.5 mg BID for use in children age 2-5 years, not for adults. Cetirizine HCl immediate release tablets are currently marketed in 5 and 10 mg strengths, to be dosed once daily in patients, 12 years and older. Pseudoephedrine HCl is available OTC, either as a single drug product or as part of a number of combination preparations, to be taken at a maximum daily dose of 240 mg by patients, 12 years and older.

It should also be noted that the sponsor on 03/27/2000 submitted

For the remainder of this review, *cetirizine HCl* and *pseudoephedrine HCl* will be referred to as *cetirizine* and *pseudoephedrine*, respectively.

Q. What studies have been submitted to the NDA?

The Human Pharmacokinetic and Bioavailability section of the NDA contained two *in vivo* pharmacokinetic studies, 143-006 and 143-007, addressing the issues of a possible interaction with food, and the comparative bioavailability between the proposed combination product and the co-administration of the individual active ingredients, respectively. The possibility of drug interaction between cetirizine and pseudoephedrine has been studied previously and information on this issue is contained in the package insert for Zyrtec (cetirizine) Immediate Release Tablets. No clinically significant drug interactions between cetirizine and pseudoephedrine have been observed. In addition to studies 143-006 and 143-007, the sponsor also submitted two non-U.S. studies, intended as supportive documentation. These were comparative bioavailability studies of the proposed bilayer tablet vs. the 5 mg cetirizine/120 mg SR pseudoephedrine after single and multiple dose administration. The formulation is not approved in the U.S.

IV FORMULATION

Q.	***What is the composition of Zyrtec-D 12 Hour?***

The composition of the cetirizine/pseudoephedrine bilayer tablet is as follows (Table 1):

Table 1.

Ingredient	mg/tablet
CORE FIRST TABLET LAYER	
Pseudoephedrine HCl (USP)	120.00
Hydroxypropyl methylcellulose (USP)	
Microcrystalline cellulose (NF)	
Colloidal silicon dioxide (NF)	
Magnesium stearate (NF)	
CORE SECOND TABLET LAYER	
Cetirizine hydrochloride (Pfizer)	5.00
Lactose monohydrate (NF)	
Croscarmellose sodium (NF)	
Microcrystalline cellulose (NF)	
Colloidal silicon dioxide (NF)	
Magnesium Stearate (NF)	
Total	
FILM COATING	
Purified Water (USP)	As required*
Total	

* essentially evaporated during manufacturing process

The proposed formulation is to be manufactured and packaged by UCB S.A., Pharma Sector, Chemin du Foriest, 1420 Braine-l'Alleud, Belgium. The sponsor is planning to submit an

Q.	***Are there any differences between the formulations used in the pharmacokinetic studies and the marketed or to-be-marketed formulations?***

The bilayer tablet formulation used in studies 143-006 and 143-007 is identical to the to-be-marketed formulation. The size of the batch ( ) used in these studies is of the intended commercial batch size, which is (Table 2).

Table 2.

Study no.	Dosage form	Lot/Batch Number	Lot/Batch Size	Formulation
143-006	Cetirizine/Pseudoephedrine bilayer tablet	Lot 8107-G1		To-be-marketed
143-007	Cetirizine/Pseudoephedrine bilayer tablet	Lot 8107-G1		To-be-marketed

Q. Are the proposed dissolution specifications acceptable?

Dissolution tests were performed on cetirizine/pseudoephedrine bilayer tablets from lot 8107-G1 used in studies 143-006 and 143-007. Dissolution profiles were generated using four different media, namely water, 0.1 M HCl, buffer pH 4.5 and buffer pH 7.4. The USP I (basket) method was used, 37 °C, 500 ml volume, agitation speed 100 rpm. Dissolution data for cetirizine and pseudoephedrine from lot 8107 are displayed in Tables 3 and 4, respectively and Figures 1 and 2, respectively.

The dissolution specifications proposed by the sponsor are as follows:
Selected medium: 0.1 N HCl
USP I (basket), 37 ± 0.5 °C, 500 ml volume, agitation speed 100 rpm
Cetirizine: Q = —, at 60 min
Pseudoephedrine: —— dissolved at 1 h, —, at 4 h and —— at 12 h

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Reviewer Comment:
The proposed dissolution specification for cetirizine is not adequate. For pseudoephedrine, the second and third time points (4 h and 12 h) were selected too late, since about [redacted] of the drug is already dissolved at 4 h. The sponsor was requested to submit additional pseudoephedrine dissolution data from early time points (e.g. 2 or 3 h), using the same lot. These data were submitted 08/04/2000 and displayed below in Table 5. Based on these data, as well as stability data, the *in vitro* dissolution specifications for the proposed method should be revised to:

Cetirizine: Q = [redacted] at 30 min
Pseudoephedrine: [redacted] dissolved at 1 h, [redacted], dissolved at 2 h, ≥ [redacted] at 6 h

Table 5.

Tablet #	% Pseudoephedrine HCl released at time interval										
	1 h	2 h	4 h	6 h	8 h	10 h	12 h	14 h	16 h	18 h	20 h
1	[redacted]										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
Mean	41	61	83	94	100	102	103	103	104	104	105
CV%	4.0	3.7	2.8	2.6	2.5	2.2	2.0	2.2	2.4	2.1	2.4

Percent pseudoephedrine released from the bilayer tablet (Lot No. 8107-G1), using the dissolution method described above.

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[redacted]

V ASSAY METHODOLOGY AND VALIDATION

Q.	*What are the assay methods for the determination of cetirizine and pseudoephedrine concentrations? Are the assays performing acceptably?*

Cetirizine and pseudoephedrine in plasma were determined by [redacted] The method was validated prior to initiating analysis of the study samples.

PRE-STUDY METHOD VALIDATION

Description of method: In short, cetirizine and pseudoephedrine in plasma, spiked with desipramine as the internal standard, were extracted with [redacted] The extracts were analyzed by [redacted] For cetirizine, chromatographic separation was achieved using a [redacted] and a mobile phase comprised of a mixture of [redacted] For pseudoephedrine, a [redacted] HPLC column was used and the mobile phase consisted of [redacted]

a) Specificity

No specific interferences were observed at the retention times of cetirizine, pseudoephedrine and the internal standard.

b) Calibration Curve

The lower limit of quantitation (LLOQ) was established at [redacted] for both analytes. The calibration curve was linear over a 5-2000 ng/ml range. Quantitation was performed using $1/x^2$ weighted linear least squares regression equations generated from the calibration data. On average, the correlation coefficient was 0.9911 for cetirizine and 0.9950 for pseudoephedrine.

c) Precision, Accuracy and Recovery

Inter-assay accuracy of the calibrators, measured in duplicate during eight analytical runs, over an assay range from 5 ng/ml to 2000 ng/ml, ranged from [redacted] for cetirizine and from [redacted] for pseudoephedrine. Inter-assay precision was 8.4% or better for cetirizine and 7.5% or better for pseudoephedrine. The recoveries for cetirizine were [redacted] at 1500 ng/ml. [redacted] at 400 ng/ml, [redacted]% at 10 ng/ml and [redacted] for the internal standard. For pseudoephedrine, the recoveries were [redacted] at 1500 ng/ml, [redacted] at 400 ng/ml, [redacted] at 10.0 ng/ml and [redacted] for the internal standard. The reproducibility of recovery was acceptable.

d) Quality Control Samples

Quality control samples were prepared at 10, 400 and 1500 ng/ml for cetirizine and pseudoephedrine and evaluated for precision and accuracy. The intra-assay accuracy for cetirizine and pseudoephedrine was satisfactory (within 15% deviation from the nominal values), and so was the intra-assay precision (CV's less than 15%). The inter-assay accuracy for cetirizine ranged from [redacted] The inter-assay precision was 9.9% or better. The inter-assay accuracy for pseudoephedrine ranged from [redacted] The inter-assay precision was 9.0% or better.

e) Stability

Benchtop stability and freeze/thaw stability of plasma samples was adequate for cetirizine and pseudoephedrine. However, sample extracts left at room temperature for a prolonged period of time, about 22 hours or more, showed a 13-18% decline from the original value for cetirizine. The decrease for pseudoephedrine was somewhat less, up to 10%.

STUDY SAMPLES

Protocol 143-007:

Reviewer Comment:

It should be noted that [redacted] conducted the analytical part of the study. According to a Pfizer statement in the Analytical Report of Study 143-007 (Section 11, Item 9, page 6525), certain analytical problems occurred during the assay of the study samples: " Following the initial assay of the samples from this study, Pfizer personnel noted some apparent anomalies in the plasma concentration versus time profiles. In an effort to corroborate these findings, [redacted] was instructed to re-assay a subset of samples in duplicate. These re-analyses 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 re-analysis, in duplicate, of all samples".

Apparently, Pfizer had selected more than 150 data points from different study subjects and requested [redacted] to re-assay the corresponding samples in duplicate (repeats 1 and 2) for cetirizine and pseudoephedrine. Subsequently, Pfizer noticed a discrepancy between the re-assay results as compared to the original values and asked [redacted] to re-assay all study samples (for cetirizine as well as pseudoephedrine) in duplicate (repeats 3 and 4). Pfizer then selected a set of reportable values (to be used for subsequent pharmacokinetic analysis and determination of bioequivalence), that were a mixture of original assay values and mean values of repeats 3 and 4. Except for the paragraph quoted above, no further explanation was given for the repeated re-assays, nor was a rationale provided for the final selection of the reportable assay values. Repeats 1 and 2 were never mentioned in the NDA submission. In summary, the originally submitted data and associated pharmacokinetic and statistical analyses of study 143-007 were unacceptable from a Clinical Pharmacology and Biopharmaceutics perspective.

From June 26-30. 2000. the Division of Scientific Investigations (DSI) conducted an audit at [redacted]. From June 29-July 7, 2000, an audit was conducted at [redacted]. A copy of the audit memorandum issued by the Division is attached to this review (Attachment 1). In short, upon inspection, DSI concluded that there were no analytical or clinical reasons to suggest that the original data were inaccurate. Pfizer provided a Re-analysis and Reporting Flowchart that was used for selection of the reportable values used in the pharmacokinetic data analysis, but the date on the Flowchart indicated that the Flowchart was created after the assays and re-assays of all the study samples. In the memorandum, DSI recommended the Division of Pulmonary and Allergy Drug Products not to accept Study 143-007 for review, unless Pfizer would reanalyze all pharmacokinetic data.

In a teleconference with the sponsor on August 30, 2000, Pfizer agreed to re-analyze the data for estimation of the pharmacokinetic parameters of cetirizine and pseudoephedrine and determination of bioequivalence using a) the original assay results only and b) the mean values of repeats 3 and 4 only. For the remainder of this review, tables and figures from this study will be displayed, showing the data from the original assay, as well as the repeats (see also Section VI).

Protocol 143-006:

Inter-assay accuracy for cetirizine quality controls with nominal concentrations of 10 ng/ml, 400 ng/ml and 1500 ng/ml was [redacted] respectively. Inter-assay precision was [redacted] respectively. Inter-assay accuracy for pseudoephedrine controls at 10 ng/ml, 400 ng/ml and 1500 ng/ml was [redacted] respectively. Inter-assay precision was [redacted] respectively.

Reviewer Comment:

The assay performance in this study was acceptable. Only few samples were re-analyzed in this study, 1% of all the cetirizine results and 2.4% of all the pseudoephedrine results, respectively. This limited re-analysis is not expected to have had significant influence on the outcome of the study.

VI CLINICAL PHARMACOLOGY

Q.	***What is the comparative bioavailability of the proposed combination tablet vs. the separate administration of the active ingredients? Is there equivalent rate and extent of absorption?***

Study 143-007 was a comparative single and multiple dose bioavailability study of the proposed cetirizine 5 mg/pseudoephedrine 120 mg bilayer tablet given BID vs. co-administration of cetirizine 5 mg and pseudoephedrine 120 mg BID. The study had an open, randomized, 2-way, 2-period cross-over design with at least a 7-day wash-out period between the two treatments. Twenty-four healthy subjects, 17 males age 20-41 years and 7 females age 20-38 years were enrolled and completed the study. Subjects were given either a single dose of cetirizine 5 mg/pseudoephedrine 120 mg bilayer tablet, followed by BID dosing for 6.5 days (treatment A) or a single dose of a 5 mg Zyrtec® (cetirizine) tablet, together with a single dose of a 120 mg pseudoephedrine caplet (Sudafed® LA 120 mg from Warner Lambert), followed by BID dosing for 6.5 days (treatment B). After the wash-out period, the subjects crossed over to the alternative treatment. The days for single (morning) dosing were day 1 and 9 during study period 1 and day 17 and 25 during study period 2, respectively. The days for multiple dosing were days 3-8 and days 19-24, respectively. Subjects were confined to the Clinical Research Unit from days 1-9 and days 17-25. All meals were standardized and the morning doses were administered with 240 ml of water at least 1 h after intake of a standardized breakfast. On days 1, 9, 17 and 25, blood samples for determination of plasma levels of cetirizine and pseudoephedrine were taken at pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 h after dosing. On days 1 and 17, additional samples were taken at 16, 24, 36 and 48 h after dosing.

For assessment of steady-state, trough concentrations collected on days 9 and 25 were compared between hours 0 and 12, for each treatment separately, using a paired t-test at the $\alpha = 0.05$ level of significance. For the evaluation of bioequivalence, an ANOVA model was used that included the factors sequence, subject within sequence, period and treatment. Ninety percent confidence intervals were calculated for the ratio of the geometric means of C_{max} and $AUC_{(0-\infty)}$ on days 1 and 17 and C_{max}, C_{min} and $AUC_{(0-12h)}$ on days 9 and 25.

Reviewer Comment:
In an biopharmaceutic amendment, submitted 04/07/2000, the sponsor clarified that Sudafed® LA 120 mg caplets are identical to Sudafed® 12 Hour Tablets, referenced in the PDR.

Reviewer Comment:
The analytical part of the study was conducted by ——— . According to the sponsor, analytical problems occurred during the assay of the samples and they requested ——— to re-assay in duplicate (repeats 1 and 2) the corresponding samples for more than 150 data points for cetirizine and pseudoephedrine. Subsequently, Pfizer noticed a discrepancy between the re-assay results as compared to the original values and asked ——— to re-assay all study samples (for cetirizine and pseudoephedrine) in duplicate (repeats 3 and 4). The sponsor then selected a set of reportable values (to be used for subsequent pharmacokinetic analysis and determination of bioequivalence), that were a mixture of original assay values and the means of repeats 3 and 4. Upon inspection by the Division of Scientific Investigations, it was concluded that there were no analytical or clinical reasons to suggest that the original data were inaccurate. In a teleconference with the sponsor on August 30, 2000, Pfizer agreed to re-analyze the data for estimation of the pharmacokinetic parameters of cetirizine and pseudoephedrine and determination of bioequivalence using a) the original assay results only and b) the mean values of repeats 3 and 4 only. In the review, tables and figures from this study will be displayed, showing the data from the original assay, as well as the mean of the repeats (for further details, see also Section IV and Attachment 1).

Statistical analysis showed no significant difference ($p>0.1$) in cetirizine or pseudoephedrine concentrations between hours 0 and 12 on the last day of the multiple dosing regimen, suggesting that steady-state had been obtained. Mean plasma cetirizine and pseudoephedrine concentrations after single and multiple dosing following administration of the bilayer tablet and the co-administration of the active ingredients, utilizing only the original assay results, are shown in Figures 3-6, respectively. Mean plasma cetirizine and pseudoephedrine concentrations after single and multiple dosing following administration of the bilayer tablet and the co-administration of the active ingredients, utilizing the mean of the two repeat-assay results, are displayed in Figures 7-10, respectively. Estimated pharmacokinetic parameters for cetirizine and pseudoephedrine after administration of the bilayer tablet and co-administration of the active ingredients are displayed in Tables 6 and 7. Ninety percent confidence intervals for the ratio of the geometric means of the pharmacokinetic parameters for cetirizine and pseudoephedrine are shown in Table 8. The findings indicate that the cetirizine/pseudoephedrine bilayer tablet is bioequivalent to the co-administration of a cetirizine tablet and a pseudoephedrine caplet, after single-dose administration and at steady-state.

Reviewer Comment:
The pharmacokinetic investigations were not conducted under strict fasting conditions, which is generally to be preferred for reasons of standardization. On 11/27/2000, the sponsor was asked to provide more detailed information about the content of the breakfast and the exact time period between completion of the breakfast and the dosing of the drug. The sponsor's reply dated 12/12/2000 indicated that the time elapsed between the completion of the meal and the dosing of the drug ranged from 1 h to 1 h and 26 minutes. The content of the meals was different for the different study days. For Days 1and 17, the composition of the breakfast was fairly close to that of a "standardized high-fat meal", perhaps with a slightly lower fat content. The composition of the breakfast was as follows: 3.25 oz scrambled eggs, 2 slices of bacon, 2 slices of toast, 5 g of margarine, jelly, 6 oz of orange juice and 8 oz of milk. A different breakfast was provided on Days 9 and 25: cereal, banana, yogurt, bagel & cream cheese, 6 oz of orange juice and 8 oz of milk. When comparing Figures 3 and 7 from this study to Figure 11 from study 143-006 (a single-dose food interaction study of the bilayer tablet), it is clear that the cetirizine plasma concentration vs. time profiles in study 143-007 were influenced by food intake. The profiles ran an intermediate course between the respective fasting profiles and the profiles after intake of a high-fat meal, as depicted in Figure 11. After single dosing in study 143-007, the cetirizine C_{max} (Table 6) was about 80% of the cetirizine C_{max} value (153 ng/ml) observed in study 143-006 under true fasting conditions, though it was not as low as the C_{max} observed after a high-fat breakfast (Table 9). For comparative purposes, results from a cetirizine pharmacokinetic dose proportionality study submitted to NDA 19-835, for cetirizine 5 and 10 mg tablets, could also be mentioned here. After single dosing of a 5 mg cetirizine tablet (to-be-marketed formulation), under fasting conditions, the observed C_{max} was 140 ng/ml. Similar to cetirizine from the bilayer tablet, the cetirizine C_{max} of the Zyrtec tablet in study 143-007 constitutes about 80% of this value. This indicates that the cetirizine plasma concentration profiles for both the bilayer tablet and Zyrtec tablet formulations were equally influenced by the intake of food and thus, the comparison between the two formulations appears to remain valid.

Table 6.

	BILAYER TABLET Mean (SD)		CO-ADMINISTRATION Mean (SD)	
CETIRIZINE Single-dose	**Original assay data**	**Mean of repeat assay data**	**Original assay data**	**Mean of repeat assay data**
C_{max} (ng/ml)	122 (28.3)	114 (22.4)	118 (22.3)	113 (24.6)
T_{max} (h)*	2.0 (	2.0 (	2.0 (	2.0 (
$AUC_{(0\text{-}tlast)}$ (h·ng/ml)	1154 (251)	1208 (226)	1174 (197)	1230 (204)
$AUC_{(0\text{-}\infty)}$ (h·ng/ml)	1179 (273)	1233 (242)	1203 (210)	1257 (218)
$t_{½}$ (h)	8.0 (2.0)	7.9 (2.0)	8.6 (2.0)	8.2 (1.7)
	BILAYER TABLET Mean (SD)		**CO-ADMINISTRATION Mean (SD)**	
CETIRIZINE Multiple-dose	**Original assay data**	**Mean of repeat assay data**	**Original assay data**	**Mean of repeat assay data**
C_{max} (ng/ml)	185 (26.8)	178 (32.0)	195 (31.7)	195 (33.3)
T_{max} (h)*	2.0 (	2.0 (	2.0	2.0 (
$AUC_{(0\text{-}12h)}$ (h·ng/ml)	1396 (221)	1370 (204)	1433 (217)	1423 (218)
C_{min} (ng/ml)	71.9 (18.3)	70.9 (17.0)	71.4 (18.6)	69.9 (16.4)

Pharmacokinetic parameters of cetirizine after single and multiple dosing of the bilayer tablet and the co-administration of cetirizine and pseudoephedrine, respectively. The table displays the parameter estimates based on the original assay results, as well as the mean of the repeat assays.
* median and range.

Table 7.

	BILAYER TABLET Mean (SD)		CO-ADMINISTRATION Mean (SD)	
PSEUDOEPHEDRINE Single-dose	**Original assay data**	**Mean of repeat assay data**	**Original assay data**	**Mean of repeat assay data**
C_{max} (ng/ml)	332 (66.4)	309 (63.1)	316 (91.9)	284 (54.3)
T_{max} (h)*	4.0 (	4.0 (	5.0 (	4.0 (
$AUC_{(0\text{-}tlast)}$ (h·ng/ml)	4055 (926)	3924 (968)	3949 (845)	3719 (683)
$AUC_{(0\text{-}\infty)}$ (h·ng/ml)	4111 (961)	3953 (997)	3976 (852)	3740 (695)
$t_{½}$ (h)	6.8 (2.9)	6.0 (1.1)	6.0 (1.3)	5.8 (0.9)
	BILAYER TABLET Mean (SD)		**CO-ADMINISTRATION Mean (SD)**	
PSEUDOEPHEDRINE Multiple-dose	**Original assay data**	**Mean of repeat assay data**	**Original assay data**	**Mean of repeat assay data**
C_{max} (ng/ml)	543 (134)	526 (144)	536 (153)	475 (100)
T_{max} (h)*	4.0 (	4.0 (	3.0	3.0
$AUC_{(0\text{-}12h)}$ (h·ng/ml)	4961 (1269)	4786 (1210)	4816 (1090)	4561 (1013)
C_{min} (ng/ml)	325 (120)	303 (92.9)	308 (79.8)	296 (78.8)

Pharmacokinetic parameters of pseudoephedrine after single and multiple dosing of the bilayer tablet and the co-administration of cetirizine and pseudoephedrine, respectively. The table displays the parameter estimates based on the original assay results, as well as the mean of the repeat assays.
* median and range.

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Table 8.

	ORIGINAL ASSAY DATA 90% CONFIDENCE INTERVALS Bilayer Tablet vs. Co-administration		MEAN OF REPEAT ASSAY DATA 90% CONFIDENCE INTERVALS Bilayer Tablet vs. Co-administration	
CETIRIZINE	***Single-dose***	***Multiple-dose***	***Single-dose***	***Multiple-dose***
C_{max} (ng/ml)	93.4% - 114.2%	88.4% - 101.4%	95.6% - 107.8%	86.5% - 96.5%
$AUC_{(0-\infty)}$ (h·ng/ml)	91.1% - 103.3%	-	93.5% - 102.1%	-
$AUC_{(0-t)}$ (h·ng/ml)	-	92.7% - 102.1%	-	93.2% - 99.6%
C_{min} (ng/ml)	-	94.1% - 108.6%	-	96.4% - 106.8%
PSEUDOEPHEDRINE	***Single-dose***	***Multiple-dose***	***Single-dose***	***Multiple-dose***
C_{max} (ng/ml)	98.8% - 116.3%	93.6% - 110.7%	102.8% - 114.6%	104.2% - 116.2%
$AUC_{(0-\infty)}$ (h·ng/ml)	98.8% - 109.6%	-	100.2% - 108.6%	-
$AUC_{(0-t)}$ (h·ng/ml)	-	97.1% - 108.3%	-	98.8% - 110.5%
C_{min} (ng/ml)	-	94.0% - 113.8%	-	92.7% - 111.2%

90% confidence intervals for the ratio of the geometric means of the pharmacokinetic parameters for cetirizine and pseudoephedrine, after single and multiple dosing of the bilayer tablet and the co-administration of cetirizine and pseudoephedrine, respectively. The table shows the 90% confidence interval estimates based on the original assay results, as well as the mean of the repeat assays.

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Cetirizine Protocol 143-007 (Original Assay)
Mean Plasma Cetirizine Concentrations vs Time Following Single Dose Administration
of Bilayer Tablet and Single Dose Co-administration of Zyrtec Tablet and Sudafed Caplet

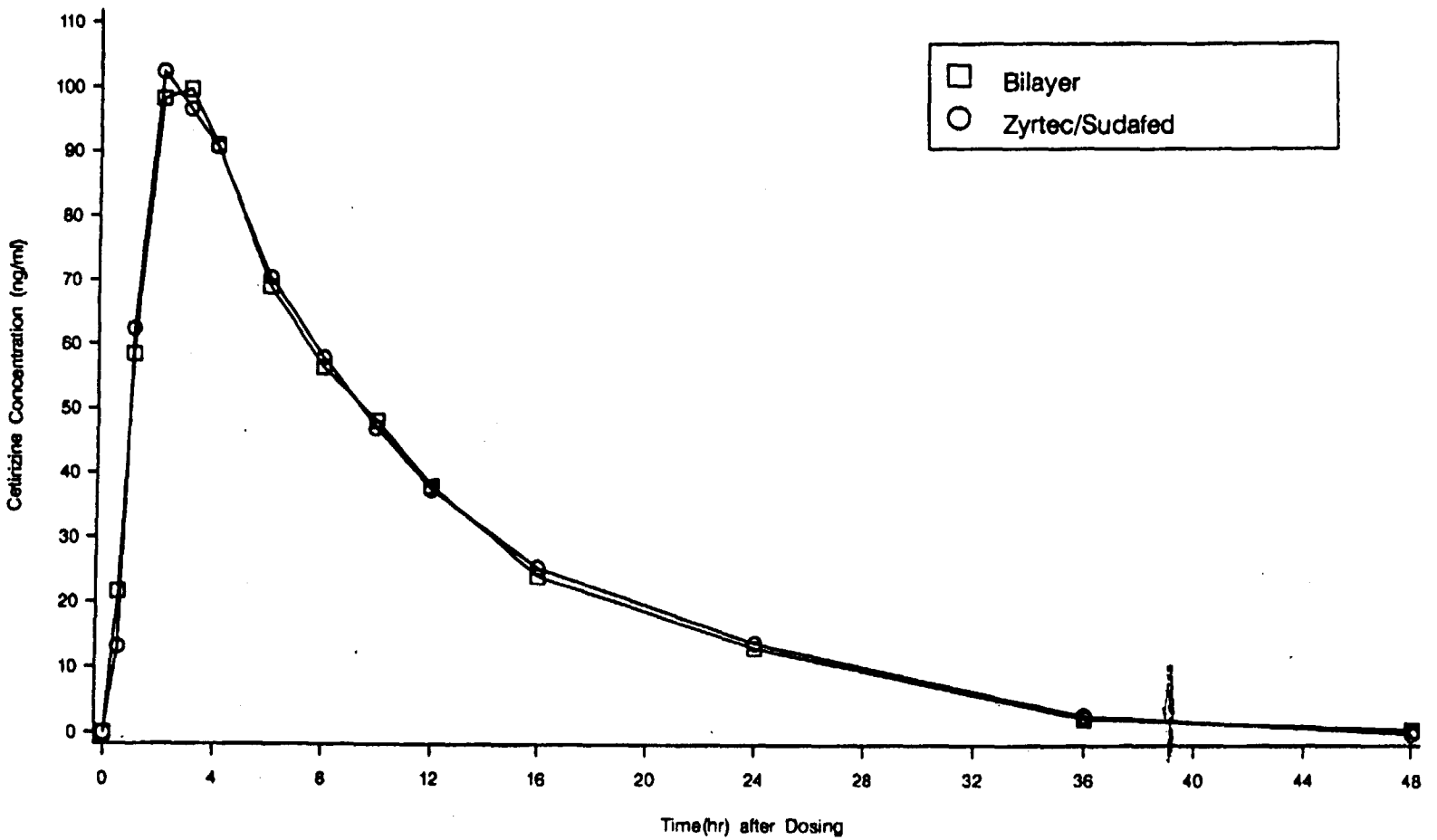

Figure 3.

Bilayer Tablet: 5 mg Cetirizine/120 mg Pseudoephedrine. Zyrtec/Sudafed: Co-administration of 5 mg Cetirizine/120 mg Pseudoephedrine.
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Cetirizine Protocol 143–007 (Original Assay)
Mean Plasma Pseudoephedrine Concentrations vs Time Following Single Dose Administration
of Bilayer Tablet and Single Dose Co–administration of Zyrtec Tablet and Sudafed Caplet

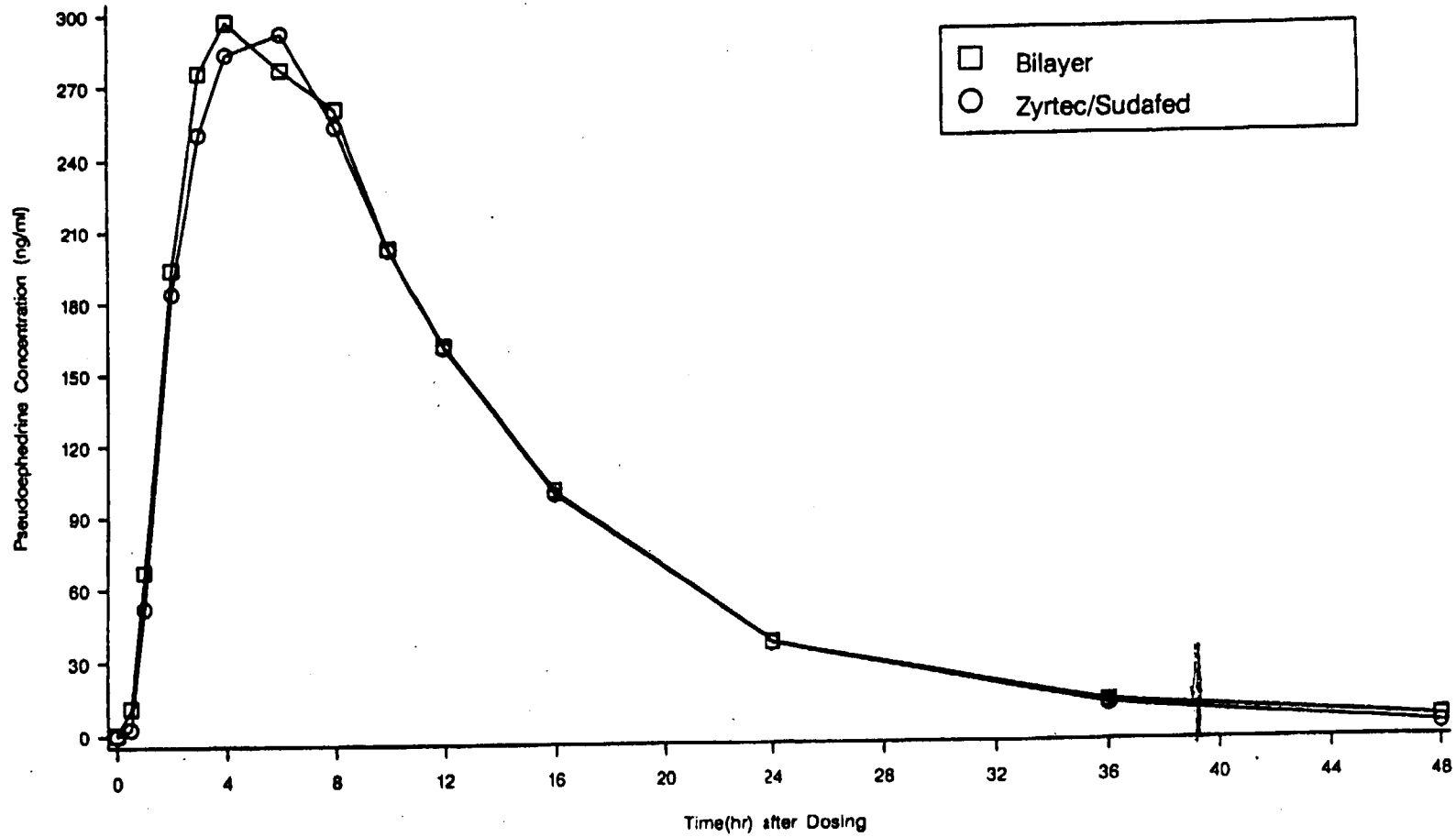

Figure 4.

Bilayer Tablet: 5 mg Cetirizine/120 mg Pseudoephedrine. Zyrtec/Sudafed: Co–administration of 5 mg Cetirizine/120 mg Pseudoephedrine.
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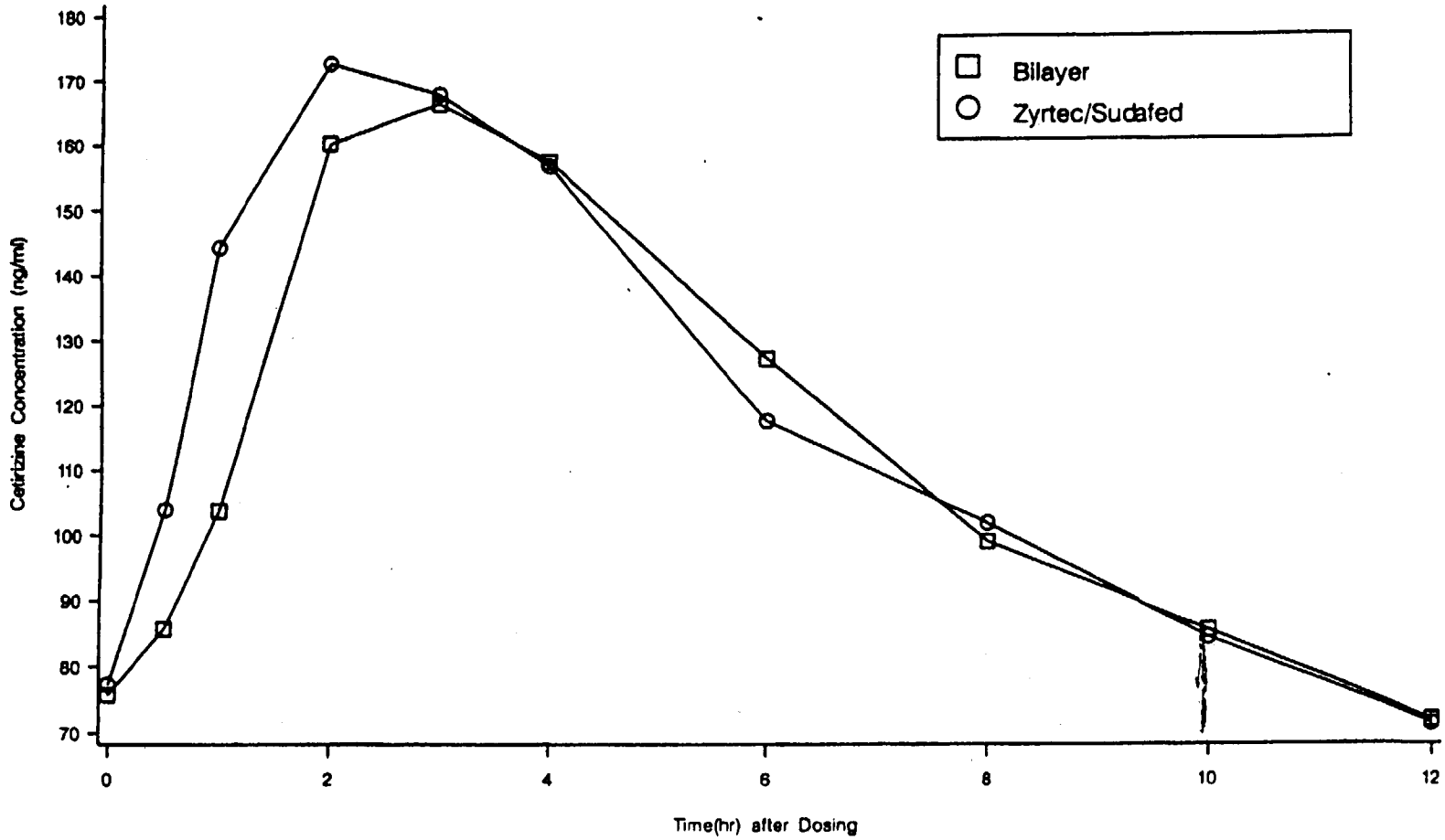
Figure 5.

Cetirizine Protocol 143–007 (Original Assay)
Mean Plasma Cetirizine Concentrations vs Time Following Multiple Dose Administration
of Bilayer Tablet and Multiple Dose Co–administration of Zyrtec Tablet and Sudafed Caplet



Bilayer Tablet: 5 mg Cetirizine/120 mg Pseudoephedrine. Zyrtec/Sudafed: Co–administration of 5 mg Cetirizine/120 mg Pseudoephedrine.
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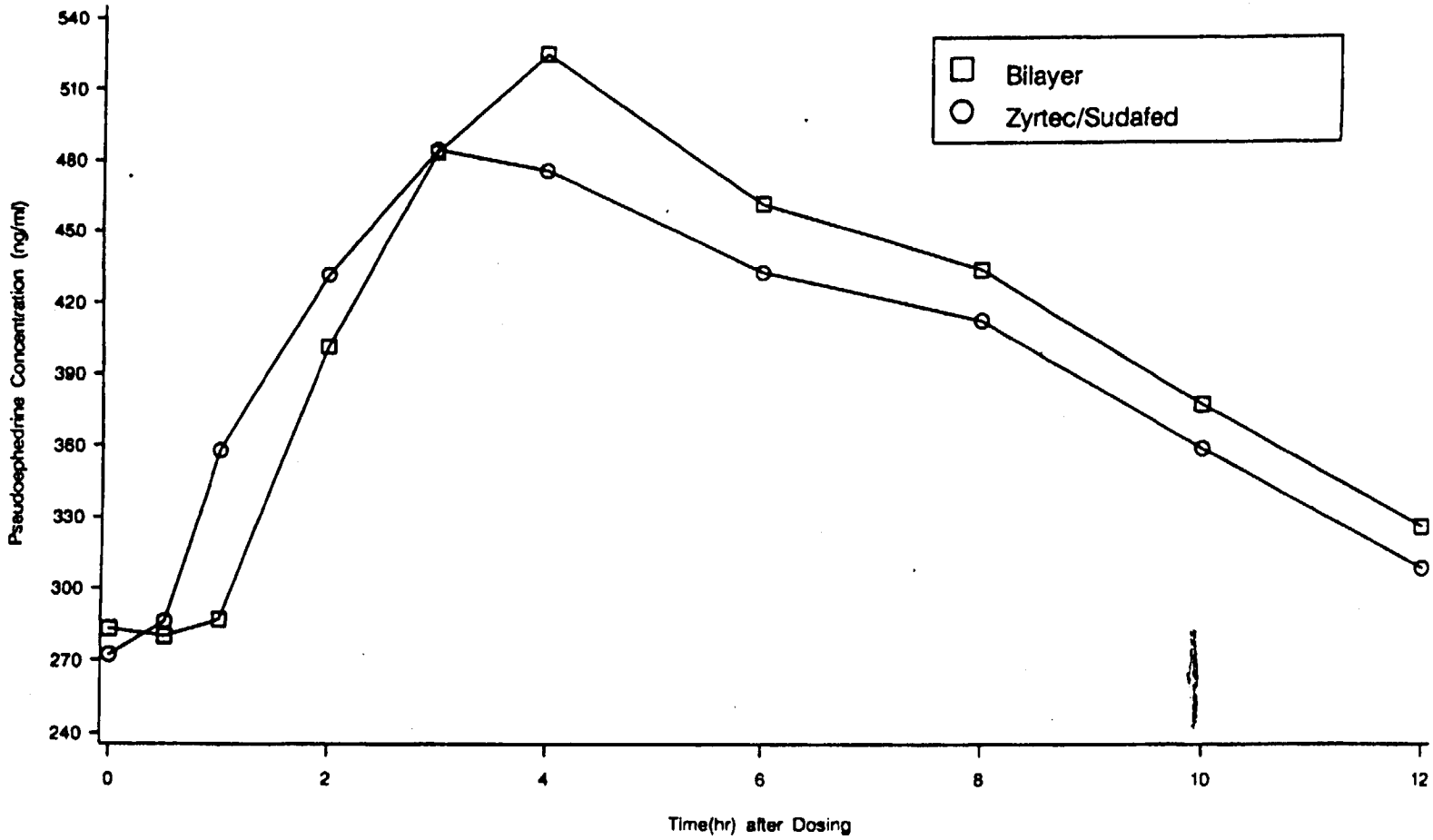
Figure 6.

Cetirizine Protocol 143–007 (Original Assay)
Mean Plasma Pseudoephedrine Concentrations vs Time Following Multiple Dose Administration
of Bilayer Tablet and Multiple Dose Co–administration of Zyrtec Tablet and Sudafed Caplet



Bilayer Tablet: 5 mg Cetirizine/120 mg Pseudoephedrine. Zyrtec/Sudafed: Co–administration of 5 mg Cetirizine/120 mg Pseudoephedrine.
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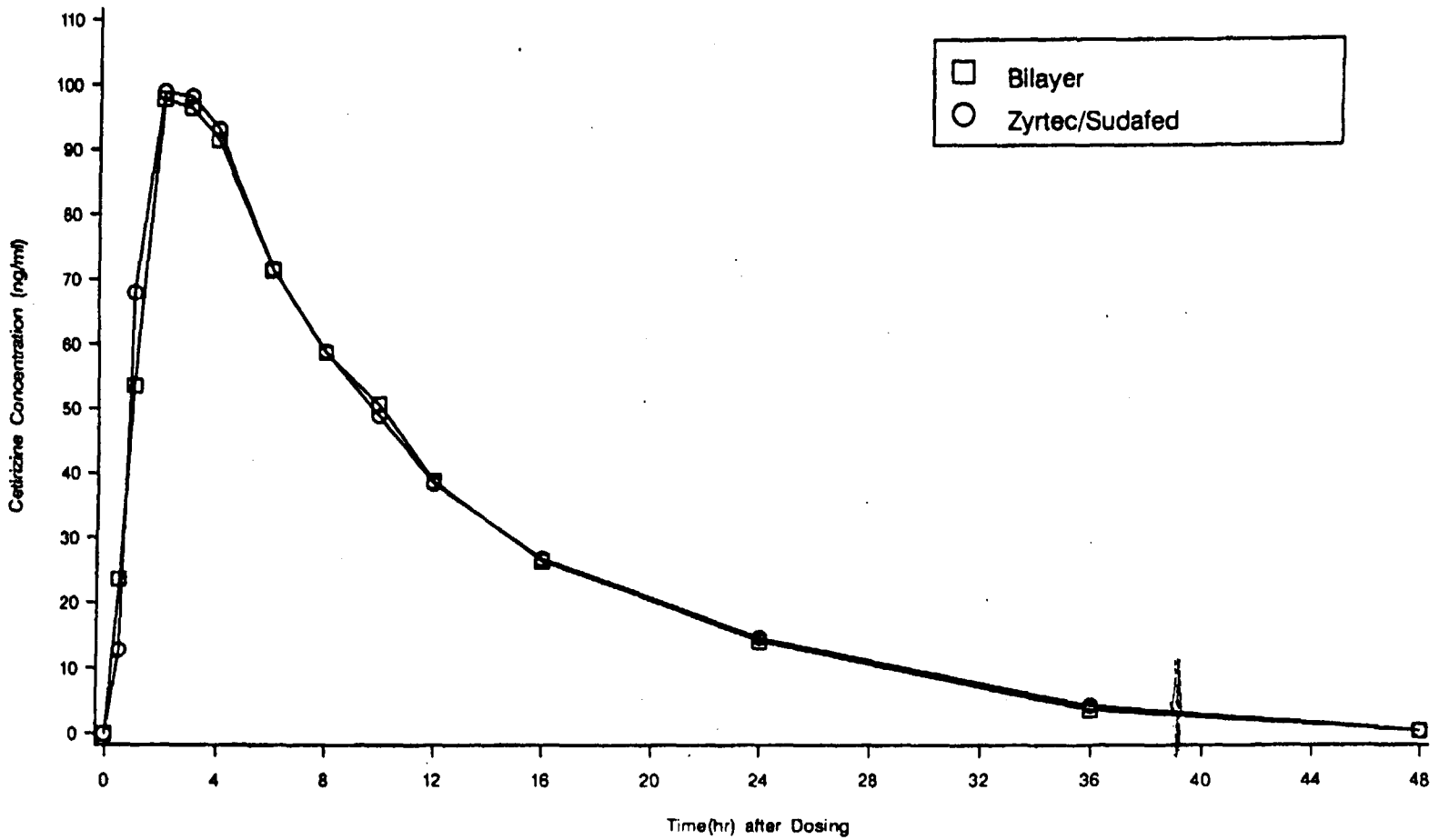
Figure 7.

Cetirizine Protocol 143–007 (Average of Repeat Assays)
Mean Plasma Cetirizine Concentrations vs Time Following Single Dose Administration
of Bilayer Tablet and Single Dose Co–administration of Zyrtec Tablet and Sudafed Caplet



Bilayer Tablet: 5 mg Cetirizine/120 mg Pseudoephedrine. Zyrtec/Sudafed: Co–administration of 5 mg Cetirizine/120 mg Pseudoephedrine.
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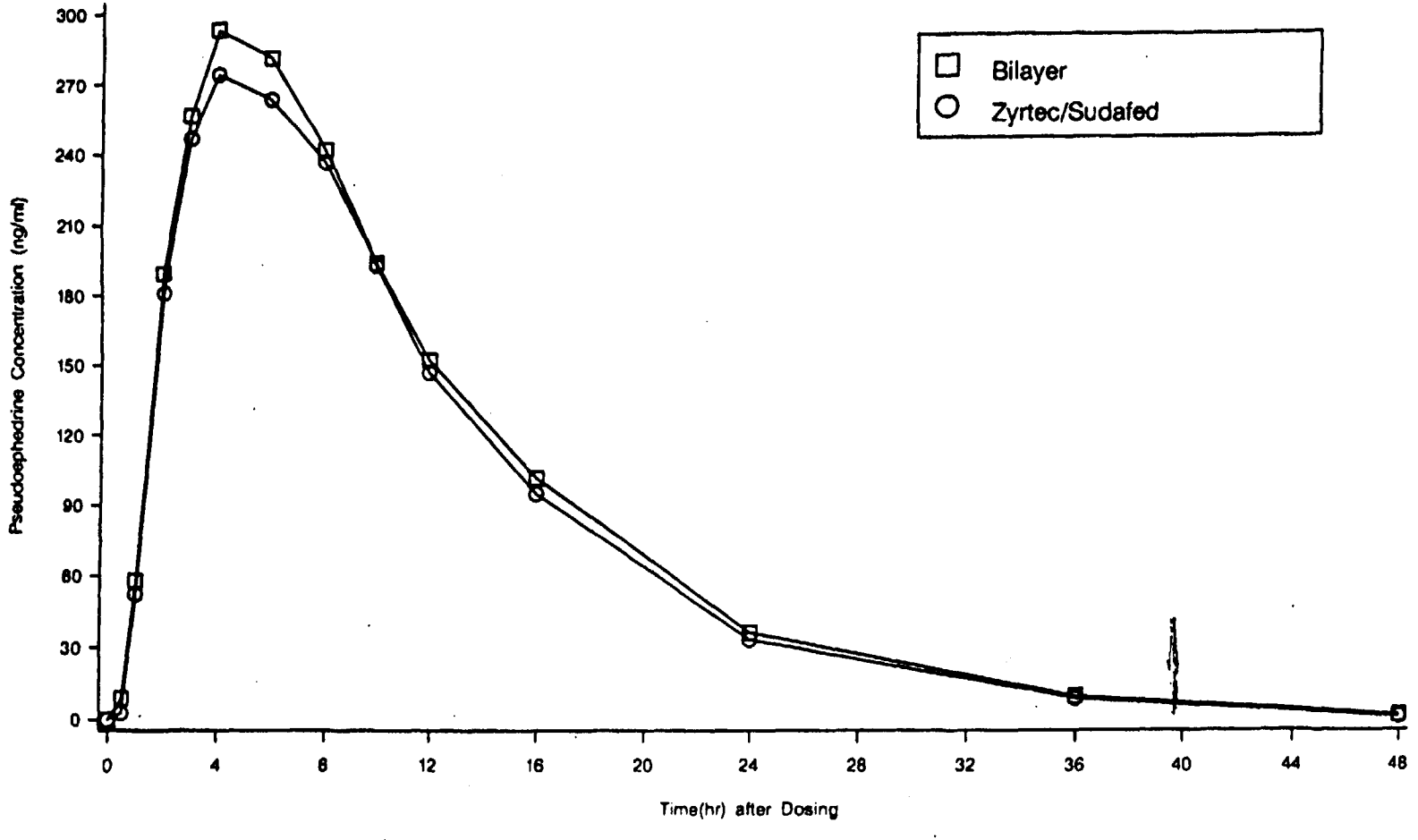
Figure 8.

Cetirizine Protocol 143–007 (Average of Repeat Assays)
Mean Plasma Pseudoephedrine Concentrations vs Time Following Single Dose Administration
of Bilayer Tablet and Single Dose Co–administration of Zyrtec Tablet and Sudafed Caplet



Bilayer Tablet: 5 mg Cetirizine/120 mg Pseudoephedrine. Zyrtec/Sudafed: Co–administration of 5 mg Cetirizine/120 mg Pseudoephedrine.
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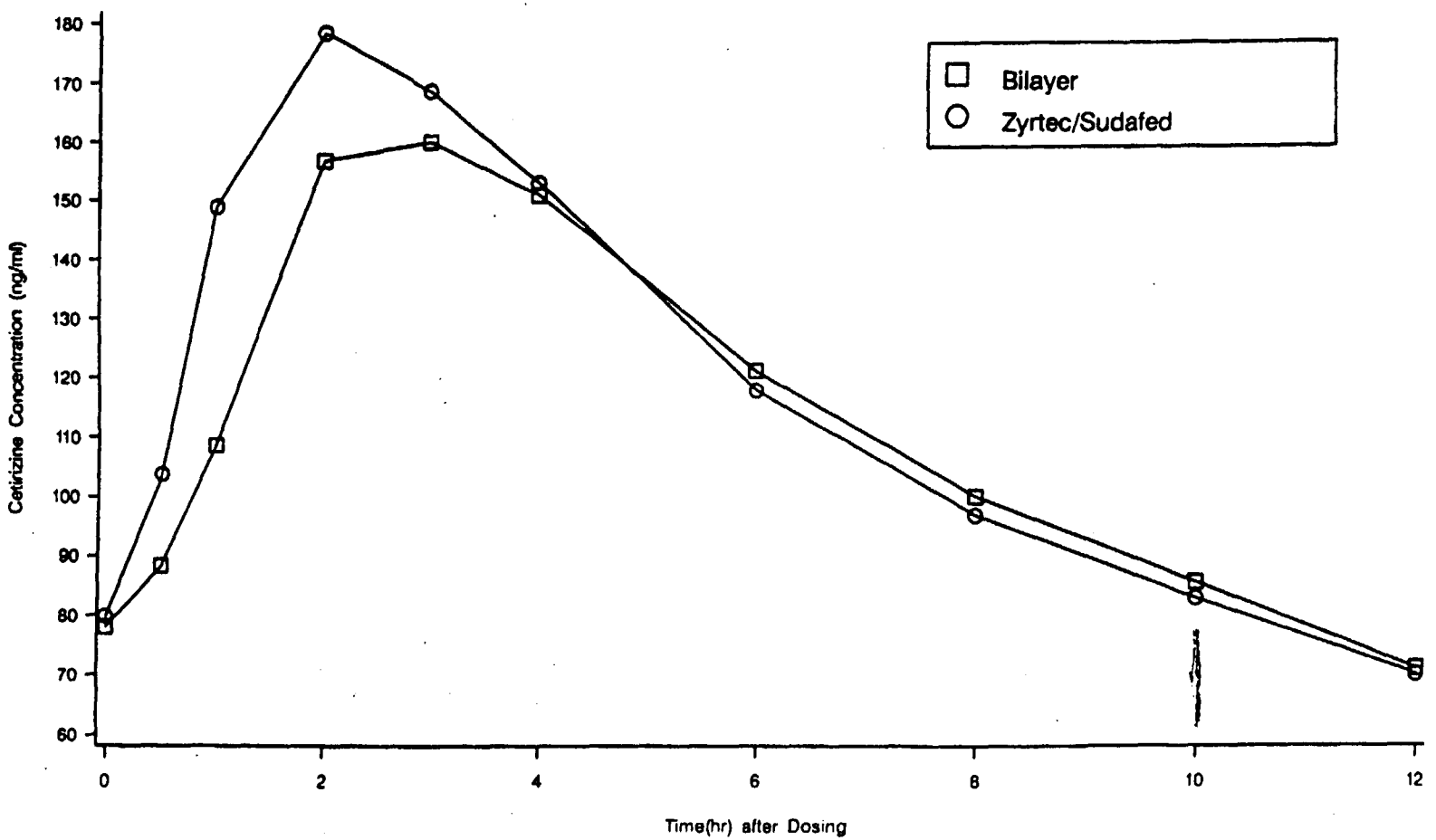
Figure 9.

Cetirizine Protocol 143-007 (Average of Repeat Assays)
Mean Plasma Cetirizine Concentrations vs Time Following Multiple Dose Administration
of Bilayer Tablet and Multiple Dose Co-administration of Zyrtec Tablet and Sudafed Caplet



Bilayer Tablet: 5 mg Cetirizine/120 mg Pseudoephedrine. Zyrtec/Sudafed: Co-administration of 5 mg Cetirizine/120 mg Pseudoephedrine.
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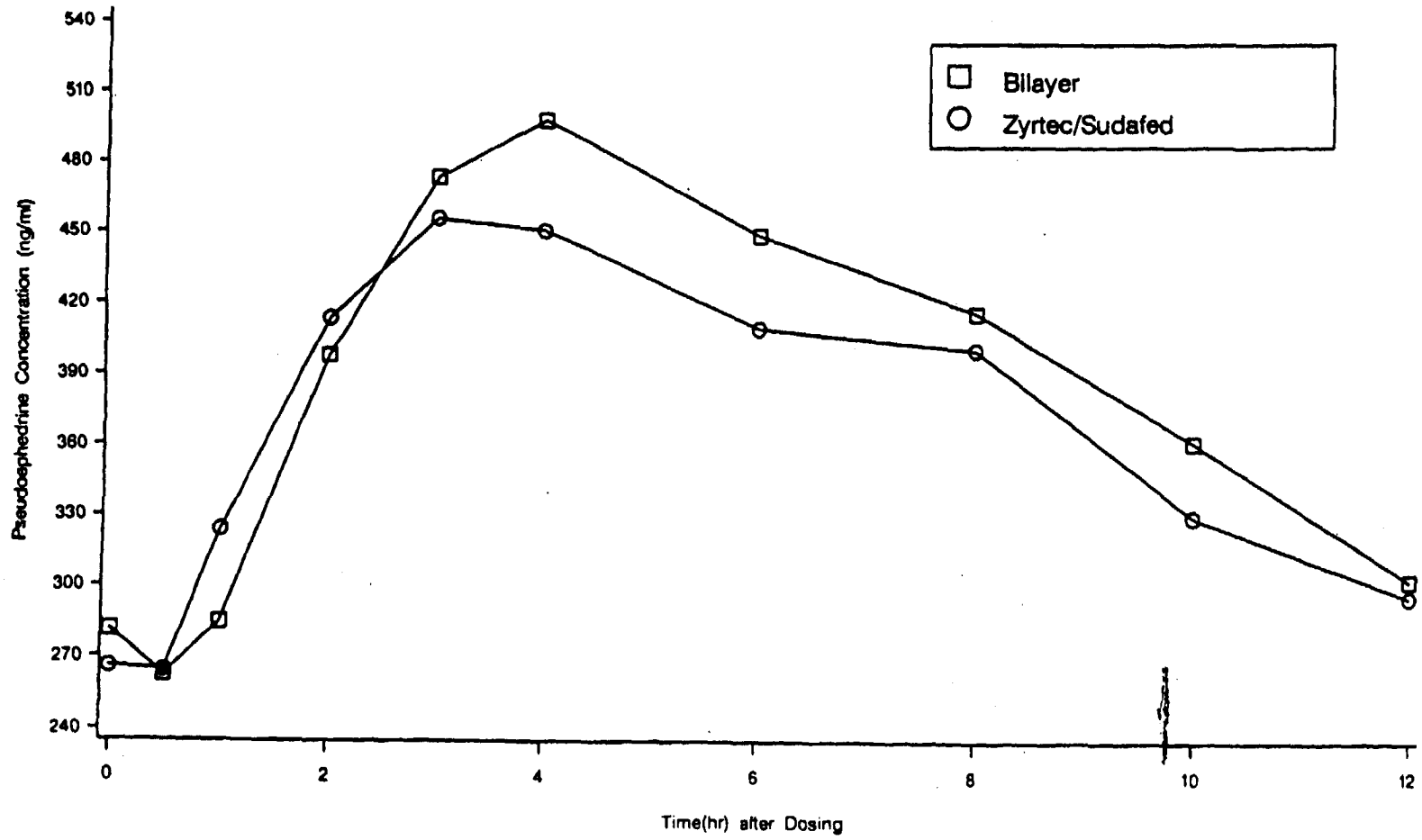
Figure 10.

Cetirizine Protocol 143–007 (Average of Repeat Assays)
Mean Plasma Pseudoephedrine Concentrations vs Time Following Multiple Dose Administration
of Bilayer Tablet and Multiple Dose Co–administration of Zyrtec Tablet and Sudafed Caplet



Bilayer Tablet: 5 mg Cetirizine/120 mg Pseudoephedrine. Zyrtec/Sudafed: Co–administration of 5 mg Cetirizine/120 mg Pseudoephedrine.
Source Data: Section 13 Tables 2.7, 2.8 Date of Data Extraction: 01SEP00 Date of Figure Generation: 13SEP00
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Q. The proposed dosing regimen for Zyrtec-D is 1 tablet BID. Cetirizine is currently not approved for BID dosing in adults. Currently marketed 5 and 10 mg cetirizine immediate release tablets are to be dosed once daily in patients, 12 years and older. Can the proposed dosing regimen for cetirizine be considered safe and effective?

The recommended doses for Zyrtec-D do not exceed the recommended daily doses for currently approved cetirizine or pseudoephedrine products. Cetirizine pharmacokinetics is known to be linear over a 5-60 mg range. For comparative purposes, results from a multiple dose pharmacokinetic study of a 10 mg cetirizine capsule formulation in healthy volunteers (submitted to NDA 19-835, for cetirizine 5 and 10 mg tablets) could also be mentioned here. After daily dosing for ten days of a 10 mg capsule formulation (bioequivalent to the to-be-marketed cetirizine 10 mg tablet), the steady-state C_{max} was 311 ng/ml, C_{min} was 29.9 ng/ml and $AUC_{(0\text{-}24h)}$ was 2502 ng·h/ml. When comparing these data to the data contained in Table 6, it can be seen that the observed fluctuations in cetirizine concentrations stay within the above-mentioned C_{max} and C_{min} levels. The $AUC_{(0\text{-}12h)}$ is half the size of the above-mentioned $AUC_{(0\text{-}24h)}$ level. Based on these exposure data, BID dosing of 5 mg cetirizine in adults is expected to be as safe and efficacious as is QD dosing of 10 mg cetirizine.

Q. Is there any significant interaction with food?

Study 143-006 was a comparative single-dose BA study of the proposed cetirizine 5 mg/pseudoephedrine 120 mg bilayer tablet under fed and fasting conditions. The study had an open, single-dose, two-way cross-over design, with a 7-day washout period between the two treatment periods. Twenty-four healthy subjects, 11 males, age 20-41 years and 13 females, age 18-43 years, entered and completed the study. Subjects were randomly assigned to one of two sequences. Subjects assigned to sequence I first received the bilayer tablet under fasting conditions with 240 ml of water. On the alternate study day, the drug was administered with 240 ml of water, immediately after intake of a standardized high-fat meal (2 fried eggs, 2 strips of bacon, 2 oz. of hash brown potatoes, 2 slices of toast with 2 pats of butter and 8 oz. of whole milk). Subjects assigned to sequence II first received the drug under fed conditions, followed by intake under fasting conditions. A standardized meal was served to all subjects at 4 h after drug intake.

Blood samples for determination of cetirizine and pseudoephedrine plasma levels were taken on days 1 and 8 at the following sampling times: at pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 h post-dose. Natural log-transformed C_{max} and AUC values were analyzed using the SAS GLM procedure and an ANOVA model containing effects for sequence, subjects within sequence, treatment and period. Mean (SD) pharmacokinetic parameters and 90% confidence intervals for the geometric mean ratios of C_{max} and $AUC_{(0\text{-}\infty)}$ for cetirizine and pseudoephedrine are displayed below in Table 9. The mean cetirizine and pseudoephedrine plasma concentration profiles under fasting and fed conditions are shown in Figure 11.

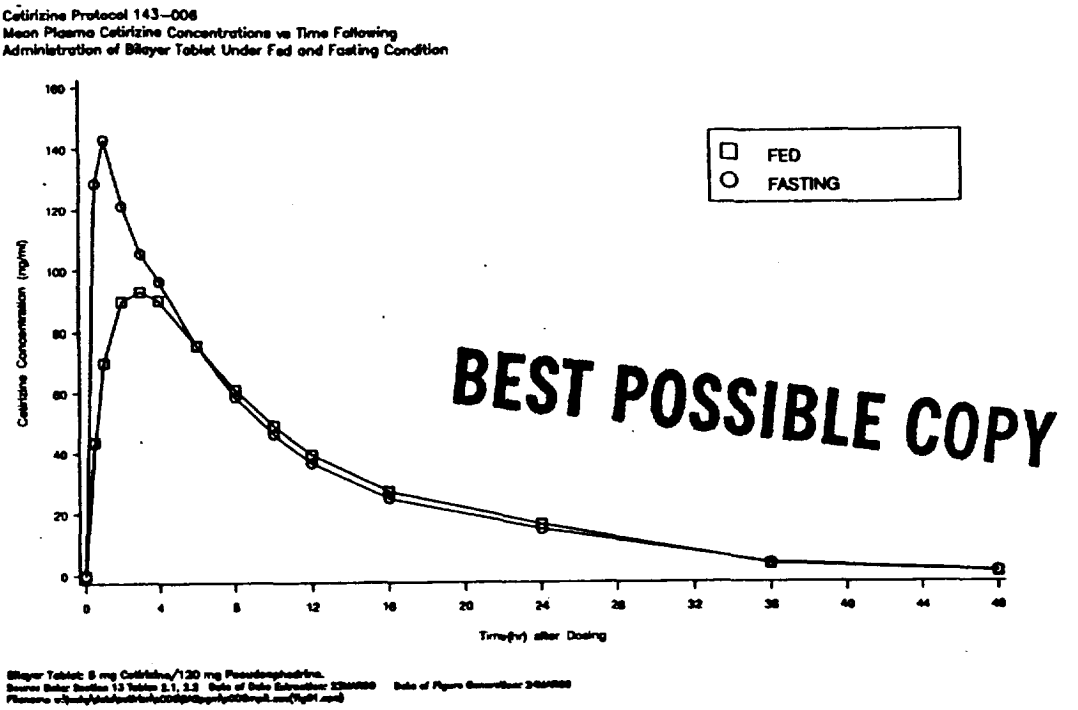
Table 9.

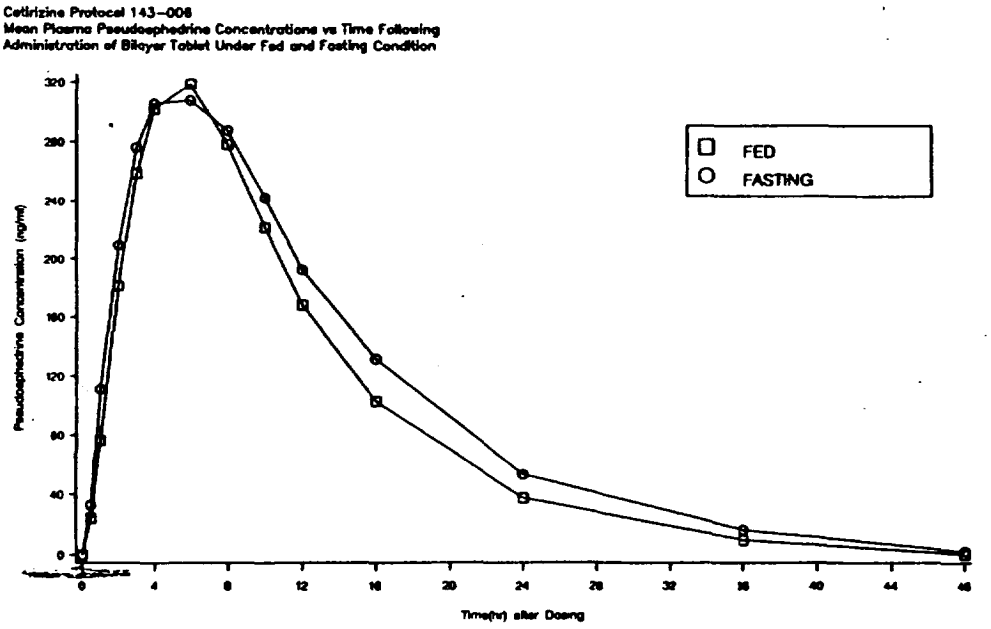
Parameter	Food (mean±SD)	Fasting (mean±SD)	90% Confidence Interval
Cetirizine			
C_{max} (ng/ml)	107 ± 28	153 ± 36	64% - 77%
$AUC_{(0-t)}$ (ng·h/ml)	1253 ± 326	1360 ± 348	-
$AUC_{(0-\infty)}$ (ng·h/ml)	1288 ± 348	1394 ± 369	86% - 99%
T_{max} (h)	2.8 ± 1.4	1.0 ± 0.8	-
$t_{½}$ (h)	8.8 ± 1.8	8.7 ± 2.2	-
Pseudoephedrine			
C_{max} (ng/ml)	339 ± 78	325 ± 69	99% - 109%
$AUC_{(0-t)}$ (ng·h/ml)	4222 ± 1070	4837 ± 1249	-
$AUC_{(0-\infty)}$ (ng·h/ml)	4244 ± 1075	4885 ± 1274	82% - 92%
T_{max} (h)	5.3 ± 1.4	5.3 ± 1.7	-
$t_{½}$ (h)	5.9 ± 0.8	6.6 ± 0.8	-

Food had no significant effect on cetirizine AUC, but C_{max} was significantly decreased, by 30%, and T_{max} was significantly prolonged, by 1.8 h, after the intake of a high-fat meal. These findings are consistent with earlier observations of food interaction with regular Zyrtec (cetirizine) tablets. There was no significant food-effect on the AUC, C_{max} and T_{max} values of pseudoephedrine. However, there was a significant difference in estimated terminal half-life between the treatments, for which no explanation could be found.

Reviewer Comment:
Regular Zyrtec® (cetirizine) Tablets are labeled to be taken either with or without food. Based on the similarity in food effect on cetirizine bioavailability between Zyrtec® (cetirizine) Tablets and the bilayer tablet and the lack of food effect on pseudoephedrine, the bilayer tablet may also be administered either with or without food.

Figure 11.





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ATTACHMENT 1.

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 18, 2000

FROM: Martin K. Yau, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: C. T. Viswanathan, Ph.D. CTV 8/24/2000
Associate Director (Bioequivalence)
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of a EIR Covering NDA 21-150 Cetirizine HCl/Pseudoephedrine HCl 12 Hour Extended Release Tablets (Zyrtec-D), sponsored by Pfizer Pharmaceuticals Inc. New York, New York.

TO: Robert Meyer, M.D.
Director,
Division of Pulmonary Drug Products (HFD-570)

As requested by the Division of Pulmonary Drug Products (HFD-570), the Division of Scientific Investigations conducted an audit of the following bioequivalence study:

Study 143-007: A comparative Single and Multiple Dose Bioavailability Study of Cetirizine(5 mg)/Pseudoephedrine (120mg) Bilayer Tablet BID Versus Co-administration of Cetirizine(5 mg) and Pseudoephedrine(120mg) BID.

The clinical portion of Study 143-007 was conducted at [redacted], on June 29 - July 7, 2000. The analytical portion of the study was conducted at [redacted] on June 26-30, 2000. At the conclusion of the inspections, no Form FDA-483 was issued to [redacted] Form FDA-483 was issued [redacted] The 483 items (Attachment 1) and our evaluation of them are listed below:

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1. Upon the request of the sponsor, specific time points from Subjects 1-24 were selected for re-assay in duplicate. These time points were selected based on the sponsor's past pharmcokinetic experiences with the compound, cetirizine/pseudoephedrine. The results of these duplicate re-assays were not included in [redacted] final analytical report. The final analytical report only included the

initial singular assay and subsequent re-assay of all time points (in duplicate) for all study subjects.

During the inspection we found that Pfizer had selected more than 200 data points (see Attachment 2) from different study subjects and requested — to re-assay (repeat 1, repeat 2). Many of these data were from time points near Cmax and Tmax. The criteria for selecting the data points for re-assay were unknown and were not provided to —

In this inspection, majority of the analytical runs, and in particular those involving data subjected to the re-assay, were reviewed by the FDA investigators. All the runs were found to meet the acceptance/rejection criteria with respect to standard curve and QC samples. The original and re-assay chromatograms were also acceptable with no significant interfering peaks. In addition, there were no source documentation suggesting sample handling, sample processing, internal standard, or instrumental problems. Based on the source documents we audited, there is no reason for Pfizer to select subject samples for re-assay other than that some subject data did not fit the pharmacokinetic profiles

Following a review of the re-assay results (repeat 1, repeat 2), Pfizer informed — that many of the re-assay data were differed from the initial results by more than 15%. Pfizer also questioned — if there were any problems with the assay. Following an in-house investigation, Pfizer and — had decided to discard the re-assay data. These data (repeat 1, repeat 2) were not submitted to the FDA and were not included in the analytical report. During the inspection, — explained to the FDA investigators that they discarded these data because they found problems with the work of one analyst who was involved with sample processing and sample extraction. This analyst was terminated solely based on his work with the Pfizer study.

The analyst issue was investigated during the audit. The — study manager who at the time supervised analyst was interviewed by the FDA investigators. Our investigation, however, revealed that nothing definitive was ever found by — on the work of analyst — We learned that the study manager had discussed the problem with analyst and reviewed his work, but found nothing abnormal. At the end, we cannot conclude that the data generated by this analyst are unreliable as claimed by —

Subsequent to the above incident, — re-assayed all subject samples (repeat 3, repeat 4). The original data, and data from repeats 3 and 4 were included in the analytical

study report. The data used in the pharmacokinetic data analysis, however, were selected according to a Reanalysis and Reporting Flowchart provided by Pfizer (Attachment 3). The date (June 4, 1999) written on the flowchart indicates that the flowchart was created after the assays and re-assays of all subject samples. Data that were not submitted to the FDA (repeat 1 and repeat 2) were obtained during the inspection and displayed in a table (Attachment 4) along with the original and the final re-assay (repeat 3 and repeat 4) data.

Following a review of all the above information obtained during the inspection, we are of the opinion that selection of a large number of subject samples for re-assay without establishing re-assay criteria a priori is biasing the study data. This is particularly true when there are no analytical or clinical reasons to suggest that the original data are inaccurate.

2. **The accuracy and precision of the cetirizine/pseudoephedrine assay were not accurately reported as QC's with significant deviation from the nominal values were considered as an outlier and were excluded from summary statistic tables.**

All QC data generated should be utilized in the calculations of assay accuracy and precision unless the QC data are questionable due to errors involving sample handling, sample processing, internal standard or instrumental conditions. QC data should not be discarded just based on the result of a statistical outlier test. This 483 item, however, should not have impact on the outcomes of the study as no QC data were discarded during acceptance and rejection of analytical runs.

3. **The 48-hour extraction stability data of cetirizine in the 6/17/98 run (File BSQ FI2) was found to be unacceptable. This stability data was not included in the final validation report.**

In the above cited extraction stability study, three replicates from each of three spiked human plasma pools with citirizine concentrations of 10, 400, and 1500 ng/ml were extracted and then injected into the LC/MS/MS after approximately 48 hours at room temperature. The cetirizine concentrations in these spiked samples were found to be 68.4%, 89.3%, 93.4% of the theoretical value at the 10 ng/ml; 79.2%, 78.6%, 84.7% of the theoretical value at 400 ng/ml; 73.5, 80.3, 71.6 of the theoretical value at 1500 ng/ml suggesting cetirizine might exhibit extraction

stability problem. Instead of reporting these results, or to investigate what went wrong with the study, conducted another 48-hour extraction stability study and presented only the results that showed cetirizine is stable in the final analytical report. The above reporting practice is objectionable. Validation data should not be discarded arbitrary without any justifications. This finding however is not likely to affect the study outcomes.

No FDA Form 483 was issued and no significant deficiency concerning the conduct of Study 143-007 was identified at the clinical site. The FDA investigator, however, was able to confirm that a sub-investigator of the study, Alexander Trusov, did not provide financial disclosure information to Pfizer.

Conclusion:

The Division of Scientific Investigations recommends that Study 143-007 be not accepted for review. The pharmacokinetic data of cetirizine and pseudoephedrine generated at are questionable due to the re-assay issue, and the potential problem with one of the analyst (see discussion under Item 1). We recommend that Pfizer should re-analyze the pharmacokinetic data using:

(a) only original data,
(b) only re-assay data (i.e., repeat 3, and repeat 4) for all subjects,

and submit the results of the data re-analysis to OCPB for evaluations. The re-analysis under (a) should eliminate any bias in the data due to re-assays and the use of the Reanalysis and Reporting Flowchart created by Pfizer. The re-analysis under (b) should eliminate the possibility of any errors in the original data introduced by analyst Pending on the outcomes of the data re-analyses, OCPB reviewer can then conclude if Pfizer needs to repeat the study.

Following your review, please attach this transmittal memo to the original NDA submission.

/S/

Martin K. Yau, Ph.D.

DSI Final Classification:

VAI - ~~_____~~

(Due to failure to disclose financial information by one sub-investigator)

VAI - ~~_____~~ **X**

cc:
HFD-45 Lepay
HFD-48 Viswanathan/Yau
HFD-48 CF/RF
HFD-570 Trout/NDA 21-150
HFD-870 SM Huang/Uppoor/Wakelkamp-Barnes
HFR-SW1540 Martinez
HFR-CE450 Grelle
HFR-CE450 Sheehan
Draft: MKY 8/18/00
DSI:5332;O:\BE\EIRCOVER\21150Pfizer.cet.doc

/s/

Monique Wakelkamp-Barnes
1/10/01 10:05:09 AM
BIOPHARMACEUTICS

Young-Moon Choi
1/10/01 10:32:33 AM
BIOPHARMACEUTICS

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Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing Memorandum

NDA:	21-150/N-000	**Sponsor:**	Pfizer Pharmaceuticals
IND:	—		
Brand Name:	Zyrtec-D™ 12 Hour Extended Release Tablets	**Priority Classification:**	3 S
Generic Name:	Cetirizine HCl/ Pseudoephedrine HCl	**Indication(s):**	Seasonal and perennial allergic rhinitis
Drug Class:	H1-receptor antagonist/ Sympathomimetic	**Date of Submission:**	01/18/2000
Dosage Form:	Tablet	**Route of Admin.:**	Oral
Dosing Regimen:	Cetirizine 5 mg/Pseudoephedrine 120 mg BID	**Due Date of Review:**	11/19/2000
Division:	DPE-II (HFD-870)	**Medical Division:**	HFD-570
Reviewer:	Monique Wakelkamp-Barnes, M.D., Ph.D.	**Team Leader:**	Ramana Uppoor, Ph.D.

Items included in NDA (CTD)	*Yes*	*No*	*Request*
Table of Contents present and sufficient to locate reports, tables, data, etc.	✔		
Tabular Listing of All Human Studies	✔		
HPK Summary	✔		
Labeling	✔		
Reference Bioanalytical and Analytical Methods	✔		
Bioavailability and Bioequivalence Studies			
Mass Balance Study		✔	
BA Studies		✔	
Absolute BA		✔	
Relative BA		✔	
BE Studies	✔		
Average BE (single dose and multiple dose)	✔		
Population BE		✔	
Individual BE		✔	
Food-Drug Interaction	✔		
Dissolution Tests (In Vitro-In Vivo Comparison Studies)	✔		
Studies Using Human Biomaterials			
Plasma Protein Binding Studies		✔	
Blood/Plasma Ratio		✔	
Metabolism Studies Using Hepatocytes, Microsomes,etc		✔	
In Vitro Drug Interaction Studies		✔	
Human Pharmacokinetics Studies			
PK, and Initial Safety and Tolerability in Healthy		✔	

Volunteers			
Single Dose		✔	
Multiple Dose		✔	
PK, and Initial Safety and Tolerability in Patient Volunteers		✔	
Single Dose		✔	
Multiple Dose		✔	
Dose Proportionality		✔	
Single Dose		✔	
Multiple Dose		✔	
PK in Population Subsets to Evaluate Effects of Intrinsic Factors			
Ethnicity		✔	
Gender		✔	
Pediatrics		✔	
Geriatrics		✔	
Renal Impairment		✔	
Hepatic Impairment		✔	
PK to Evaluate Effects of Extrinsic Factors			
Drug-Drug Interaction: Effects on Primary Drug		✔	
Drug-Drug Interaction: Effects of Primary Drug		✔	
Population PK studies		✔	
Summary Table of PK/PD Studies		✔	
PK/PD studies in Volunteers		✔	
PK/PD studies in Patients		✔	
Individual Datasets for all PK and PK/PD studies in electronic format		✔	
Other			
Genotype/Phenotype Studies		✔	
Chronopharmacokinetics		✔	

This application is filable.
(if not filable, discuss reasons why below:)

1. QBR questions: (Key Issues to be Considered)

- Is there bioequivalence between the proposed combination product and the co-administration of the individual active ingredients?

- The formulation is a bilayer tablet, containing cetirizine in an immediate release form and pseudoephedrine in a sustained release form. Is there any interaction with food?

2. Reviewer remarks

- The package insert for Zyrtec Tablets already contains information on drug interaction between cetirizine and pseudoephedrine.

- On 3/10/2000, a request was submitted to DSI to initiate an audit (see below).

3. Summary

NDA 21-150/N-000 for Zyrtec-D 12 Hour Extended Release Tablets was submitted 01/18/2000 by Pfizer Pharmaceuticals, Inc. The product contains 5 mg of cetirizine HCl and 120 mg of pseudoephedrine HCl in an extended release tablet formulation. The formulation is a bilayer tablet, containing cetirizine in an immediate release form and pseudoephedrine in a sustained release form, intended for twice-daily administration at a total daily dose of 10 mg cetirizine HCl and 240 mg of pseudoephedrine HCl. The proposed indication is seasonal and perennial allergic rhinitis with nasal congestion, for patients 12 years and older. BID dosing is currently only approved for Zyrtec Syrup (5 mg cetirizine/5 ml), 2.5 mg BID for children age 2-5 yrs.

The sponsor is planning to demonstrate c

The Human Pharmacokinetics and Bioavailability section of the NDA includes a total of four studies, two of which were conducted in the U.S. and two in Belgium. The first U.S. study (143-006) is a food interaction study, with the aim to examine the influence of intake of a standard high-fat meal on the bioavailability of the combination tablet in healthy subjects. The second study (143-007) is a single and multiple dose study, comparing the combination tablet to the co-administration of a commercially available 5 mg Zyrtec (cetirizine HCl) tablet plus a standard pseudoephedrine product (Sudafed LA, 120 mg). The objective of the study is to demonstrate bioequivalence for a single dosing situation, as well as for steady-state. The two non-U.S. studies are intended as supportive documentation, comparing the co-administration of cetirizine and pseudoephedrine as single ingredients and as a combined capsule formulation.

The combination formulation used in studies 143-006 and 007 is identical to the to-be-marketed formulation. The size of the batch (, used in these studies is of the intended commercial batch size.

Notes:

1) On 03/10/2000, a request was submitted to DSI to initiate an audit. The purpose of the audit will be to evaluate the bioequivalence study (study 143-007), including the analytical methodology, as well as to investigate the refusal to submit financial disclosure information by one of the study investigators.

2) The package insert for Zyrtec® Tablets already contains information on drug interaction between cetirizine and pseudoephedrine.

4. Comments to the sponsor

1) The sponsor is requested to provide multi-point dissolution profiles for both active ingredients in the bilayer tablet for the different media investigated (water, 0.1N HCl, pH 4.5 buffer and pH 7.4 buffer) and to provide the individual and mean values of the percentage dissolved for each sampling time in a table format. The sponsor is also asked to provide multi-point dissolution profiles and tables, for both active ingredients, using the dissolution medium that was selected (0.1N HCl), for the same batch as used in study 143-007.

2) The sponsor is requested to submit the following items in electronic format (disk, zipdisk or CD-ROM):

a) The Human Pharmacokinetics and Bioavailability Overview (Vol. 12, pages 6-5 through 6-23).

b) Study 143-006: the Final Study Report (Vol. 12, pages 6-24 through 6-45), the Summary Tables (Vol. 12, pages 6-46 through 6-81), the Figures (Vol. 12, pages 6-82 through 6-87) and the Subject Data Listings under Section 13 (Vol. 12, pages 6-285 through 6-305).

c) Study 143-007: the Final Study Report (Vol. 12, pages 6-306 through 6-332), the Summary Tables (Vol. 12, pages 6-333 through 6-401), the Figures (Vol. 12, pages 6-402 through 6-413) and the Subject Data Listings under Section 13 (Vol. 13 pages 6-875 through 6-907).

3) The sponsor is asked to clarify whether Sudafed LA 120 mg caplets (Warner Lambert), that were used in study 143-007, are identical to Sudafed 12 hour tablets (Warner Lambert) that are referenced in the PDR.

5. Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II, finds NDA 21-150 (submitted 01/18/2000) acceptable for filing. Comments 1, 2 and 3 should be conveyed to the sponsor as appropriate.

Reviewer Date

/S/ 04/20/2000

Monique Wakelkamp-Barnes, M.D., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Concurrence: Ramana Uppoor, Ph.D., teamleader

/S/ 04/19/2000

cc NDA 21-150:
Division File
HFD-850: Peter Lee
HFD-870: Shiew-Mei Huang
HFD-570: Ramana Uppoor
Monique Wakelkamp-Barnes
Richard Nicklas
Gretchen Trout
CDR: Barbara Murphy