CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20786

PHARMACOLOGY REVIEW(S)

MAR 1 4 1997

DIVISION OF PULMONARY DRUG PRODUCTS

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Original Review No. 1

NDA 20-786

Date of Submission: 12/20/96

Information to be Conveyed to Sponsor: YES (X), NO ( )

Reviewer: Lawrence F. Sancilio, Ph.D.

Date Review Completed: 3/12/97

Sponsor: Hoechst Marion Roussel, Inc.
10236 Marion Park Drive
P.O. Box 9627
Kansas City, Missouri 64134-0627

Drug Names: Fexofenadine, MDL 16,455A, TAM (terfenadine active metabolite) and Pseudoephedrine HCl (Allegra-D)

Chemical Names: Fexofenadine HCl, Benzeneacetic acid, 4-[1-(hydroxydiphenylmethyl)-1-piperidinyl]butyl'-α,α- dimethyl-, hydrochloride salt ±

Pseudoephedrine HCl, [S-(R*.R*)]-α-[1-(methylamino)ethyl]-benzenemethanol hydrochloride

Molecular Weight: Fexofenadine HCl, 538.13
Pseudoephedrine HCl, 201.7

Related INDs and NDAs: IND NDA 18-849 (Terfenadine)
NDA 19-664 (Seldane-D, Terfenadine and Pseudoephedrine HCl)
IND
NDA 20-625 Fexofenadine HCl

Pharmacological Classes: Fexofenadine HCl, H_1 receptor blocker
Pseudoephedrine HCl, indirect sympathomimetic

Indication: Treatment of symptoms associated with Seasonal Allergic Rhinitis

Route: Oral.

Formulation: 60 mg of fexofenadine HCl and 120 mg of pseudoephedrine HCl in a tablet form containing a fexofenadine HCl layer and a pseudoephedrine HCl layer. The components of the tablet are:

Component	Mg/tablet
Fexofenadine HCl Layer	
Fexofenadine Hcl	60
Microcrystalline Cellulose (Avicel PH101)	
Pregelatinized Starch	
Microcrystalline Cellulose (Avicel PH102)	
Croscarmellose Sodium	
Magnesium Stearate	
Pseudoephedrine HCl Layer	
Pseudoephedrine HCl	120
Carnauba Wax	
Stearic Acid Flakes	
Colloidal Silicon Dioxide	

All the inert components have been used in approved products.

Proposed Dose Level

Allegra-D is a fixed combination coated tablet consisting of 60 mg immediate release fexofenadine HCl and 120 mg of sustained release pseudoephedrine HCl. The daily dose of Allegra-D will be one tablet twice a day.

Preclinical Studies Submitted: None

Review and Evaluation

Terfenadine is a pro drug being metabolized primarily to an active acid metabolite, fexofenadine HCl. The exposure of fexofenadine HCl following oral administration to rats and dogs was greater following the oral administration of terfenadine. Consequently, the toxicity profile of fexofenadine HCl was best determined from the oral administration of terfenadine rather than the oral administration of fexofenadine HCl. The toxicological data for terfenadine were used in the approval of fexofenadine HCl in 1996.

The doses of fexofenadine HCl and pseudoephedrine HCl were the same as those in the marketed combination product, Seldane D, i.e., 60 mg of terfenadine and 120 mg of pseudoephedrine HCl. The daily dose is two tablets.

No preclinical data are needed for approval of this NDA since both fexofenadine HCl (NDA 20-625 review is attached) and pseudoephedrine hydrochloride (Final Monograph for OTC Nasal Decongestant Products) are approved drugs by the oral route. Further, pseudoephedrine hydrochloride is considered safe and effective under the Final Tentative monograph for OTC Cold, Cough, Allergy Bronchodilator and Antihistasminic Combination Drug Products. The Agency will conditionally approved this NDA if the sponsor meets the requirements for an acceptable human pharmacokinetics approach. The sponsor should provide data showing that the proposed combination is bioequivalent to the marketed fexofenadine HCl 60 mg capsules and the commercially available 120-mg pseudoephedrine HCl modified release caplet. Since the pharmacology and toxicology of both compounds are well known, the evaluation will focus on the preclinical data cited in the labeling.

Labeling Review

The **additions** and ~~**deletions**~~ **(strikeout)** are listed under the sections cited below.

ALLEGRA-D™

(fexofenadine HCl 60 mg and pseudoephedrine HCl 120 mg) Tablets

CINICAL PHARMACOLOGY

Mechanism of Action

Pseudoephedrine hydrochloride is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. Pseudoephedrine hydrochloride is recognized as an effective agent for the relief of nasal congestion due to allergic rhinitis. Pseudoephedrine produces peripheral effects similar to those of ephedrine and central effects similar to, but less intense than, amphetamines. It has the potential for excitatory side effects (*Ref 4,*

2 pages purged

DRAFT Labeling

Recommendations

This NDA is approvable from a preclinical standpoint.

Changes as cited above in the labeling are recommended.

Lawrence F. Sancilio 3/12/97

Lawrence F. Sancilio, Ph.D.
Pharmacologist/Toxicologist

Clyde Johnston March 14, 1997

cc: Orig. NDA 20-786
HFD-570/Division File
HFD-570/LSancilio
HFD-570/Worobec
HFD-570/CSO

Attachment: NDA 20-625 review

Approved by J.Sun

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STRANGE

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DIVISION OF PULMONARY DRUG PRODUCTS
EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
REVIEW

NDA 20-625

Date of Submission: 7/31/95

Information to be Conveyed to Sponsor: YES (X), NO ( )

Reviewer: Lawrence F. Sancilio, Ph.D.

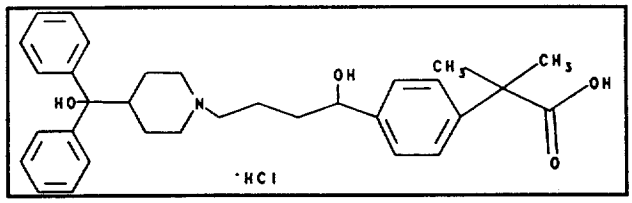
Date Review Completed: 6/24/96

Sponsor: Marion Merrell Dow Inc.
Marion Park Drive
P.O. Box 9627
Kansas City, Missouri 64134-0627

Drug Name: Fexofenadine HCl, MDL 16,455A, TAM (terfenadine active metabolite)
MDL 9,918 (terfenadine)

Chemical Name: Benzeneacetic acid, 4-[1-(hydroxydiphenylmethyl)-1-piperidinyl]butyl'-α,α-dimethyl-, hydrochloride salt ±

Structure:



Molecular Weight: 538.13, $C_{32}H_{39}NO_4$. HCl

CAS No.:138452-21-8

Related INDs and NDAs: IND · NDA 18-849 (terfenadine)

Pharmacological Class: H1 receptor blocker

Indication: Treatment of Seasonal Rhinitis

Route: Oral

Formulation: 60 mg capsule containing croscarmallose sodium, gelatin, lactose, microcrystalline cellulose and pregelatinized starch.

Amended Reviews, Reviewer Dates:

NDA 19-949, Terfenadine, C. G. Oberlander, 4/28/83

Background

Fexofenadine is the active metabolite of terfenadine, a marketed H_1 receptor blocker with little or no sedative properties. The uniqueness of fexofenadine is that unlike terfenadine, fexofenadine does not prolong QT_c intervals or inhibit the delayed rectifier potassium current channel. Consequently, fexofenadine is unlikely to produce Torsades de point, a cardiac arrhythmia seen in terfenadine patients under certain conditions.

List of Unpublished Reports and Pertinent Preclinical Articles Submitted

PHARMACOLOGY

The following were reviewed.

1. Mechanism of the cardiotoxic actions of terfenadine, JAMA 1993;269:1532-1536, vol. 16, p P174.

2. Interactions of the nonsedating antihistamines astemizole and loratadine with a voltage-dependent K+ channel cloned from human heart, No. C-94-0645-D, vol. 16, p 207.

3. Antiallergic effects of terfenadine on immediate type hypersensitivity reactions. Immunopharmacol. Immunotoxicol. 9:257-279, 1987, vol. 16, p 220.

4. Intracellular calcium release induced by histamine releasers and its inhibition by some antiallergic drugs, Ann Allergy 56:464-469, 1986, vol. 16, p 379.

The following were not reviewed since they were previously reviewed or were not relevant.

Second-generation H1-receptor antagonists, Annals of Allergy 1991; 66:5-19, vol. 15, p 79 .

Histamine and 5-hydroxytryptamine (serotonin) and their antagonists. In: The Pharmacological Basis of Therapeutics, 7th ed., Gilman AG, Goodman LS, Rall TW, and Murad F, ed. MacMillan Publishing Co., New York, 1985, vol. 15, p 95.

Cardiotoxic effects with convulsions in terfenadine overdose, Br Med J. 1989:298, vol. 15, p 133.

Pharmacokinetics and biotransformation studies of terfenadine in man, Arzneim-Forsch/Drug Res. 1982,32: 1185-1190, vol.15 p 133.

Effects of intravenous infusion of terfenadine and MDL 16,455A on QTc interval in anesthetized rabbits, N. C.-93-0235-R, vol. 15, p 140.

Effect of intravenous terfenadine infusion on QTc interval in anesthetized dogs, No. C-93-0234-R, vol. 16, p 180.

Effect of repeated ascending doses of terfenadine and MDL 16,455A, the acid metabolite of terfenadine, on the electrocardiogram of dogs, No. C-93-0248-R, vol. 15, p 164.

Effect of terfenadine, MDL 16,455A, and the stereoisomers MDL 15,171 and MDL 15,172 on action potential and membrane currents in guinea pig ventricular cells, No. C-91-0084-R, vol. 15, p 193.

Time course of the antihistaminic effects of MDL 16,455A and terfenadine on histamine skin wheals in guinea pigs, No. C-93-0145-R, vol. 15, p 206.

Oral effects of terfenadine and MDL 16,455A on histamine wheals in guinea pigs, No. C-84-0054-R, vol. 15, p 218 .

The effects of MDL 16,455A on the vascular effects of histamine and phenylephrine in the dog hindlimb preparation, No. C-84-0068-R, vol. 15, p 233.

The effects of terfenadine or chlorpheniramine on the vascular effects of phenylephrine and histamine in the dog hindlimb preparation, No. C-83-0054-R, vol. 15, p 245.

Antagonism of histamine-induced bronchoconstriction by MDL 9,918 and MDL 16,455A in anesthetized guinea pigs, No. C-93-0215-R, vol. 15, p 260.

Competitive receptor binding studies with MDL 16,455A and its enantiomers to rat brain

histamine-H1 receptors, No. C-93-0247-R, vol. 15, p 271.

Antihistaminic effect of MDL 16,455A, a major metabolite of terfenadine, No. C-84-0066-R, vol. 15, p 279.

Primary CNS evaluation of MDL 16,455A, No. C-93-0233-R, vol. 15, p 1.

General pharmacology of an antiallergic drug terfenadine, No. J-92-0010-R, vol. 16, p 11.

Effects of terfenadine and MDL 16,455A on histamine wheals in guinea pigs, No. C-84-0067-R, vol. 16, p 121.

Effect of MDL 16,455A on the isolated guinea pig ileum, No. C-77-0015-R, vol. 16, p 132.

Effect of RMI 16,218A on the isolated guinea pig ileum. A comparison with terfenadine, No. C-77-0014-R, vol. 16, p 146.

Block of a human delayed rectifier K+ channel by terfenadine and its metabolites, No. C-93-0182-R, vol. 16, p 165 .

Cumulative dose-response curves: Technique for the making of dose-response curves in isolated organ and the evaluation of drug parameters. Arch Int Pharmacodyn Ther 1963;143:299-330, vol.15, p 304.

PHARMACOKINETICS

Absorption/Excretion

1. Pharmacokinetics in Beagle dogs following oral administration of terfenadine, No. J-91-0005-D, vol. 19, p 277.

Distribution

1. Tissue distribution of radioactivity in the rat following a single oral dose of [14C]MDL 16,455A, No. K-93-0668-D, vol. 16, p 244.

2. One-month dietary pharmacokinetic study of terfenadine in CD-1 mice (PK 206), No.K-93-0411-D, vol. 17, p 259

3.One-month dietary pharmacokinetic study of terfenadine in Sprague-Dawley rats (PK 233), No. K-93-0409-D, vol. 17, p 275.

4. Terfenadine and fexofenadine plasma concentrations following a 10 mg/kg oral dose of terfenadine in male Sprague-Dawley rats, No. K-93-0528-D, vol. 19-P123

Metabolism

1. Incubation of fexofenadine with rat and human hepatic microsomes, No. K-93-0186-D, vol. 20, p 202.

The following were not reviewed since they were previously reviewed or were not relevant.

Plasma concentrations of MDL 16,455 in male and female Sprague-Dawley rats given a single 5 g/kg oral suspension doses of MDL 16,455A (PK-236), No. K-93-0364-D, vol. 17 p 86.

Acute oral toxicity of MDL 16,455A administered to dogs, No. C-90-0240-T, vol. 17, p 101.

Plasma concentrations of MDL 16,455 in female Beagle Dogs given a 500 mg/kg oral suspension dose of MDL 16,455A (PK-235), No. K-93-0370-D, vol. I7, p 114.

Plasma concentration of MDL 16,455 and terfenadine in Beagle dogs given 80 mg/kg/day capsule doses of terfenadine for one month (PK 234), No. K-93v0431-D, vol.17, p 292.

Maternal and fetal plasma concentrations of MDL 16,455 and terfenadine in Sprague-Dawley rats given daily 300 mg/kg oral doses of terfenadine (PK-251), No.K-94-0222-D, vol. 18, p 1.

Maternal and fetal plasma concentrations of MDL 16,455 and terfenadine in Dutch-Belted rabbits given daily oral 300 mg/kg doses of terfenadine (PK-250), No. K-94-0159-D, vol., 18 p 27.

MDL 16,455, MDL 17,523, and terfenadine in mouse plasma, No. WARS-2135V, vol.18, p 186.

The pharmacokinetics and oral bioavailability of MDL 16,455A in Sprague-Dawley rats, No. K-93-0442-D, vol. 19, p 54.

The bioavailability and urinary excretion of terfenadine acid metabolite (MDL 16,455A) and terfenadine in Sprague-Dawley rats, No. K-93-0071-D, vol. 19, p 80.

Terfenadine and Fexofenadine plasma concentrations following a 10 mg/kg oral dose of Terfenadine in male Sprague-Dawley rats, No. K-93-0528-D, vol.19, p 123.

A comparison of the absorption and elimination of oral MDL 16,455A and terfenadine in Beagle dogs, No. K-93-0145-D, vol. 19, p 141.

Plasma concentrations of MDL 16,455 in Beagle Dogs given 90, 300, or 900 mg/kg/day oral doses of MDL 16,455A in a one-month toxicity study (TI93-033), No. K-93-0460-D, vol. 19, p 195.

Physiological parameters in laboratory animals and humans, Pharm Res. 10:1093-1095,1993, vol. 19, p 216.

Metabolism studies on terfenadine (II), No. J-94-0006-D, vol.19, p 220.

Pharmacokinetics in Beagle dogs following oral administration of terfenadine, No. 91-0005-D, vol. 19, p 277.

Protein binding of MDL 16,455 in serum of healthy, drug-free human subjects, No. C-88-0198-D, vol. 20, p 21.

Metabolic disposition of terfenadine in laboratory animals.
Arzneim-Forsch/Drug Res. 32(11):1173-1178, 1982, vol. 20, p 11.

Pharmacokinetics, p 238. In: Drugs and the pharmaceutical sciences,
ed. James Swarbrick. 1975:vol 1, vol. 6, p 18.

Predicted human whole body and tissue exposures to radioactivity from an oral dose of 14C-labeled terfenadine, No. K-93-0470-D, vol. 20, p 46.

Metabolic studies on terfenadine (I): Absorption, distribution, metabolism and excretion in rats, No. J-94-0005-D, vol. 20, p 58.

Marion Merrell Dow Inc., No. K-93-0186-D, vol. 20, p 202.

Relative Bioavailability of MDL 16,455 from Two Oral Suspension Formulations in Dogs, No. K-95-0092-D, vol. 20, p 272.

Validation of a method based on liquid chromatography with fluorescence detection for quantification of fexofenadine and terfenadine in rat plasma, No. K-93-0634-D, vol. 20, p 295.

Validation of a method based, on liquid chromatography with fluorescence detection for quantification of fexofenadine and terfenadine in dog plasma, No. K-93-0500-D, vol. 20, p 327.

Validation of a method based on liquid chromatography with fluorescence detection for quantification of terfenadine in rat and dog urine, No. K-95-0441-D, vol. 20, p 361.

The pharmacokinetics and oral bioavailability of MDL 16,455A in Sprague-Dawley rats, No. 93-0442-D. vol. and page number not given.

TOXICOLOGY

Genotoxicity

1. MDL 16,455A: Mutagenicity test in the Salmonella-Escherichia coli/mammalian-microsome reverse mutation assay, No.K-94-059-T, vol. 18, p 51.

2. MDL 16,455A: Evaluation of the Chinese Hamster ovary cell/hypoxanthine-guanine-phosphoribosyl transferase (CHO/HGPRT) forward mutation assay, No. K-94-0621-T, vol.18, p 80.

3. MDL 16,455A: Evaluation of an in vitro chromosomal aberration assay utilizing rat lymphocytes, No. K-9k-062-T, vol. 18, p 118.

4. MDL 16,455A: Evaluation in the mouse bone marrow micronucleus test, No. K-94-0635-T, vol. 18, p 151.

The following were not reviewed since they were previously reviewed or were not relevant.

Acute oral study with MDL 16,455, terfenadine metabolite I, in mice. No. J-2-0020-T, vol. 17, p 54.

Acute oral toxicity of MDL 16,455A in mice and rats, No. C-90-0241-T, vol. I7, p 68.

Acute oral toxicity of MDL 16,455A administered to dogs. Project Report C-90-0240-T, vol. 17, p 101.

MDL 16,455A: Exploratory acute oral toxicity study in Beagle dogs, No. -934046-T, vol. 17, p 129.

Fexofenadine: Two-week oral tolerance screen in Beagle dogs, No. 93-0048-T, vol. 17, p 143.

Fexofenadine: One-month oral toxicity study in Beagle dogs, 93-0051-T, vol.17 p 154.

REVIEW

PHARMACOLOGY

1. Mechanism of the cardiotoxic actions of terfenadine, JAMA 1993;269:1532-1536, vol. 16, p 174.

Episodes of Torsades de pointes in humans are the result of a quinidine like action. This was attributed to blockade of the delayed rectifier potassium current. Terfenadine like quinidine blocked the potassium current in isolated feline myocytes while its metabolite, fexofenadine, was inactive at concentrations up to 5μM which is up to 30 times higher than that of terfenadine which produces a half maximal inhibition of the delayed rectifier potassium current in isolated feline myocytes.

2. Interactions of the nonsedating antihistamines astemizole and loratadine with a voltage-dependent K+ channel cloned from human heart, No. C-94-0645-D, vol. 16, p 207.

Using a delayed rectifier K+ channel (fHK) cloned from the human heart, both astemizole and loratidine blocked the K+ channel fHK with an IC_{50} of 1μM. However, the two drugs differed in their effect on current deactivation. Astemizole like terfenadine in a time dependent manner slowed current deactivation while loratidine did not affect the current deactivation.

3. Antiallergic effects of terfenadine on immediate type hypersensitivity reactions. Immunopharmacol. Immunotoxicol. 9:257-279, 1987, vol. 16, p 220.

The activity of terfenadine on immediate hypersensitivity reactions were compared with its 2 metabolites, fexofenadine and Metabolite II. The results are shown in the following table.

Model	Route	Potency (Terfenadine: 1)		
		Fexofenadine	Metabolite II	Ketotifen
Passive Cutaneous Reaction in Rats	p.o.			2
Antigen-Induced Bronchospasm in Guinea Pigs	p.o.	0.5	0.07	2.5
Histamine Release from Rat Mast Cells Induced by Compound 48/80	In Vitro	0.33	Inactive at 100 μM	0.1

Model	Dose /Concentration Activity Was Noted	
	Terfenadine	Ketotifen
Antagonism of ↑Ca Uptake of Mast Cells Induced by Compound 48/80	2-10 μM	Not Tested
↑ Cyclic AMP Levels		
Rat Mast Cells	5-20 mg/kg p.o.	Inactive at 20 mg/kg p.o.
Guinea Pig Lungs	5-20 mg/kg p.o.	Inactive at 20 mg/kg p.o.
↑ Adenylate Cyclase Levels		
Rat Lung, Ex Vivo	5-20 mg/kg p.o.	Inactive at 20 mg/kg p.o.
Phosphodiesterase Activity		
Rat Lung, Ex Vivo	Inactive at 20 mg/kg p.o.	Inactive at 20 mg/kg p.o.

4. Intracellular calcium release induced by histamine releasers and its inhibition by some antiallergic drugs, Ann Allergy 56:464-469, 1986, vol. 16, p 379.

Terfenadine and fexofenadine and not Metabolite II at 10 μM inhibited Ca release from stored intracellular Ca. This was shown with mast cells who require Ca ions to release histamine. Consequently, in a calcium free media the Ca comes from released stored intracellular Ca. By blocking the release of histamine induced by Compound 48/40 in a Calcium free medium, terfenadine and fexofenadine thus exert their effect by inhibiting the release of stored Ca.

Summary of Pharmacology (Reviewed Reports/Articles)

Fexofenadine was different from terfenadine as it did not inhibit the delayed rectifier current in isolated feline myocytes at a concentration (5 μM) that was 30 times higher than an effective concentration of terfenadine. Terfenadine was similar to astemizole and different from loratidine on their effects on the voltage- dependent K+channel cloned from the human heart. Although all 3 drugs inhibit this channel at 1 μM, terfenadine like astemizole slowed the current deactivation while loratidine showed no effect on the current deactivation.

Studies were conducted with terfenadine and its 2 metabolites, fexofenadine and Metabolite II. Orally, terfenadine was twice as potent as fexofenadine and 14 times as potent as Metabolite II in protecting guinea pig from anaphylactic shock. Terfenadine was 3 times as potent as fexofenadine in inhibiting Compound 48/80 induced release of histamine from rat mast cells. Metabolite II was inactive in this model. Studies showed that terfenadine inhibited the release

of histamine by terfenadine and fexofenadine by inhibiting the release of intracellular Ca^{++}. Terfenadine was different from ketotifen since it 1. antagonized the increased uptake of Ca^{++} of mast cells induced by Compound 48/80, 2. increased the cyclic AMP levels of rat mast cells and guinea pig lungs and 3. increased the adenylate cyclase levels of rat lungs ex vivo. Both terfenadine and ketotifen were not phosphodiesterase inhibitors.

PHARMACOKINETICS

Absorption/Excretion

1. Pharmacokinetics in Beagle dogs following oral administration of terfenadine, No. J-91-0005-D, vol. 19, p 277.

Method

M Beagle dogs (12-13 kg) were given a 60 mg tablet of terfenadine. Blood samples were drawn at 0.5, 1, 2, 3, 4, 6, 10, and 24 h. Urine and feces were collected at 24 h for 72 h.

Results

Plasma level for terfenadine was less than 50 ng/ml; no terfenadine was found in the urine and fecal excretion accounted for 0.8% of the dose. The results for the 2 major metabolites, fexofenadine and MDL 4829 (N-dealkylated terfenadine), are summarized in the following table.

APPEARS THIS WAY
ON ORIGINAL

Parameter	Fexofenadine	MDL 4829
C_{max}, ng/ml	1770	71
T_{max}, h	2.7	2.5
AUC_{0-24h}, ng.h/ml	13263	857
$T_{1/2}$, h	2.0	12.0
Excretion, % of Dose		
Urine	0-24 h, 3.7% 24-72 h, 0.4%	0-24 h, 6.8% 24-48 h, 1.6% 48-72 h, 0.3
Feces	0-24 h, 34% 24-48 h, 14% 48-72 h, 2%	0-72 h, 0.8%

Conclusion

In beagle dogs, approximately 5 mg/kg p.o. (1 x 60 mg tablet), of terfenadine was rapidly metabolized predominantly to fexofenadine and to minor degree to the N-dealkylated terfenadine. Very little or no terfenadine was found in the plasma, urine and feces. The primary excretory route for the metabolite, fexofenadine, was fecal in contrast to urinary for the N-dealkylated metabolite.

Distribution

1. Tissue distribution of radioactivity in the rat following a single oral dose of [14C]MDL 16,455A, No. K-93-0668-D, vol. 16, p 244.

Ten mg/kg of radioactive fexofenadine were administered by gavage as a single dose to M Sprague-Dawley and Long Evans rats. At various periods up to 72 h, animals were sacrificed and plasma levels and tissues were analyzed for radioactivity. In the Sprague-Dawley rat 23 tissues were examined while in the Long Evans rat levels were determined only in the plasma, eyes, skin (pigmented area) and erythrocytes. The results are summarized in the following table.

Parameter	Sprague Dawley Rat	Long Evans Rat
C_{max}, μg equiv./ml	0.019	0.049
$AUC_{0\text{-}TF}$[a], μg equiv. x hr/ml	0.092	0.179
$T_{1/2}$, terminal, hr	13.3	1.42
Highest Concentration of Radioactivity		
AUC $_{0\text{-}TF}$[a] μg equivalents x hr/g		
Stomach	105	
Small Intestine	149	
Large Intestine	119	
Liver	9.8	
Excretion, 0-72 hr		
% of Radioactive Dose		
Urine	0.87	1.5
Feces	91.7	90.2

[a] AUC from the time 0 to the last measureable C^{14} concentration

2. One-month dietary pharmacokinetic study of terfenadine in CD-1 mice (PK 206), No.K-93-0411-D, vol. 17, p 259

Method

Animals: M (26-32 g)and F (24-29g) CD mice were used.

Compound: Terfenadine (Lot No. Z 0575-007)

Formulation: Terfenadine was administered in the diet at a daily dose of 150 mg/kg; this dose was the HD in the carcinogenicity study.

Plasma Levels: Blood from 12 mice/sex was obtained at 4 h intervals from 8 PM on day 30 to 4 PM on day 31. Concentrations of terfenadine and 2 metabolites, fexofenadine and MDL 17523 were determined from the plasma by HPLC with fluorescence detection. The lower quantification limit for each compound was 25 ng/ml in a sample volume of 0.2 ml.

Results

The results are summarized in the following table.

Compound	C_{max}, ng/ml M	F	AUC_{24h} ng.h/ml M	F
Terfenadine	< 25	< 25	[a]	[a]
Fexofenadine	355	689	5,655	11,444
MDL 17523	< 25	< 25	[a]	[a]

[a]Could not be determined due to undetectable levels

Conclusion

In a 30 day dietary administration of 150 mg/kg terfenadine to mice, no detectable levels of terfenadine or one of its metabolites, MDL 17523, was detected. Fexofenadine, another metabolite, was found in high levels. The C_{max} and $AUC_{24\,h}$ in the F were approximately 2 x those found in M.

3.One-month dietary pharmacokinetic study of terfenadine in Sprague-Dawley rats (PK 233), No. K-93-0409-D, vol. 17, p 275.

Method

Animals: M (232-275 g)and F (159-201 g) Crl:CD (SD)BR (VAF/PLUS) rats were used.

Compound: Terfenadine (Lot No. 70733)

Formulation: Terfenadine was administered in the diet at a daily dose of 150 mg/kg; this dose was the HD in the carcinogenicity study.

Plasma Levels: Blood from 3 rats/sex was obtained at 4 h intervals from 8 PM on day 28 to 8 PM on day 29. Concentrations of terfenadine and its metabolite, fexofenadine, were determined from the plasma by HPLC with fluorescence detection. The lower quantification limits were 5 ng/ml for fexofenadine and 10 ng/ml for terfenadine in a sample volume of 0.5 ml.

Results

The results are summarized in the following table.

Compound	C_{max}, ng/ml		AUC_{24h} ng.h/ml	
	M	F	M	F
Terfenadine	96	152	1,175	[a]
Fexofenadine	675	702	11,618	9,091

[a] Could not be determined since the levels in many animals were not detectable.

Conclusion

In a 30 day dietary administration of 150 mg/kg terfenadine to rats, the plasma levels for fexofenadine were in both sexes markedly higher than those seen with terfenadine. The respective C_{max}s and $AUC_{24\ h}$s for fexofenadine were essentially similar in both sexes.

4. Terfenadine and fexofenadine plasma concentrations following a 10 mg/kg oral dose of Terfenadine in male Sprague-Dawley rats, No. K-93-0528-D, vol. 19, p 123.

Method

Terfenadine at 10 mg/kg was administered by gavage as a micellar solution to M Sprague-Dawley rats. Groups of 3 rats were sacrificed at 0, 0.25, 0.5, 1, 1.5, 2, 3, 5, 7, 10, 14, 18, and 24 h and the plasma assayed for terfenadine and fexofenadine.

The results are shown in the following table.

Parameter	Terfenadine	Fexofenadine
C_{max}, ng/ml	35.7	257
T_{max}, h	1.5	1.5
$AUC_{0-\infty}$, ng.h/ml	61.3	683.8

Conclusion

In rats terfenadine was administered as a micellar solution at dose of 10 mg/kg p.o. It was

rapidly metabolized to fexofenadine since at 1.5 h, the plasma level of fexofenadine was approximately 7 x higher than the parent compound. In addition the AUC for fexofenadine was approximately 10 x higher that for terfenadine.

Metabolism

1. Incubation of fexofenadine with rat and human hepatic microsomes, No. K-93-0186-D, vol. 20, p 202.

Method

Fexofenadine (30 μM) was incubated with microsomes from rats for 2 h and from humans 1 h. The rat microsomes were from untreated animals and from animals treated with dexamethasone to induce P-450 enzymes. Human microsomes were obtained from 2 normal volunteers. They were characterized for P-450 enzymes.

Results

The results are summarized in the following table.

Microsome Preparation	Results
Rat Untreated, naive (2 h incubation)	No change in fexofenadine substrate
Dexamethasone-treated (1 h incubation)	No change in fexofenadine substrate; Vehicle controls showed a chromatographic peak which co-eluted with MDL 4829 (N-dealkylated fexofenadine). Mass spectroscopy was not performed to confirm the presence of MDL 4829.
Human Untreated, naive (1 h incubation)	8% decrease in fexofenadine substrate; a small peak related to MDL 4829 was detected.

Conclusion

In human microsomes and possibly in rat microsomes, fexofenadine undergoes oxidative dealkylation at a very slow rate.

Summary of Pharmacokinetics

In Beagle dogs receiving approximately 5 mg/kg p.o. (1 x 60 mg tablet) of terfenadine, rapid and complete metabolism occurred since little or no detectable levels of parent compound were found. Two metabolites, fexofenadine and MDL 4829, N-dealkylated terfenadine, were found in the plasma, urine and feces. Fexofenadine was the prominent metabolite as its $AUC_{0\text{-}24\ h}$ was 15 x higher than that for MDL 4829. Fexofenadine excreted mainly in the feces accounted for 50 % of the dose. Most of excretion of MDL 4829 which accounted for 8% of the dose was urinary.

Following the administration of a single dose of 10 mg/kg p.o. of radiolabeled fexofenadine to Sprague-Dawley and Long Evans rats, The Cmax in the Long Evans rat was higher than that in the Sprague-Dawley rat; however, the reverse was seen with their AUCs. The terminal half life in the Sprague-Dawley rat was approximately twice that of the Long Evans rat. In distribution studies, the highest levels based on AUC, terfenadine was seen in the small intestine, large intestine, stomach and liver. None of the assayed tissues from the Long Evans rats showed any radioactivity indicating that fexofenadine was not distributed to any degree in the eyes, skin and erythrocytes. In both strains, excretion was predominantly in the feces as > 90% of the total radioactivity was found in the feces.

In Sprague-Dawley rats terfenadine was administered 10 mg/kg p.o. as a micellar solution. Terfenadine was rapidly metabolized to fexofenadine as the C_{max} and $AUC_{0\text{-}\infty}$ for fexofenadine were approximately 7 x and 10 x that of terfenadine, respectively.

Two dietary 30 day pharmacokinetics studies of terfenadine were conducted in mice and rats. Both species received a daily dose of 150 mg/kg p.o., the dose used in the carcinogenicity studies. In the mouse, terfenadine was metabolized predominantly to fexofenadine since no detectable levels of terfenadine and MDL 17523 were found in the plasma on day 30. F showed an $AUC_{24\ h}$ and C_{max} that were approximately twice those in the M.

In rats, the plasma was assayed for terfenadine and fexofenadine. The C_{max}s for fexofenadine were similar in both sexes; they were approximately 5-7 x higher than terfenadine. However, the $AUC_{24\ h}$s of fexofenadine although similar in both sexes, were 10 x that for terfenadine in the M. However, the AUC_{24h} for terfenadine in the F could not be determined since in many animals, terfenadine levels were not detectable indicating the it was metabolized faster in the F than in the M.

TOXICOLOGY

Genotoxicity

1. MDL 16,455A: Mutagenicity test in the Salmonella-Escherichia coli/mammalian-microsome reverse mutation assay, No.K-94-059-T, vol. 18, p 51.

GLP signed statement: Yes

Study Dates: 3/23/94-4/25/94.

Site the study was conducted:

Method

Organisms: Salmonella typhimurium TA98, TAI00, TA1535 and TA1537 and Escherichia coli WP2uvrA. Liver microsomal enzyme reaction mix (S9 mix) was prepared from M Sprague-Dawley rats injected i.p. with Aroclor.

Positive Controls are listed in the following table:

Organism	With S9, Conc. (μg/plate)	Without S9, Conc. (μg/plate)
Salmonella typhimurium		
TA98	2-Aminoanthracene, (2.5)	2-Nitrofluorene (1.0)
TA100	2-Aminoanthracene, (2.5)	Na azide, (2.0)
TA1535	2-Aminoanthracene, (2.5)	Na azide, (2.0)
TA1537	2-Aminoanthracene, (2.5)	ICR-191 (2.0)
Escherichia coli		
WP2uvrA	2-Aminoanthracene, (25)	N-Nitroquinoline-N- oxide, (1.0)

With each organism the tests were conducted twice in triplicate for the test compound and in duplicate for the positive controls. The response to the positive control should be a 3-fold increase in the number of revertants per plate over that of the vehicle. A positive response and a valid assay were a reproducible dose response and ≥3 X increase in the number of revertant colonies with more than 1 dose.

Compound: Fexofenadine Lot No. 73038

Test for Cytotoxicity: For TA100 and WP2uvrA, 10 concentrations ranging from 6.67 μg - 5000 μg/plate were tested. Cytotoxicity was seen at 3330 and 5000 μg/plate (33-37%) in the absence of S9 and at 5000 μg/plate (15%) in the presence of S9.

Concentrations: 100, 333, 667, 1000 and 3300 μg/plate in the presence and absence of S9 mix for each organism.

Vehicle: Dimethylsulfoxide

Results

Fexofenadine, was not genotoxic in the presence and absence of S9 mcg/plate. The respective positive controls produced more than a 3 fold increase in the number of revertant colonies.

Conclusion

Fexofenadine was not mutagenic in the bacterial assay. This was a valid and acceptable assay.

2. MDL 16,455A: Evaluation of the Chinese Hamster ovarycell/hypoxanthine-guanine-phosphoribosyl transferase (CHO/HGPRT) forward mutation assay, No. K-94-0621-T, vol.18, p 80.

GLP signed statement: Yes; Fexofenadine sample was not audited.

Study Dates: 2/15/94-8/26/94.

Site the study was conducted:

Method

Chinese hamster CHO-K_1-BH_4 cell line was used. Liver microsomal enzyme reaction mix (S9 mix) was prepared from M Sprague-Dawley rats injected i.p. with Aroclor.

Vehicle: Dimethylsulfoxide

Test Compound: Fexofenadine (Lot No. 73038)

Positive Controls are listed in the following table:

With S9, Conc. (μg/ml)	Without S9, Conc. (μg/ml)
20-Methylcholanthrene , 4	Ethylmethane sulfonate, 621

An acceptable test was a statistical increase in the mutation frequency by the positive control, and the mutation frequency in the negative controls should be within the historical controls. Test compound is positive if it produces a statistical significant, dose related, reproducible increase in mutation frequency. Tests were conducted in duplicate whenever possible at each concentration.

Cytotoxicity Study: 200 cells/petri dish; concentrations tested, 218.75-3500 μg/ml (5 concentrations with and without S9. No cytotoxicity was noted at the concentrations tested.

Results

The highest concentration, 3500 μg/ml, in the absence and presence of S9, showed a 10.3% and 24.2% of control cell survival. The test compound showed no mutagenicity under both conditions and the positive control showed a high number of revertant cells. This was a valid and acceptable assay.

Conclusion

Fexofenadine was not mutagenic in the Chinese Hamster (CHO/HGPRT) forward mutation assay.

3. MDL 16,455A: Evaluation of an in vitro chromosomal aberration assay utilizing rat lymphocytes, No. K-9k-062-T, vol. 18, p 118.

GLP signed statement: Yes; Fexofenadine sample was not audited.

Study Dates: 2/15/94-8/26/94.

Site the study was conducted:

Method

Lymphocytes were taken from M Sprague-Dawley rats, 13-15 weeks old. At each concentration the number of cells/assay were 200 for the test compound and 100/ positive

control. Liver microsomal enzyme reaction mix (S9 mix) was prepared from M Sprague-Dawley rats injected i.p. with Aroclor. Two complete assays were conducted, a preliminary and confirmatory test. In the preliminary test the cells were harvested at 24 h after treatment while in the confirmatory test, the cells were harvested at 24 and 48 h post treatment.

Vehicle: Dimethylsulfoxide

Test Compound: Fexofenadine (Lot No. 73038)

Positive Controls are listed in the following table:

With S9, Conc. (μg/ml)	Without S9, Conc. (μg/ml)
Cyclophosphamide, 6	Mitomycin, 0.5

An acceptable test was a statistical increase in the chromosomal aberration frequency by the positive control, and the chromosomal aberration frequency in the negative controls should be within the historical controls. Test compound is positive if it produces a statistical significant, dose related, reproducible increase in chromosomal aberration frequency. Each test was conducted in triplicate.

Mitotic Indexes were determined in both tests. Concentrations tested, Assay 1, 35, 116.7, 350, 1167 and 3500 μg/ml with and without S9. Assay 2, 350, 1167, 3000 and 3500 μg/ml with and without S9.

Results

Mitotic Index (MI): Assay 1: At 3500 μg/ml the MI was reduced by 70% in the absence of S9 and 96.6% in the presence of S9. Assay 2: At 3500 μg/ml the MI was reduced by 65% and 100% in the absence of S9 at 24 and 48 h, respectively. At 3000 and 3500 μg/ml in the presence of S9, the MI was reduced by 100% at 24 and 48 h. At 1167 μg/ml, the MI was reduced by 13% at 24 and 36% at 48 h.

Chromosomal Aberration: Assay 1 and 2: No chromosomal aberration was noted in the absence of and presence of S9. In both tests the positive controls showed a marked increase in the number of chromosomal aberrations in the absence and presence of S9. The assay was valid and acceptable.

Conclusion

Fexofenadine was not clastogenic in the lymphocyte chromosomal aberration assay.

4. MDL 16,455A: Evaluation in the mouse bone marrow micronucleus test, No. K-94-0635-T, vol. 18, p 151.

GLP signed statement: Yes

Study Dates: 2/5/94-9/2/94

Site the study was conducted:

Method

Animals: 9 Week old M and F CD-1 Charles River mice (5/sex/group).

Test Compound: Fexofenadine (Lot No. 73038)
Positive Control: Cyclophosphamide

Formulation: Suspension containing 0.5% Methocel/ 0.5%Tween 80, 20 ml/kg for vehicle and fexofenadine treated animals and 10 ml/kg for reference treated animals.

Time of sacrifice: 24, 48 or 72 h for fexofenadine treated animals and 24 h for positive control group. 1000 cells from bone marrow of each animal were examined and the ratio of the number of micronucleated polychromatic erythrocytes (MN-PCE) to the number of normal polychromatic erythrocytes (NPE) was determined.

Doses: Vehicle (20 ml/kg by gavage), 625 mg/kg (LD), 1250 mg/kg (MD), 2500 mg/kg (HD). The HD was selected since a dose of 5000 mg/kg could not be given due to poor consistency of the suspension made it difficult to administer with a dosing needle. Reference: Cyclophosphamide: 120 mg/kg p.o.

Results

Dose ranging study: 2500 mg/kg was not toxic over a 4 day period.

At doses of 625, 1250 and 2500 mg/kg, fexofenadine produced no increase in the number of micronucleated polychromatic erythrocytes in M and F mice. Cyclophosphamide caused a marked increase in the frequency of abnormal erythrocytes (M, 28 vs 0.8; F, 40.3 vs 1.6). This a valid and acceptable study.

Conclusion

Fexofenadine was not mutagenic in the mouse micronucleus test.

Summary of Genotoxicity

Fexofenadine was not mutagenic in the Salmonella-Escherichia coli/mammalian microsome reverse mutation, the (CHO/HGPRT) forward mutation and the rat lymphocyte chromosomal aberration in vitro assays and in the mouse bone marrow micronucleus in vivo test.

OVERALL SUMMARY AND EVALUATION

Terfenadine is a non sedative H_1 receptor blocking drug. Terfenadine is metabolized to fexofenadine, a compound that possesses H_1 receptor blocking properties. Since the biotransformation to fexofenadine through the P450 system is fairly rapid in animals and in humans, the antihistaminic activity of terfenadine is attributed to a large degree to fexofenadine. The advantage of fexofenadine over terfenadine is that it does not possess the undesirable cardiac actions of terfenadine alone. Consequently, the potential for fexofenadine to produce Torsades de pointes, a potential fatal cardiac arrhythmia, is minimal. This cardiac action is seen with terfenadine in allergic patients especially those being treated with drugs like erythromycin that block the P450 enzymes thereby increasing the level of terfenadine.

The H_1 receptor blocking properties of fexofenadine in vitro and in vivo models are summarized in the following table. Its potencies relative to terfenadine ranged from 0.2 to 3.

Model	Activity
Binding Studies Rat Cerebral Cortex Membranes	2 x Potency of Terfenadine
Histamine-Induced Skin Wheal Test in Guinea Pigs	p.o., 0.4-0.6 x Potency of Terfenadine i.v., 3 x Potency of Terfenadine
Histamine-Induced Bronchoconstriction in Guinea Pigs	p.o., Equipotent to Terfenadine
Anaphylactic Shock in Guinea Pigs	p.o., 0.5 x Potency of Terfenadine
Histamine-Induced Contraction of Guinea Pig Ileum	0.3-1 x p.o., x Potency of Terfenadine
Histamine-Induced Vasodepression in Perfused Dog Hindlimb	i.v., Approximately equipotent to Terfenadine

Terfenadine may also exert its effectiveness in allergic diseases by inhibiting the release of histamine from mast cells. Compound 48/80 causes the release of histamine from rat peritoneal mast cells in a calcium free medium. This is due to a release of intracellular released calcium. Terfenadine, fexofenadine and disodium chromoglycate at 10 μM inhibited the release of histamine induced by Compound 48/80; this indicates that these compounds may exert this effect by affecting intracellular calcium or by exerting a stabilizing effect on mast cell. membrane.

Other properties that fexofenadine may possess since they were determined in vivo and ex vivo only for terfenadine. This is suggested since terfenadine is metabolized predominantly to fexofenadine. These properties observed at 5- 20 mg/kg p.o. were: 1.↑ Cyclic AMP levels in rat mast cells, 2.↑ Cyclic AMP levels in guinea pig lungs, and 3. ↑ Adenylate cyclase Levels in rat lungs.

The cardiac actions of terfenadine compared with fexofenadine are shown in the following table. The results show that fexofenadine possesses little or no effect on the heart; consequently, the potential for causing Torsades de pointes clinically in little or none at all.

Model	Activity	
	Fexofenadine	Terfenadine
In Vitro Studies		
Blockade of Human Delayed Rectifier K+ Channel, fKH, EC_{50}, μM	214	0.367
Blockade of Delayed Rectifier K+Current in Feline Myocytes, EC_{50}, μM	Inactive at 5	0.17
Blockade of Delayed Rectifier K+Current Using Embryonic Kidney Cells Cloned from Human Heart, Potency	0.0017	1
In Vivo Studies		
Increased QTC Interval in Anesthetized Rabbits, Compound Infused i.v. over 1 h	No effect at 10 mg/kg	23.5% at 1 mg/kg
QTC Interval in Unanesthetized Dogs, Compound given p.o. twice daily for 5 days	No effect at 3 and 10 mg/kg; At 30 mg/kg ↓ QTC	10 mg/kg ↑ the QTC >10% by day 3

In the general pharmacology studies involving the central nervous, cardiovascular, gastrointestinal, coagulating and renal systems, terfenadine possesses no potential clinical adverse effects.

In pharmacokinetics studies, fexofenadine at 30 mg/kg p.o. administered as a solution (98.5% propylene glycol-1.5% glacial acetic acid) to rats showed a 2.9% systemic bioavailability. This was attributed to 2 factors, poor absorption (24%) and high clearance (30 ml/min/kg). In dogs, receiving 8.7 and 27 mg/kg p.o. as a solution the absorption was 53.7 and 47.3%, respectively, showing greater absorption than the rat.

The following table compares the pharmacokinetics of a single dose p.o. fexofenadine in rats, dogs and humans. The dose in the rat (30 mg/kg) was slightly higher than that in the dog (27 mg/kg); both were higher than humans (2.4 mg/kg). In comparing dogs with rats, the dog showed a markedly higher C_{max}, $AUC_{0-\infty}$, elimination half-life (initial and terminal phases) and a

much lower clearance. The t_{max}s and MRTs (mean residence time) were similar. The 17 fold difference in the clearance resulting in longer elimination half lives contributed to higher levels in the dog. With humans, the percent bioavailability fell between that of the dog and rat, and the clearance was much lower than either the rat or dog. When the data was normalized based on mg/kg , the AUC and C_{max} for humans fell between the rat and dog.

Parameter	Rats 30 mg/kg	Dogs 27 mg/kg	Humans 2.4 mg/kg
C_{max}, ng/ml	457	26,640	427
Normalized C_{max}, ng/ml	15	987	178
T_{max}, h	0.5	0.7	1-3
$AUC_{0-\infty}$, ng.h/ml	436	107,505	2682
Normalized $AUC_{0-\infty}$, ng.h/ml	15	3,982	1,118
Elimination Half-Life			
Initial Phase, h	0.4	1.96	
Terminal Phase, h	4.8	33.5	13
Cl_s, ml/min/kg	30	1.75	0.00079
MRT_b, h	3.7	4.0	
% Bioavailability	2.9	47.3-53.7	33

Distribution studies following the administration of 10 mg/kg p.o. fexofenadine were determined in Sprague-Dawley rats. Based on AUC_{0-TF}, fexofenadine was predominantly distributed in the stomach, small intestine, large intestine and to a lesser degree in the liver. In this study 91.7% and 0.87% of the radioactive dose was excreted in the feces and urine, respectively.

Following the administration of 300 mg/kg p.o. of terfenadine to pregnant animals, levels of fexofenadine were determined in the plasma levels of the dams and in the plasma levels of the fetuses. Fexofenadine was found in greater amounts in the plasma of the fetuses of the rabbits (477 ng/ml) than in the fetuses of rats (223 ng/ml); the AUC in the rabbits was approximately 9 x higher than that in the rat showing different pharmacokinetics. The dam/fetal ratio of the plasma levels in the rabbit was higher than rat (52 vs 4.1).

The following table compares the excretion pattern of fexofenadine in rats, dogs and humans. Humans, dogs and rats show similar excretory pattern, i.e., fexofenadine was excreted predominantly in the feces by way of the biliary tract and a small amount in the urine.

Species Dose, mg/kg	% of Dose Excreted	
	Feces	Urine
Rat		
10, p.o.	87.2	1.2
1, i.v	82.4	11.1
1, portal vein	84.5	4.7
Dog		
1, i.v.	78.1	13.1
Human		
	80	11

In the excretion studies no metabolites were found in the rat (feces), dog (feces) and human (urine and feces). In an in vitro study, fexofenadine was incubated with rat microsomes alone, in microsomes from dexamethasone-treated rats to induce P-450 enzymes and in human microsomes. After 1 h incubation a small amount of the N-dealkylated fexofenadine was found. Thus, fexofenadine undergoes oxidative dealkylation in both species at a slow rate. Since this metabolite was not found in the primary excretory route of rats, dogs and humans, fexofenadine undergoes little or no metabolism in rats, dogs and humans.

In binding studies with plasma, the binding of fexofenadine to plasma proteins of rats and humans was similar and slightly lower than the binding to dogs. At concentrations from 0.1-0.8 μg/ml, the binding ranged from 88.4%-89.7% for rats, 88.9%-90.8% for humans and 93.0%-94.3% for dogs.

In toxicity studies fexofenadine was administered p.o. to rats, mice and dogs in single dose studies and in multidose studies up to 1 month in rats and dogs. The results from the reproductive and longer term toxicity studies for terfenadine were acceptable for fexofenadine since 1. terfenadine is predominantly metabolized to fexofenadine which contributes substantially to its antihistaminic activity, and 2. greater exposure to fexofenadine occurred when terfenadine was administered particularly in rats. The systemic bioavailability for fexofenadine in rats following p.o. administration of terfenadine was approximately 10 x higher (29% vs 2.9%) than when fexofenadine was administered.

The following compares the single dose p.o. toxicity studies of fexofenadine and terfenadine in mice and rats. In rats and mice both fexofenadine and terfenadine were similar as their LD_{50}s were > 5000 mg/kg p.o. This may be attributed to poor absorption due to poor aqueous solubility. From this submission, poor systemic bioavailability in rats to fexofenadine also contributed to the low toxicity. Fexofenadine was also not toxic in dogs.

Compound Species	Doses, mg/kg, p.o.	Results
Fexofenadine		
Mice	4310 5146	No toxicity, LD_{50} > 5146 mg/kg p.o.
Rat		
	4310 5146	No toxicity, unabsorbed compound in feces LD_{50} > 5146 mg/kg p.o.
Dogs		
	1000 2000	Ataxia, LD_{50} > 2000 mg/kg p.o.
Terfenadine		
Mice		LD_{50} > 5000 mg/kg p.o.
Rats		LD_{50} > 5000 mg/kg p.o.

The results from multidose studies (10-14 days) in dogs with fexofenadine and terfenadine are summarized in the following table. Terfenadine was administered daily in single and/or divided doses. Terfenadine was more toxic than fexofenadine.

Compound	Doses, mg/kg, p.o.	Results
Fexofenadine	10, 30, 100, 300	No toxicity
Terfenadine	150, 500, 1000	At all doses, emesis, ↓ food consumption, ↓ body weight gained; 1000 mg/kg, pituitary, renal and cardiac changes were seen.

In a 3 month toxicity study in rats terfenadine was 10, 100 and 300 mg/kg were administered by gavage. Pharmacokinetics were not conducted in this study, but for a dose of 150 mg/kg from a 30 day dietary study, the AUC ranged from 9,091-11,618 ng.h/ml for F and M, respectively. This was 3.4-4.3 x the AUC for the clinical therapeutic dose. Thus, the AUC for the 300 mg/kg is higher than 4.3. At all doses the reticulocyte count was increased. The M showed an increase in the absolute and relative weights of the seminal vesicles at the 100 and 300 mg/kg p.o. At 300 mg/kg, there was a decrease in the absolute and relative weights of the heart and prostate. The F showed a dose related increase in the absolute and relative weights of the pituitary and thyroid and adrenal glands. Unabsorbed (?) terfenadine was found in 4 M and 9 F 300 mg/kg treated animals. No histopathology was noted.

No chronic toxicity studies was conducted on terfenadine in rats.

In a 1 month toxicity study in dogs, fexofenadine was administered 90, 300 and 900 mg/kg daily in 3 divided doses. The C_{max}s and AUCs were dose related, and the F showed higher AUCs than the M. No accumulation or decrease in plasma levels were seen. At 900 mg/kg salivation and emesis were seen; there was a dose related decrease in absolute and relative thymus weights at the MD and HD. No histopathology was seen. The NOEL was 90 mg/kg p.o. Based on the above results in the 10- 14 day studies, these results further support that in the dog fexofenadine was less toxic than terfenadine.

In dogs, the 2 year study with terfenadine was acceptable since terfenadine (80 mg/kg/day, LOEL) resulted in an exposure to fexofenadine based on AUCs that was 8.5-17.4 x the human exposure (2.4 mg/kg/day). In this study 30 and 100 mg/kg were dosed initially. The low dose was well tolerated. After 2-3 weeks due to toxicity, i.e., tremors, convulsions, impaired and death in 2/8 animals, the daily 100 mg/kg dose was reduced to 80 mg/kg after the treatment was temporarily stopped to allow for recovery. At this dose some central nervous system effects and constipation was seen during the latter part of the study; upon histological

examination, 2/2 M showed tubular atrophy in the testes at 80 mg/kg. The NOEL was 30 mg/kg.

In the carcinogenicity studies in mice and rats, 50 and 150 mg/kg of terfenadine were administered in the diet. No neoplasms were seen in the mice. In rats there was some increase in the incidence of adenocarcinomas in the uterus (C, 0/18, 50, 3/22, 150, 2/18) and mammary glands (C, 0/18, 50, 0/22, 150, 3/18) ; these were not considered significant to pursue when reviewed by one reviewer, C. Oberlander. When Dr. Taylor reviewed these data in 1990, two of his recommendation was: 1. to request the historical control data, and to request another carcinogenicity study if there are other findings that warrant this. This reviewer feels that since: 1. the incidence was not statistically significant when analyzed by the Fishers Exact test, 2. the incidence was low, and there was no dose relationship at least with the uterine neoplasm, 3. fexofenadine was not genotoxic, and 4. terfenadine has been on the market for a long period with no reported incidence or any indication of neoplasms, these findings are not considered clinically important. The following table shows that at the 150 mg/kg dose level, the AUC in F mice was twice that of the M while in rats, the AUCs were comparable, and that the ratio of the mice/rat AUC to the clinical dose AUC ranged from 2.1 to 4.3. The AUC for the lower dose was not reported. By today's standard, the MTD was not tested in the mouse. However, the ratios of the AUCs for the 150 mg/kg dose in mice and rats to the AUC for the human clinical exposure were 2.1 and 4.3. The above 4 factors were considered in conceiving this conclusion.

Parameter	Mice 150 A	Rats 150 A	Relative to Human AUC A/B Mice	Rats
$AUC_{24\,h}$, μg.h/ml, M	5.66	11.6	2.1	4.3
F	11.44	9.1	4.3	3.4
Human $AUC_{0-\infty}$ for 2.4 mg/kg dose: 2.682 μg.h/ml, B				

Fexofenadine was not mutagenic in the Salmonella-Escherichia coli/mammalian microsome reverse mutation, the (CHO/HGPRT) forward mutation and the rat lymphocyte chromosomal aberration in vitro assays and in the mouse bone marrow micronucleus in vivo test. This was further supported by studies in which terfenadine was inactive in the mouse bone marrow micronucleus in vivo test at 500, 1000 and 2000 mg/kg.

Based on reproductive toxicity studies with terfenadine in which significant exposure to

fexofenadine was achieved, no teratogenic effects were seen in mice, 50, 100 and 200 mg/kg p.o. by gavage, in rats, 50, 150 and 300 mg/kg p.o. by gavage or dietary administration and in rabbits, 30, 100 and 300 mg/kg p.o. by dietary administration. In rats administration of 50, 150 and 300 mg/kg in the diet did not affect fertility. At 150 and 300 mg/kg there was decreased food consumption and body weight gained in the dams and decreased body weight and survival of the fetuses. No AUC was reported in mice for 200 mg/kg p.o. However, in a month dietary study the AUC for 150 mg/kg the AUC_{24h} was 11,444 ng.h/ml. This was 4.3 x the human therapeutic exposure of 2,682 ng.h/ml for a daily dose of 160 mg. The AUC_{24h}s for the 300 mg/kg p.o. were 11,927 ng.h/ml for the rat and 101,631 ng.h/ml for the rabbit. They were 4.4 and 37.9 times the human therapeutic exposure.

Recommendation

Based on the preclinical data, there is no objection to approval of fexofenadine.

Comments for further studies: None.

Labeling

Changes were recommended in the submitted label. They are listed in **BOLD** under the Clinical Pharmacology (page 2), Carcinogenesis, Mutagenesis, Impairment of Fertility, Pregnancy and Overdosage Sections of the label which is appended.

Lawrence F. Sancilio 6/24/96

Lawrence F. Sancilio, Ph.D.
Pharmacologist/Toxicologist

June 24, 1996

cc. /Division File, NDA 20-625
/MSevka, HFD-570
/MHimmel, HFD-570
/C.S.O., HFD-570
/LFSancilio, HFD-570
/ JSun, HFD-570

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20786

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

Date: DEC 15 1997

NDA#:	**20-786**
Applicant:	**Hoechst Marion Roussel, Inc.**
Name of Drug:	**Allegra-D (Fexofenadine HCL 60 mg - Pseudoephedrine HCL 120 mg Combination)**
Indication:	**Seasonal Allergic Rhinitis**
Documents Reviewed:	**12-20-96 Volumes 30-39;** **1-17-97 Volumes 1.30-1.33;** **4-30-97 Volumes 1-2, 14;** **5-20-97 Volumes 4.1-4.4 (electronic data in Volume 4.4)**
Statistical Reviewer:	**Barbara Elashoff, M.S.**
Medical Input:	**Alexandra Worobec, M.D.**

Summary

Biopharmaceutical studies demonstrating bioequivalence between Allegra-D and each component of Allegra-D were submitted for approval of this product. The results of one of the single-dose studies did not provide conclusive evidence that the decongestant component, pseudoephedrine, was bioequivalent to Allegra-D (see Dr. Gillespie's review). Therefore, at the request of the Agency, the sponsor submitted the results of a double-blind, active-controlled clinical trial, Study 35, to evaluate Allegra-D in reducing nasal congestion symptoms. Study 35 had three treatment groups: Allegra (fexofenadine), Eltor (pseudoephedrine), and Allegra-D (fexofenadine + pseudoephedrine).

Results from Study 35 support the conclusion that there were statistically significant differences in reduction of

1. histamine-mediated symptoms (sneezing; rhinorrhea; itchy nose, palate and/or throat; and itchy, watery, red eyes), between Allegra-D and pseudoephedrine, and
2. nasal congestion, a non-histamine-mediated symptom, between Allegra-D and fexofenadine,

at the end-of-dosing interval *and* over the 12-hour period prior to the 7 PM dose.

A five-point rating scale was used to assess nasal congestion (NCS). The average reduction in NCS (defined as the average change between baseline and treatment period at the end-of-dosing interval - over the previous 1 hour) was -0.29 units for fexofenadine, -0.35 units for pseudoephedrine, and -0.48 units for the combination product.

The primary reason the Agency requested that the sponsor submit the results of Study 35 was to evaluate Allegra-D in reducing nasal congestion symptoms at the end-of-dosing interval in comparison to fexofenadine, an antihistamine. This assessment will be the focus of this review.

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1. Background Information

Allegra-D is a combination of two approved products, Allegra (fexofenadine) and Eltor (pseudoephedrine). Four adequate and well-controlled Phase III studies were submitted in July 1995 to support the approval of fexofenadine in NDA 20-625. The statistical and medical reviews for NDA 20-625 (June 19, 1996), concluded that the results of Studies 10, 23 and 24 were evidence of the efficacy of fexofenadine in the reduction of total symptom score in the treatment of seasonal allergic rhinitis patients. Eltor is a form of 12-hour sustained 120 mg pseudoephedrine, approved for the indication of relief of non-histamine related symptoms, such as nasal congestion.

Instead of Phase III controlled clinical trials, biopharmaceutical studies designed to demonstrate bioequivalence between Allegra-D and each component of Allegra-D were initially submitted for approval of this application. According to the biopharmaceutical reviewer, Dr. Gillespie, the results of the single-dose study comparing the pseudoephedrine and Allegra-D, did not provide evidence that pseudoephedrine was bioequivalent to Allegra-D. Therefore, at the Agency's request, the applicant has submitted one active-controlled clinical trial, Study 35, to support the efficacy of the combination product in reducing histamine- and non-histamine-mediated symptoms. Study 35 is a parallel-design, double-blind, randomized clinical trial with three treatment groups: Fexofenadine, Pseudoephedrine, and Allegra-D. Pseudoephedrine was the comparator for the histamine-mediated symptoms (sneezing; rhinorrhea; itchy nose, palate and/or throat; and itchy, watery, red eyes). Fexofenadine acted as the control for the non-histamine-mediated symptom, nasal congestion. The Agency requested the results of this study to evaluate Allegra-D's role in reducing nasal congestion symptoms at the end-of-dosing interval. This review presents and evaluates the results of Study 35.

2. Active-controlled Clinical Trial, Study 35

2.1 Objectives

The primary objective of this study was to compare the safety and efficacy of Allegra-D (fexofenadine HCl 60 mg-pseudoephedrine HCl 120 mg combination) versus each of its components in the treatment of ragweed seasonal allergy.

Secondary objectives were: 1) to study the population pharmacokinetics of Allegra-D; 2) to evaluate the effect of the treatments on patient productivity impairment (work and school); and 3) to assess patient's health state preferences.[1]

Reviewer Comment

As noted above, the primary reason the Agency requested that the sponsor submit the results of Study 35 was to evaluate the combination product, Allegra-D, in reducing nasal congestion symptoms at the end-of-dosing interval in comparison to fexofenadine, an anti-histamine. This assessment will be the focus of this review.

[1] The results of the analyses on patient productivity impairment can be found on page 136 of the Clinical Study Report of Study 35 which is in Section 9, Volume 1, Page 145 of the April 30, 1997 submission. Patient's health state preferences evaluation analyses were not presented in the study report. The sponsor stated that they would be presented in a separate report.

2.2 Design

Study 35 was a multicenter, randomized, double-blind, parallel-design safety and efficacy study of 600 ragweed-allergic patients. The study was conducted during the ragweed pollen season. The duration of the study for a given patient was approximately 3 weeks, during which s/he was seen by the investigator on 4 occasions: 2 screening/baseline visits (weeks 1 and 2), and two treatment visits (weeks 3 and 4). Patients first entered into a three to five day single-blind placebo lead-in period to qualify for the study and establish their baseline allergy symptoms. Patients who met study criteria were then randomized to double-blind study medication:

- fexofenadine HCl 60 mg BID;
- pseudoephedrine HCl 120 mg BID; or
- combined product Allegra-D, fexofenadine HCl 60 mg - pseudoephedrine HCl 120 mg BID;

and treated for two weeks. The randomization was stratified based upon the sum of the three most recent 12-hour reflective TSS established during baseline. A patient with a sum of 32 or less was in the "low" sum baseline group. A patient with a sum of greater than 32 was in the "high" baseline group.

Efficacy variables were based on the patient's assessment of symptom severity. A total of 5 symptoms were assessed: nasal congestion; sneezing; rhinorrhea; itchy nose, palate and/or throat; itchy, watery, red eyes. A 5-point subjective rating scale was used. The following symptom scores were used to assess the efficacy of the treatments: Total Symptom Score (TSS = Sum of Individual Symptom Scores), Nasal Congestion Score (NCS), and Total Symptom Score minus Nasal Congestion Score (TSS-NCS).

Throughout the study patients assessed their allergy symptoms daily at 7:00 PM (± 1 hour) prior to taking study medication. Symptoms were assessed **reflectively** (for the previous 12-hour period) and **instantaneously** (for the previous 1-hour period).

Additionally, patients assessed their symptoms at bedtime, 1 to 3 hours after the **first** 7:00 PM dose of study medication during the single-blind baseline lead-in and the double-blind treatment period (see Table 1). The bedtime symptoms were assessed **instantaneously** (for the previous 1-hour period). In the fexofenadine application, the bedtime assessment following the first dose was subsequently used to support the data from the onset of action study. This may be the reason that a single bedtime assessment was included in the design of the study.

Table 1: Assessments

Assessments	Type of Assessment	# of Times Recorded:
7 AM	Reflective*	Every day of study
	Instantaneous**	Every day of study
7 PM	Reflective	Every day of study
	Instantaneous	Every day of study
Bedtime	Instantaneous	Only recorded twice: 1. After 1st dose of single-blind medication during placebo lead-in period 2. After 1st dose of double-blind medication during treatment period

* Reflective (patient assesses symptoms over previous 12 hours)

** Instantaneous (patient assesses symptoms over previous hour)

The primary efficacy variables were

1) Change from baseline in average daily 7:00 PM reflective TSS-NCS: comparing the combination to pseudoephedrine alone; and
2) Change from baseline in average daily 7:00 PM reflective NCS: comparing the combination to Allegra (fexofenadine) alone.

> "These primary efficacy variables were selected to demonstrate that each active component of the combination product makes a contribution to the claimed effects. This objective can be met by demonstrating that 1) the combination is more effective than the decongestant for histamine-mediated symptoms (TSS-NCS), and 2) the combination is more effective than the antihistamine for the non-histamine-mediated symptom (NCS)."
>
> Final Protocol (May 9, 1996) p.18.
> April 30, 1997 submission; S9-V2-P24.

The protocol also stated that each simple null hypothesis was to be tested at the two-sided 0.05 level.

Reviewer Comment
Since the primary reason that the Agency requested the results of this study was to evaluate Allegra-D in reducing nasal congestion symptoms at the end-of-dosing interval in comparison to fexofenadine, the Agency was particularly interested in the change from baseline in average daily 7:00 PM instantaneous *NCS: (not* reflective *NCS, one of the two primary efficacy variables specified in the protocol).*

Change from baseline was computed by subtracting the average 7PM reflective or instantaneous TSS-NCS (or NCS) during the placebo lead-in period (baseline) from the average 7PM reflective or instantaneous TSS-NCS (or NCS), respectively, during the double-blind period (postbaseline). If there were any missing values of a symptom in the symptom complex, the missing values were imputed using the average of the non-missing values of the complex. If any of the daily TSS scores were missing, then the average TSS over the treatment period was calculated using the recorded values.

Reviewer Comment
In the NDA for fexofenadine, if the individual symptoms of any day in the diary were missing, then that day's TSS evaluation was coded as missing for the analyses. One concern with the method used in the present NDA is that nasal congestion is a non-histamine-mediated symptom and should not be used to impute the histamine-mediated symptoms (and vice versa). This concern was related to the sponsor and the sponsor responded that there was only one case in which nasal congestion was missing and other symptoms were recorded[2]. In this case, the other symptoms were not used *to impute this symptom. In addition, there were 30 cases of missing histamine-mediated symptoms (where nasal congestion was recorded), and nasal congestion* was not used *to impute the data. Only the histamine-mediated symptom(s) that were recorded were used to impute the missing histamine-mediated symptom(s). Furthermore, there were only 31 missing symptoms out of a potential total of 24,523 (0.13%) symptom records (computed using the number of days a patient recorded at least one symptom). Thus, the results of these imputations would not be expected to have seriously affected the conclusions of the trial.*

Secondary efficacy variables were analyzed to further characterize the efficacy of the combination. These were:

1) Change from baseline in average 7:00 PM reflective TSS;

[2] Memorandum, October 21, 1997.

2) Change from baseline in average 7:00 PM instantaneous TSS, NCS, and TSS-NCS;
3) Change from baseline in bedtime instantaneous TSS, NCS, and TSS-NCS; and
4) Change from baseline in average 7:00 PM reflective individual symptom scores.

2.3 Statistical Methods

As previously stated, this trial had two objectives, thus there were two null hypotheses:

Null Hypothesis 1: There is no difference between 120 mg pseudoephedrine alone and the combination with respect to TSS-NCS;

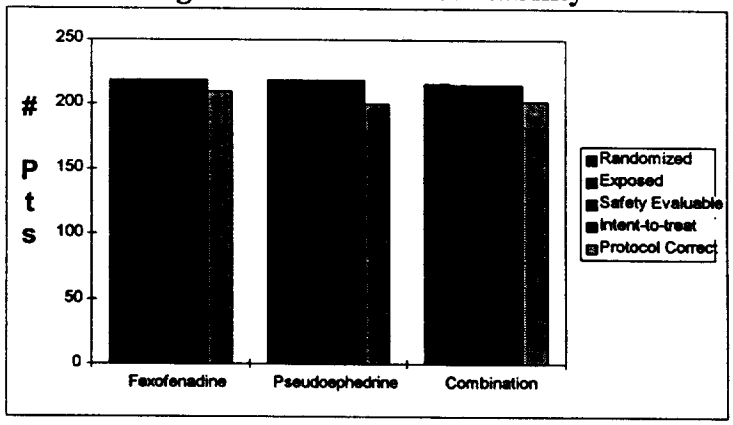
Null Hypothesis 2: There is no difference between 60 mg fexofenadine alone and the combination with respect to NCS.

Each hypothesis was tested as a simple null hypothesis using a two-sided, $\alpha = 0.05$ level of significance (as stated in protocol). The primary efficacy variables were analyzed using an analysis of covariance (ANCOVA) model in which either the baseline average TSS-NCS (null hypothesis 1), or baseline average NCS (null hypothesis 2), was the covariate, and center and treatment were included as independent classification variables.

Both the site-by-treatment interaction and the baseline-by-treatment interaction were separately assessed for inclusion in the model. These interactions terms were considered for inclusion in the final model if significant at an $\alpha = 0.10$, as per protocol.

2.4 Patient Accounting and Demographics

Figure 1: Patient Accountability



There were seventeen centers, with between 22 and 66 patients.

Table 2: Comparison of Baseline Demographics

Variable	Fexofenadine (n=218)	Pseudoephedrine (n=218)	Combination (n=215)	p-value
Gender				
Male	94 (43.1)	90 (41.3)	91 (42.3)	
Female	124 (56.9)	128 (58.7)	124 (57.7)	0.9270
Race				
Caucasian	186 (85.3)	194 (89.0)	186 (86.5)	
Black	13 (6.0)	9 (4.1)	13 (6.0)	
Asian/Oriental	18 (8.3)	12 (5.5)	12 (5.6)	0.5100[1]
Multiracial	1 (0.5)	3 (1.4)	4 (1.9)	(Caucasian vs. Other)
Age (yrs)	34.9 ± 12.35	31.7 ± 11.12	33.0 ± 11.41	
	12-64	12-66	13-66	0.0503[2]
Weight (kg)	74.0 ± 17.33	72.3 ± 15.09	71.0 ± 15.09	
	42.2-144.0	36.5-123.5	38.8-126.0	0.2685[2]
Height (cm)	168.0 ± 9.01	168.3 ± 9.11	168.2 ± 8.86	
	145-195	146-190	148-193	0.8744[2]
Years since first episode of SAR Occurred	15.2 ± 9.79	15.9 ± 10.06	14.9 ± 9.65	
	2.0-46.2	1.0-46.0	14.10 2.0-55.0	0.5333[2]

1 P-value comparing the 3 treatment groups using Chi-square test.
2 P-value comparing the 3 treatment groups using ANOVA on ranked observations adjusting for site.

Reviewer Comment

The age of the patients was marginally statistically significantly different between the three treatment groups (p=0.0503). The patients randomized to fexofenadine were slightly older on average than those randomized to pseudoephedrine and the combination. This small difference in age would not appear to have a clinically significant effect on the comparison of the combination to fexofenadine, the primary comparison of interest.

2.5 Dropouts / Early Withdrawals

Patients who did not "successfully complete the study" were labeled "early withdrawals" by the investigator. The sponsor identified the numbers of patients whom the investigator labeled as "early withdrawals" (Table 3).

Table 3: Early Withdrawals

Primary Reason for Withdrawal	Fexofenadine (n=218)	Pseudo-ephedrine (n=218)	Combination (n=215)	TOTAL (n=651)
Adverse Events	1 (0.5)	9 (4.0)	8 (3.7)	18 (2.8)
Subject/investigator decision to discontinue	6 (0.3)	17 (7.8)	2 (0.9)	25 (3.8)
Lost to Follow-Up	0 (0.0)	2 (0.9)	0 (0.0)	2 (0.3)
Use of prohibited medication requiring discontinuation	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.1)
Other	8 (3.7)	6 (2.8)	3 (1.4)	17 (2.6)
Total	15 (6.9)	34 (15.6)	14 (6.5)	63 (9.7)

Reviewer Comment

The overall percentage of early withdrawals was 9.7%, somewhat high for a three-week study, two weeks of which all patients received some type of active drug. This percentage is highly influenced by the pseudoephedrine group, which had a notably higher early withdrawal rate than the other treatment groups. The primary reason for early withdrawal within the pseudoephedrine treatment group was "subject/investigator decision to discontinue". This reason could be related to adverse events or lack of effect. The difference between the percentage of early withdrawals of the pseudoephedrine group (15.6%) and the combination treatment group (6.5%) has an unknown effect on the conclusions of the analyses of the histamine-related symptoms.

The label "early withdrawal" was given to a patient on a patient-to-patient basis. The investigators were given the authority to name a patient as "early withdrawal" based on his/her opinion of whether or not the patient successfully completed the study. The patient did not necessarily need to complete the entire two weeks of double-blind treatment period in order to be considered a successful completer. The number of days the "completers" were on study may not have been consistent within investigator or across investigator. The sponsor explained this in a teleconference in response to the reviewer's difficulties in replicating the numbers of "early withdrawals"[3]. Table 4 presents the patients' last days with data for at least one symptom. A few patients had close to two weeks on study treatment before they returned for the second week. It is unclear whether these patients were considered "early withdrawals" or "completers" by the investigators.

Table 4: Number of Patients by Last Diary Entry with Data

Week	*1*													*2*					*Total*		
Last Diary Entry with Data for at least 1 symptom	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*1*	*2*	*3*	*4*	*5*	*(up to day 5)*	*6*	*≥7*
Fexofenadine	-	-	*1*	*3*	-	-	*4*	*4*	*1*	*1*	-	-	-	-	*2*	-	-	*2*	*18*	*7*	*193*
Pseudoephedrine	*1*	*1*	*1*	*5*	*1*	*2*	*8*	*6*	*3*	*2*	*1*	-	*1*	-	-	*1*	-	*2*	*35*	*17*	*166*
Combination	*1*	-	-	*1*	*1*	*1*	*3*	*1*	*2*	*2*	*1*	-	-	-	-	*2*	-	*1*	*16*	*8*	*181*

The numbers calculated in Table 4 above are similar to those of "early responders" if the cutoff for an "early withdrawal" is Day 5, or Day 2. However, the numbers do not necessarily represent the same patients. For example, one fexofenadine patient who dropped out on Day 6 was included in the sponsor's total of "early withdrawals".[4] An objective definition of "early withdrawal" defined in the protocol is recommended to avoid these discrepancies in future trials.

2.6 Efficacy Results

2.6.1 Primary Analyses

In general, the results for the two primary efficacy variables demonstrate that the combination product is both more effective than 1) the decongestant in reducing the histamine-mediated symptoms (TSS-NCS), and 2) the anti-histamine in reducing the non-histamine-mediated symptoms (NCS).

As stated previously, the Agency was primarily interested in the comparison of the combination product to fexofenadine of the change from baseline average daily 7PM instantaneous NCS.

[3] Memorandum of teleconference, October 28, 1997.

[4] Memorandum of teleconference, October 28, 1997.

The means and treatment effects, with associated p-values are presented in the Table 3 below. The daily means for the nasal congestion 7PM instantaneous scores are plotted in the Appendix Figure A1.

Table 3: Results of the Two Primary Efficacy Variables

Symptom	Assessmt	Timepoint	COMBO MEANS*	FEXO MEANS*	FEXO vs COMBO TRT EFF+	FEXO vs COMBO P-VALUE	PSEUDO MEANS*	PSEUDO vs COMBO TRT EFF+	PSEUDO vs COMBO P-VALUE
TSS - Nasal	Bedtime Instantan	Baseline	6.26	6.73			6.16		
Congestion	Δ fr baseline	Day 1	-1.15	-1.21	0.20	0.3921	-0.64	0.50	0.0341
	7PM Instantan	Baseline	6.97	7.42			7.01		
Scale 0-20	Δ fr baseline	Week 1	-1.58	-1.45	0.33	0.0889	-0.67	0.92	<0.0001
		Week 2	-2.49	-2.50	0.24	0.3093	-1.49	0.93	<0.0001
		Weeks 1&2	-1.98	-1.89	0.31	0.1206	-1.03	0.96	<0.0001
	7PM Reflective	Baseline	7.84	8.19			7.97		
	Δ fr baseline	Week 1	-1.88	-1.77	0.24	0.1914	-1.13	0.80	<0.0001
		Week 2	-2.81	-2.76	0.25	0.2922	-1.87	0.92	<0.0001
		Weeks 1&2	-2.30	-2.20	0.27	0.1579	-1.46	0.90	<0.0001
Nasal	Bedtime Instantan	Baseline	1.97	1.99			1.93		
Congestion	Δ fr baseline	Day 1	-0.29	-0.21	0.10	0.1939	-0.28	0.00	0.9505
	7PM Instantan	Baseline	2.11	2.19			2.11		
Scale 0-5	Δ fr baseline	Week 1	-0.39	-0.22	0.20	[redacted]	-0.26	0.13	[redacted]
		Week 2	-0.59	-0.49	0.16	[redacted]	-0.48	0.10	0.1641
		Weeks 1&2	-0.48	-0.33	0.19	[redacted]	-0.35	0.13	[redacted]
	7PM Reflective	Baseline	2.32	2.37			2.34		
	Δ fr baseline	Week 1	-0.45	-0.30	0.17	[redacted]	-0.38	0.08	0.1330
		Week 2	-0.68	-0.51	0.19	[redacted]	-0.58	0.10	0.1596
		Weeks 1&2	-0.56	-0.39	0.19	[redacted]	-0.46	0.11	0.0590

* All means in this table are unadjusted.

+ Treatment effect is the additional reduction in symptom scores that one treatment provides over another. The treatment effect was calculated using an Analysis of Covariance with baseline as a continuous covariate, and treatment and center as factors. Therefore, the difference of the (unadjusted) means in this table does not equal the treatment effect. For example, the mean change from baseline at day 1 for TSS-Nasal Congestion in the combination group = -1.15 and in the fexofenadine group = -1.21. The difference in these two means (fexofenadine - combination) = -0.06. On average across all centers, the fexofenadine group reduced symptoms slightly more than the combination group. However, the least squares mean adjusted for baseline and center for the combination group = -1.24 and for the fexofenadine group = -1.04. Note that with the adjustment for center and baseline, the combination group appears to be numerically superior to fexofenadine. The difference in these means (fexofenadine - combination) = 0.20. The treatment effect is the difference between the least squares means (0.20).

The results of the analyses of covariance adjusted for baseline, investigative site and treatment demonstrated that both protocol-specified primary efficacy variables were statistically significantly different between the two treatment groups (pseudoephedrine and the combination for the histamine-mediated symptoms, and fexofenadine and the combination for the non-histamine-mediated symptoms). The treatment effects were similar across investigative sites. The combination product was numerically superior to fexofenadine for Nasal Congestion at 13 out of the 17 sites and numerically superior to pseudoephedrine for the total of the histamine related symptoms at 16 out of the 17 sites (see Appendix Figures A2-A3). Neither the site-by-treatment nor the baseline-by-treatment interactions were significant at the $\alpha = 0.10$ level in the analysis of either primary efficacy variable. In fact, all the interaction p-values were greater than 0.25.

2.6.2 Secondary Analyses

Results of the secondary efficacy variables support those of the primary efficacy variables. Recall, the secondary efficacy variables were:

1) Change from baseline in average 7:00 PM reflective TSS;
2) Change from baseline in average 7:00 PM instantaneous TSS, NCS, and TSS-NCS;
3) Change from baseline in bedtime instantaneous TSS, NCS, and TSS-NCS; and
4) Change from baseline in average 7:00 PM reflective individual symptom scores.

The Agency was most interested in the average 7PM instantaneous NCS comparison of the combination to fexofenadine.

The combination product was numerically superior to each relevant comparison (i.e., pseudoephedrine or fexofenadine). The difference in mean 7PM assessments were statistically significant at each week and over the two-week average for all symptoms and total symptom scores, however, the bedtime assessments were not as consistently positive.

The combination was more effective than pseudoephedrine for every histamine-mediated symptom using the 7PM reflective and instantaneous scores. Even the difference between the mean scores of the *non*-histamine-mediated symptom, nasal congestion, reached statistical significance at the 0.05 level for the overall 2-week average of the instantaneous assessment (p=.0186), and approached statistical significance for the overall 2-week average of the reflective assessment (p=.0590). See Appendix Table A1 for results of analyses over the two-week treatment period and Table A2 for weekly results.

The combination was also statistically significantly different than fexofenadine (at the .05 level) for the total of the histamine-mediated symptoms plus nasal congestion, TSS, on both the instantaneous and reflective assessments; and for two individual histamine-mediated symptoms on the instantaneous assessment (rhinorrhea and sneezing). (See Appendix Tables A1 and A2.)

The results for the day 1 bedtime scores (TSS, NCS, TSS-NCS and the individual symptoms) were not consistently statistically significant, however Allegra-D was numerically superior in every relevant comparison (Appendix Table A3). The reduction in bedtime assessment scores of the combination product was statistically significantly greater than that of pseudoephedrine for the primary variable of interest, TSS-NCS (p=0.0341) and itchy, watery, red eyes (p=0.0269). Allegra-D was also numerically superior to pseudoephedrine for the other individual symptom scores. Furthermore, Allegra-D was numerically superior to fexofenadine for nasal congestion (-0.29 vs. -0.21), however, this difference was not statistically significant (p=0.1939). See Appendix Table A3 for bedtime assessment results.

Reviewer Comment
The results of the primary efficacy variables and secondary efficacy variables were highly favorable towards Allegra-D. Allegra-D was statistically significantly superior to fexofenadine for the non-histamine-mediated symptom, nasal congestion, at each week and the two-week average, for both instantaneous and reflective assessments. Similarly, Allegra-D was statistically significantly superior to pseudoephedrine for the total of the histamine-mediated symptoms at each week and the two-week average, for both instantaneous and reflective assessments, and additionally, the bedtime assessment.

Bedtime assessments were made twice: after the first dose of single-blind medication during the placebo lead-in period and after the first dose of double-blind medication during the double-blind treatment period. The mean reduction in the day 1 bedtime assessment of the combination product for nasal congestion was greater than that of fexofenadine, but not statistically significantly different. However, the study was not powered to detect a difference in day 1 bedtime scores. The study was

powered using the results of the 7PM reflective symptoms scores in Studies 23 and 24 from the Allegra NDA, 20-625. The reductions in day 1 bedtime TSS (excluding nasal congestion) from Studies 9 and 10 (also from the Allegra NDA) were generally about two-thirds the magnitude of the 7 PM reflective scores over the two-week double-blind treatment period in Studies 23 and 24. Therefore, the lack of significance of the difference in reduction of the day 1 bedtime assessment does not appear to substantially detract from the overall positive results of the trial.

2.6.3 Subgroup Analyses

The consistency of treatment effect was assessed across subgroups of patients by investigative site, by four baseline characteristics (age, gender, race, and weight), by disease severity of the baseline symptoms, and by regional ragweed pollen levels. This was performed on the primary efficacy variables for the intent-to-treat sample. The covariates were categorized as follows:

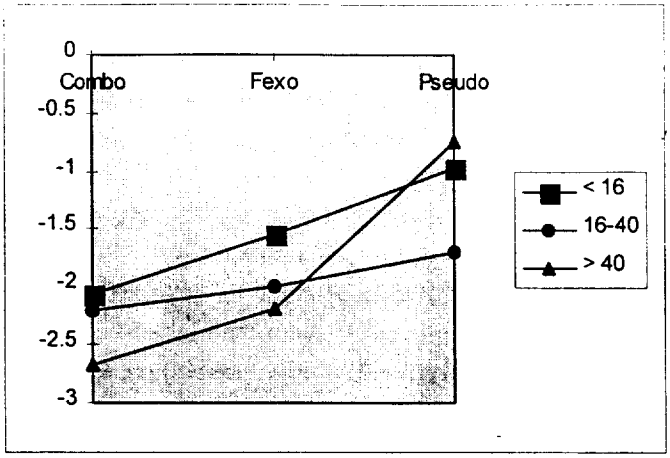
Age	< 16 yrs	Weight	< 60 kg
	≥ 16 up to but not including 40 yrs		≥ 60 up to but not including 90 kg
	≥ 40 yrs		≥ 90 kg
Gender	Male	Pollen	< 100 grains/m3
	Female		> 100 grains/m3
Race	Caucasian	Severity of Baseline Symptoms at Randomization	< 33 points
	Other		≥ 33 points

These covariates were introduced into separate ANCOVA models as classification variables. There were no statistically significant subgroup by treatment interactions for site, gender, race, weight, disease severity or pollen counts. There was, however, a statistically significant age-by-treatment interaction (p=0.0193) in the analysis of 7PM reflective TSS-NCS.

Reviewer Comment

The significant age-by-treatment interaction reflects the fact that the age groups had different relative responses in the three treatment groups. As Figure 2 shows, the pseudoephedrine treatment arm was the cause of the observed interaction. Within each age group, the relative efficacy of the three treatments was the same (combination > fexofenadine > pseudoephedrine). However, the relative efficacy in the three age groups was not the same. In both the combination and fexofenadine treatment groups, efficacy increased with age, but in the pseudoephedrine group, the oldest age group had the least efficacy. Since both the medical and biopharmaceutical reviewers believe there was no biological reason for this observation, the estimate of the interaction may not be estimating the true relative responses. Furthermore, the Agency was most interested in the comparison of nasal congestion scores of the combination to fexofenadine, not the histamine-related scores of the combination to pseudoephedrine.

Figure 2: Age-by-Treatment Interaction
7PM Reflective TSS-NCS Reductions



2.7 Adverse Events

The percent of patients who experienced one or more adverse events was 43.0%, overall; 51.2% combination; 45.4% pseudoephedrine; and 32.6% fexofenadine. The sponsor performed a chi-square analysis and reported that, "the occurrence rate for fexofenadine was statistically significantly lower than that of the combination ($p<0.001$)." The sponsor referenced the 2x3 table (shown below).

Table 5: 2x3 table of Numbers of Patients Who Experienced 1 or More Adverse Events

	Fexofenadine	Pseudoephedrine	Combination	Total
No	147	119	105	371
	67.43%	54.59%	48.84%	
Yes	71	99	110	260
	32.57%	45.41%	51.16%	
Total	218	218	215	651

Chi-Square p=0.001

April 30, 1997 submission; S9-V14-P8

The most commonly reported adverse events were headache and insomnia (Table 6).

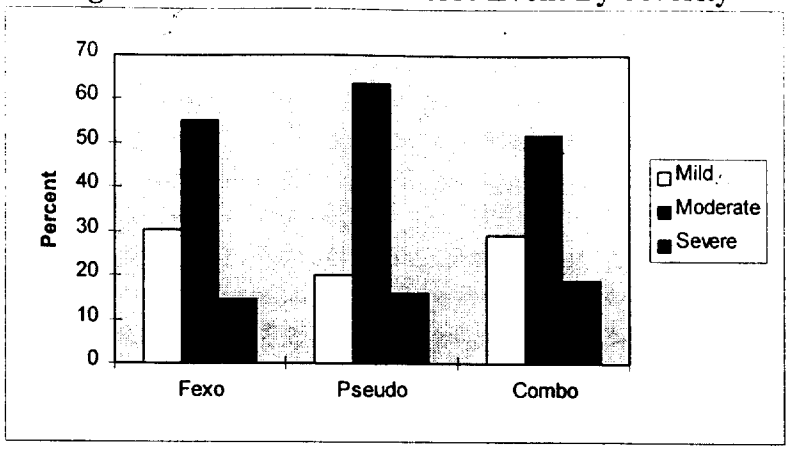
Table 6: Most Commonly Reported Adverse Events

Adverse Event	Fexofenadine	Pseudoephedrine	Combination
Headache	11.5%	17.4%	13.0%
Insomnia	3.2%	13.3%	12.6%

Pseudoephedrine had the highest rates of headache and insomnia.

All adverse events were rated by the investigator and/or patient as either mild, moderate or severe. Figure 3 presents the incidence of treatment emergent adverse event by severity. There was no obvious difference in the severity of adverse events among the three treatment groups.

Figure 3: Incidence of Adverse Event By Severity



Reviewer Comment

It seems most appropriate to perform chi-square analyses on the pairwise comparisons, the results of which are presented below:

Table 7: P-values For Comparisons of Patients Who Experienced 1 or More Adverse Events

Comparison	*p-value*
Fexofenadine (32.6%) vs. Combination (51.1%)	*0.0001*
Fexofenadine (32.6%) vs. Pseudoephedrine (45.4%)	*0.0060*
Pseudoephedrine (45.4%) vs. Combination (51.1%)	*0.2312*

Both the combination and pseudoephedrine treatment groups had statistically significantly greater adverse event rates than did the fexofenadine group. An increase in the reporting of adverse events would be anticipated with the addition of pseudoephedrine to any product.

2.8 Compliance

The sponsor measured compliance by the number of doses of treatment drug the patient returned.

> "Compliance with double-blind treatment was determined by dividing the total number of doses taken by the patient (i.e., total number of doses that should have been taken (based on the number of days the patient was exposed to double-blind medication.) Average compliance ranged from 106.0% to 107.2% and was similar across treatment groups and between study periods."
>
> April 30, 1997 submission; S9-V1-P70

In response to a request by the medical officer for explanation of the high compliance rates, the sponsor realized a mistake in the calculations. The compliance rates were presented in the response with the mistake corrected. The corrected average rates ranged from 98.6% to 99.3% and were similar across treatment groups and between study periods.[5]

2.9 Data Validation

The sponsor provided the data from this study to the statistical reviewer in an electronic form. All the analyses presented in this review were performed by the reviewer. The results obtained from the

[5] Submission dated 11-17-97.

reviewer's analyses substantially validated the analyses reported by the sponsor , with the exception of the early withdrawal tables (see Section 2.5, page 7).

2.10 Fexofenadine in other studies

Four adequate and well-controlled Phase III studies were submitted in July 1995 to provide evidence of fexofenadine in NDA 20-625. Two of these studies (Studies 23 and 24) reflectively assessed symptoms at 7 PM. The placebo groups in both studies reduced nasal congestion symptoms slightly (-0.14 units in Study 23 and -0.13 units in Study 24). The following table compares and contrasts the results from the study in the present application, Study 35, with Studies 23 and 24.

Table 8: 7PM Reflective Nasal Congestion Scores

Stud		Placebo	Fexo 40 mg	Fexo 60 mg	Fexo 120 mg	Fexo 240 mg	Pseudo	Comb
23	n	141	NA	141	144	144	NA	NA
	Mean±SE	-0.14±0.05		-0.40±0.05	-0.31±0.05	-0.35±0.05		
24	n	137	135	138	135	NA	NA	NA
	Mean±SE	-0.13±0.05	-0.12±0.05	-0.18±0.05	-0.22±0.05			
35	n	NA	NA	218	NA	NA	218	215
	Mean±SE			-0.36±0.04			-0.45±0.04	-0.56±0.04

* The means in this table are adjusted for site, treatment and baseline. Thus, the means for Study 35 in this table are slightly different from the means reported in Table 3 and appendix Table A1.

The reductions in nasal congestion symptom scores among all the fexofenadine treatment groups were statistically significantly greater than that of placebo in Study 23. This finding was not supported by Study 24. However, in Study 35, the 60 mg fexofenadine treatment group almost achieved the same reduction in symptoms as it did in Study 23 in reducing nasal congestion symptoms. Even with this large reduction in the active control group, the reduction in the Allegra-D treatment group was statistically significantly larger.

Reviewer Comment

The fexofenadine treatment group in Study 35 reduced nasal congestion symptoms by an average of .36 units on a scale of 0 to 5. This is almost three times the size of the placebo responses in Studies 23 and 24 - similarly conducted clinical trials. Without a placebo control group in Study 35, the only group against which the non-histamine symptom reduction properties of Allegra-D could be compared, was the anti-histamine, fexofenadine. The strong response by Allegra-D is compelling evidence that the decongestant component of Allegra-D is efficacious in reducing non-histamine related symptoms.

2.11 Conclusions

Study 35 was submitted by the sponsor to support the efficacy of the combination product in reducing histamine- and non-histamine-mediated symptoms. The question which most interested the Agency was the average 7PM instantaneous NCS comparison of the combination to fexofenadine.

The results from Study 35 found Allegra-D statistically significantly superior to fexofenadine in reducing non-histamine-mediated symptoms (both instantaneously and reflectively assessed), and to pseudoephedrine in reducing histamine-mediated symptoms (both instantaneously and reflectively assessed).

The mean reduction in bedtime assessment scores of the combination product was statistically significantly greater than that of pseudoephedrine for TSS-NCS. The bedtime assessments of nasal congestion were numerically superior, but not statistically significantly different between Allegra-D and fexofenadine. However, the study was not powered to detect a difference in day 1 bedtime scores, therefore this finding does not substantially detract from the positive results of the trial.

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Appendix Figure A1: Weekly Means of 7 PM Instantaneous Nasal Congestion Scores

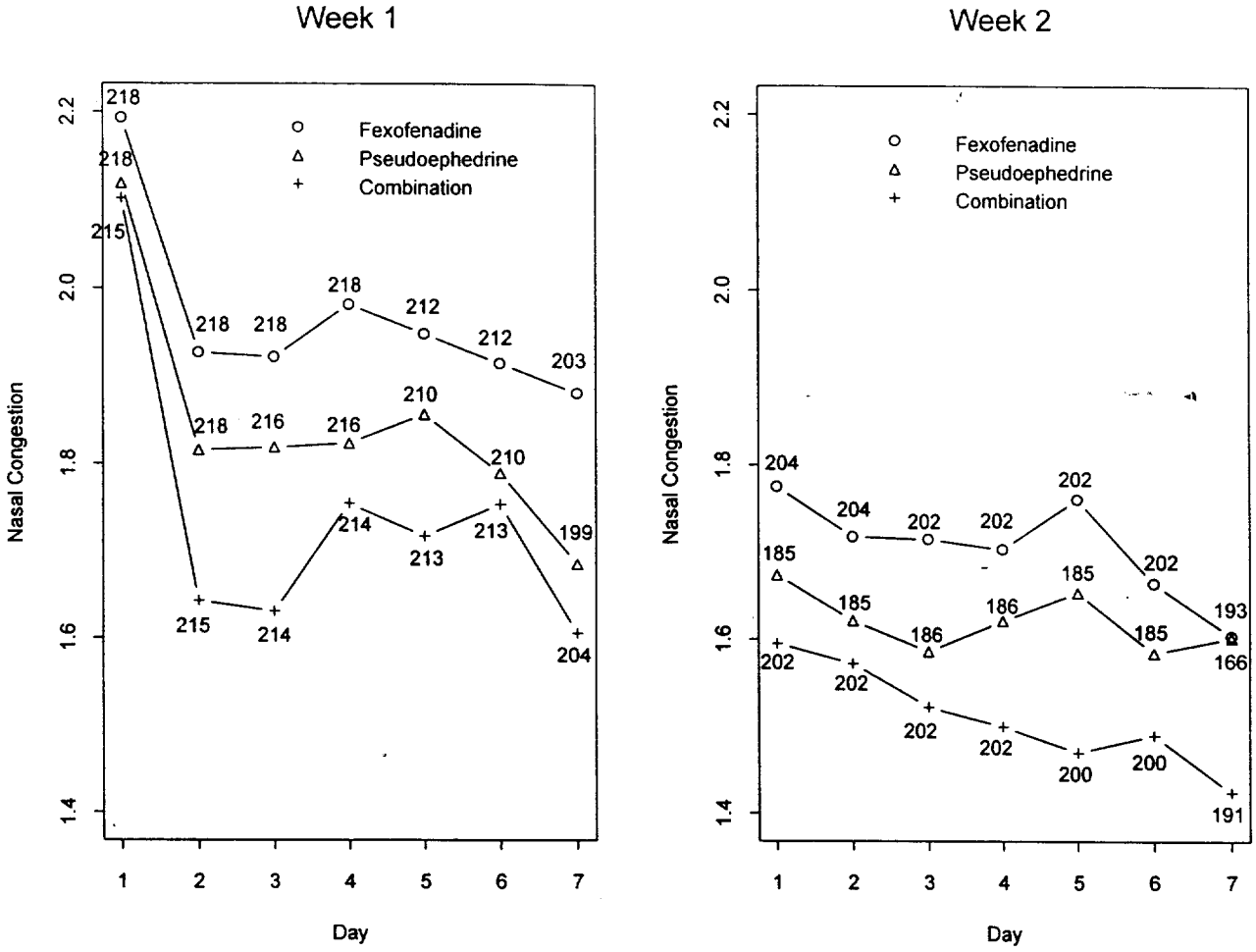

Figure A2

Individual Investigative Site Treatment Effects for Comparison of Allegra-D and Fexofenadine in the Reductions of Nasal Congestion

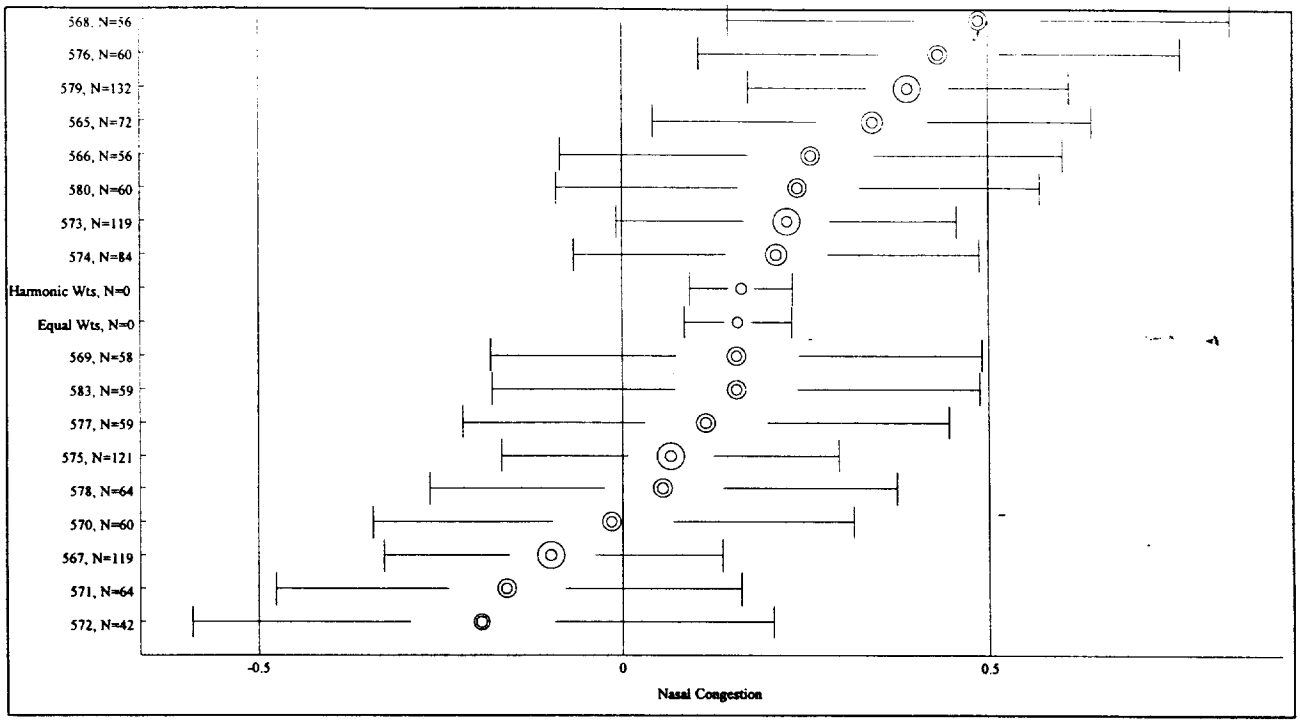

Figure A2: The variable on the x-axis is the size of the treatment effect. The numbers to the left of the y axis indicate the investigative site number and sample size for each confidence interval. The confidence intervals identified as "equal weights" and "harmonic weights" are the overall treatment effect sizes weighting all investigative sites equally and weighting each investigative site by sample size, respectively. The size of the circle represents the size of the investigative site.

These results are from analyses of covariance (baseline, treatment, site, and site-by-treatment interaction) performed in Crossgraphs. The results in the review were from analyses of covariance with baseline, treatment and site in the model. The interaction term was not included. Furthermore, unlike SAS, Crossgraphs fits the covariates first. Therefore, the results graphed in this figure are similar, but not identical to, the results from SAS, reported in the review.

Figure A3

Individual Investigative Site Treatment Effects for Comparison of Allegra-D and Pseudoephedrine in the Reductions in the Total of the Histamine Related Symptoms

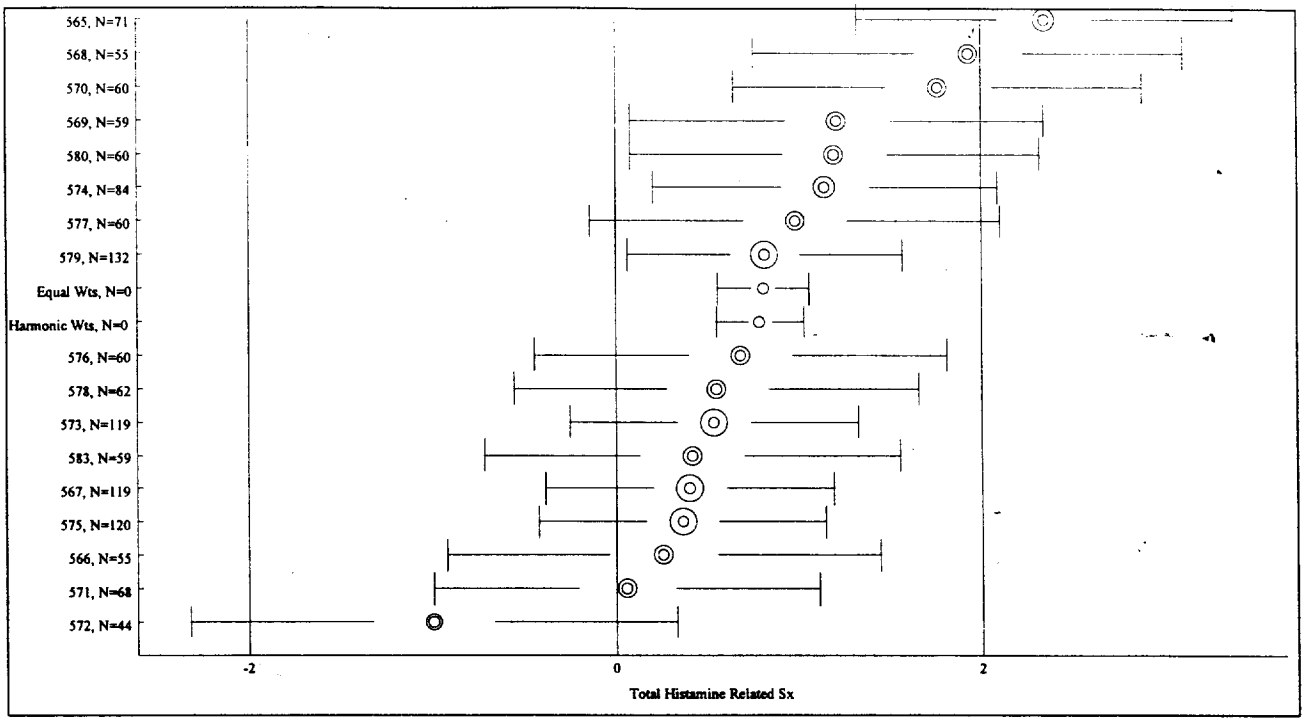

Figure A3: The variable on the x-axis is the size of the treatment effect. The numbers to the left of the y axis indicate the investigative site number and sample size for each confidence interval. The confidence intervals identified as "equal weights" and "harmonic weights" are the overall treatment effect sizes weighting all investigative sites equally and weighting each investigative site by sample size, respectively. The size of the circle represents the size of the investigative site.

These results are from analyses of covariance (baseline, treatment, site, and site-by-treatment interaction) performed in Crossgraphs. The results in the review were from analyses of covariance with baseline, treatment and site in the model. The interaction term was not included. Furthermore, unlike SAS, Crossgraphs fits the covariates first. Therefore, the results graphed in this figure are similar, but not identical to, the results from SAS, reported in the review.

Appendix Table A1: Secondary Efficacy Variables for Two-Week Average of 7PM Assessments

	Assessmt	Timepoint	COMBO MEANS	FEXO MEANS	FEXO vs COMBO TRT EFF	FEXO vs COMBO P-VALUE	PSEUDO MEANS	PSEUDO vs COMBO TRT EFF	PSEUDO vs COMBO P-VALUE
Itchy Nose/ Palate/Throat	Instantaneous	Baseline	1.88	1.89			1.84		
	Δ fr baseline	Weeks 1&2	-0.55	-0.53	0.03	0.6731	-0.28	0.24	<0.0001
	Reflective	Baseline	2.06	2.07			2.04		
	Δ fr baseline	Weeks 1&2	-0.64	-0.62	0.03	0.6365	-0.41	0.23	0.0002
Itchy, Watery, Red, Eyes	Instantaneous	Baseline	1.76	1.83			1.79		
	Δ fr baseline	Weeks 1&2	-0.51	-0.50	0.05	0.4388	-0.29	0.24	0.0001
	Reflective	Baseline	1.92	1.95			1.99		
	Δ fr baseline	Weeks 1&2	-0.58	-0.54	0.06	0.2998	-0.41	0.21	0.0006
Rhinorrhea	Instantaneous	Baseline	1.78	1.94			1.80		
	Δ fr baseline	Weeks 1&2	-0.45	-0.41	0.13	0.0247	-0.23	0.23	<0.0001
	Reflective	Baseline	1.99	2.12			2.04		
	Δ fr baseline	Weeks 1&2	-0.50	-0.48	0.09	0.1031	-0.31	0.21	0.0002
Sneezing	Instantaneous	Baseline	1.55	1.75			1.58		
	Δ fr baseline	Weeks 1&2	-0.47	-0.46	0.12	0.0346	-0.23	0.26	<0.0001
	Reflective	Baseline	1.87	2.05			1.90		
	Δ fr baseline	Weeks 1&2	-0.57	-0.56	0.10	0.0609	-0.33	0.25	<0.0001
TSS	Instantaneous	Baseline	9.08	9.61			9.11		
	Δ fr baseline	Weeks 1&2	-2.46	-2.23	0.50	0.0030	-1.38	1.10	<0.0001
	Reflective	Baseline	10.15	10.56			10.31		
	Δ fr baseline	Weeks 1&2	-2.85	-2.58	0.47	0.0183	-1.92	1.00	<0.0001
TSS - Nasal Congestion	Instantaneous	Baseline	6.97	7.42			7.01		
	Δ fr baseline	Weeks 1&2	-1.98	-1.89	0.31	0.1206	-1.03	0.96	<0.0001
	Reflective	Baseline	7.84	8.19			7.97		
	Δ fr baseline	Weeks 1&2	-2.30	-2.20	0.27	0.1579	-1.46	0.90	<0.0001
Nasal Congestion	Instantaneous	Baseline	2.11	2.19			2.11		
	Δ fr baseline	Weeks 1&2	-0.48	-0.33	0.19	0.0140	-0.35	0.13	0.0186
	Reflective	Baseline	2.32	2.37			2.34		
	Δ fr baseline	Weeks 1&2	-0.56	-0.39	0.19	0.0178	-0.46	0.11	0.0590

Means shown in this table are unadjusted.

Assessment: Instantaneous: 7PM Assessment over previous 1 hour; Reflective: 7PM Assessment over previous 12 hours.

FEXO: Fexofenadine; PSEUDO: Pseudoephedrine; COMBO: Combination Product (Allegra-D)

TRT EFF: Treatment effect is the additional reduction in symptom scores that one treatment provides over another. Computationally, the treatment effect is equal to the difference between two least squares means (not shown in this table) from an ANCOVA with Baseline, Treatment and Investigative Site.

P-values are pairwise comparisons between each component (Fexofenadine and Pseudoephedrine) and the combination product (Allegra-D).

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Appendix Table A2: 7PM Assessments at Each Week

Symptom	7PM Assessmt	Timept	COMBO MEANS	FEXO MEANS	FEXO vs COMBO TRT EFF	FEXO vs COMBO P-VALUE	PSEUDO MEANS	PSEUDO vs COMBO TRT EFF	PSEUDO vs COMBO P-VALUE
Itchy Nose/ Palate/Throat	Instantan	Baseline	1.88	1.89			1.84		
	Δ fr base	Week 1	-0.44	-0.39	0.06	0.3389	-0.20	0.23	0.0001
		Week 2	-0.68	-0.71	-0.02	0.8025	-0.39	0.26	0.0004
	Reflective	Baseline	2.06	2.07			2.04		
	Δ fr base	Week 1	-0.53	-0.49	0.05	0.4262	-0.32	0.20	0.0009
		Week 2	-0.79	-0.80	0.00	0.9728	-0.50	0.26	0.0005
Itchy, Watery, Red, Eyes	Instantan	Baseline	1.76	1.83			1.79		
	Δ fr base	Week 1	-0.40	-0.37	0.06	0.3222	-0.18	0.24	0.0001
		Week 2	-0.65	-0.65	0.03	0.6896	-0.45	0.18	0.0132
	Reflective	Baseline	1.92	1.95			1.99		
	Δ fr base	Week 1	-0.47	-0.42	0.06	0.3222	-0.31	0.18	0.0019
		Week 2	-0.74	-0.69	0.05	0.4873	-0.56	0.19	0.0118
Rhinorrhea	Instantan	Baseline	1.78	1.94			1.80		
	Δ fr base	Week 1	-0.34	-0.30	0.12	[redacted]	-0.16	0.19	[redacted]
		Week 2	-0.59	-0.55	0.13	0.0563	-0.31	0.26	[redacted]
	Reflective	Baseline	1.99	2.12			2.04		
	Δ fr base	Week 1	-0.40	-0.37	0.08	0.1381	-0.25	0.17	[redacted]
		Week 2	-0.61	-0.61	0.08	0.2374	-0.38	0.23	[redacted]
Sneezing	Instantan	Baseline	1.55	1.75			1.58		
	Δ fr base	Week 1	-0.39	-0.38	0.11	0.0559	-0.13	0.27	[redacted]
		Week 2	-0.57	-0.58	0.11	0.0963	-0.34	0.23	[redacted]
	Reflective	Baseline	1.87	2.05			1.90		
	Δ fr base	Week 1	-0.48	-0.49	0.07	0.2016	-0.24	0.25	[redacted]
		Week 2	-0.67	-0.66	0.12	0.0705	-0.43	0.24	[redacted]
TSS	Instantan	Baseline	9.08	9.61			9.11		
	Δ fr base	Week 1	-1.96	-1.67	0.52	[redacted]	-0.92	1.05	[redacted]
		Week 2	-3.08	-2.98	0.40	0.1720	-1.97	1.02	[redacted]
	Reflective	Baseline	10.15	10.56			10.31		
	Δ fr base	Week 1	-2.33	-2.07	0.41	0.0677	-1.50	0.88	[redacted]
		Week 2	-3.49	-3.27	0.44	0.1244	-2.45	1.02	[redacted]
TSS - Nasal Congestion	Instantan	Baseline	6.97	7.42			7.01		
	Δ fr base	Week 1	-1.58	-1.45	0.33	0.0889	-0.67	0.92	[redacted]
		Week 2	-2.49	-2.50	0.24	0.3093	-1.49	0.93	[redacted]
	Reflective	Baseline	7.84	8.19			7.97		
	Δ fr base	Week 1	-1.88	-1.77	0.24	0.1914	-1.13	0.80	[redacted]
		Week 2	-2.81	-2.76	0.25	0.2922	-1.87	0.92	[redacted]
Nasal Congestion	Instantan	Baseline	2.11	2.19			2.11		
	Δ fr base	Week 1	-0.39	-0.22	0.20	[redacted]	-0.26	0.13	[redacted]
		Week 2	-0.59	-0.49	0.16	[redacted]	-0.48	0.10	0.1641
	Reflective	Baseline	2.32	2.37			2.34		
	Δ fr base	Week 1	-0.45	-0.30	0.17	[redacted]	-0.38	0.08	0.1330
		Week 2	-0.68	-0.51	0.19	[redacted]	-0.58	0.10	0.1596

Means shown in this table are unadjusted.

Assessment: Instantaneous: 7PM Assessment over previous 1 hour; Reflective: 7PM Assessment over previous 12 hours.

FEXO: Fexofenadine; PSEUDO: Pseudoephedrine; COMBO: Combination Product (Allegra-D)

TRT EFF: Treatment effect is the additional reduction in symptom scores that one treatment provides over another. Computationally, the treatment effect is equal to the difference between two least squares means (not shown in this table) from an ANCOVA with Baseline, Treatment and Investigative Site.

P-values are pairwise comparisons between each component (Fexofenadine and Pseudoephedrine) and the combination product (Allegra-D).

Appendix Table A3: Bedtime Assessments

Symptom	Bedtime Assessmt	Timept	COMBO MEANS	FEXO MEANS	FEXO vs COMBO TRT EFF	FEXO vs COMBO P-VALUE	PSEUDO MEANS	PSEUDO vs COMBO TRT EFF	PSEUDO vs COMBO P-VALUE
Itchy Nose/ Palate/Throat		Baseline	1.74	1.70			1.68		
	Δ fr baseline	Day 1	-0.33	-0.28	0.05	0.5221	-0.19	0.12	0.1134
Itchy, Watery, Red, Eyes		Baseline	1.63	1.74			1.59		
	Δ fr baseline	Day 1	-0.32	-0.28	0.10	0.1998	-0.14	0.17	0.0269
Rhinorrhea		Baseline	1.58	1.79			1.59		
	Δ fr baseline	Day 1	-0.24	-0.34	0.03	0.6651	-0.18	0.08	0.3383
Sneezing		Baseline	1.31	1.50			1.30		
	Δ fr baseline	Day 1	-0.25	-0.31	0.06	0.4538	-0.12	0.13	0.0743
TSS		Baseline	8.22	8.72			8.09		
	Δ fr baseline	Day 1	-1.43	-1.42	0.29	0.2986	-0.92	0.50	0.0772
TSS - Nasal Congestion		Baseline	6.26	6.73			6.16		
	Δ fr baseline	Day 1	-1.15	-1.21	0.20	0.3921	-0.64	0.50	0.0341
Nasal Congestion		Baseline	1.97	1.99			1.93		
	Δ fr baseline	Day 1	-0.29	-0.21	0.10	0.1939	-0.28	0.00	0.9505

Means shown in this table are unadjusted.

Assessment: Bedtime was defined as 1-3 hours after 1st 7PM dose; symptoms assessed over previous 1 hour

FEXO: Fexofenadine; PSEUDO: Pseudoephedrine; COMBO: Combination Product (Allegra-D)

TRT EFF: Treatment effect is the additional reduction in symptom scores that one treatment provides over another. Computationally, the treatment effect is equal to the difference between two least squares means (not shown in this table) from an ANCOVA with Baseline, Treatment and Investigative Site.

P-values are pairwise comparisons between each component (Fexofenadine and Pseudoephedrine) and the combination product (Allegra-D).

Barbara Elashoff 12-15-97
Barbara Elashoff
Mathematical Statistician

Concur: Ed Nevius BEN 12-15-97
Steve Wilson SEW 12-15-97

cc:
Orig. NDA 20-786
HFD-570 / Division File
HFD-570 / GTrout, AWorobec, MHimmel, JJenkins
HFD-715 / Chron
HFD-715 / BElashoff, SWilson, ENevius

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20786

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology & Biopharmaceutics Review

Allegra®-D Tablets (60 mg Immediate Release Fexofenadine HCl and Sustained Release 120 mg Pseudoephedrine HCl)	**Type of Submission:** New NDA, 3S
	Submission Dates:
	12/20/96
	06/02/97
NDA 20-786	07/02/97
	07/25/97
Hoechst Marion Roussel, Inc Kansas City, MO 64134-0627	**Reviewer:** Brad Gillespie, PharmD

Synopsis Intended for twice daily administration, each Allegra®-D tablet contains 60 mg of immediate release fexofenadine hydrochloride (MDL 16,455A) and 120 mg sustained release pseudoephedrine.

In support of this application, the sponsor has submitted the results of one clinical efficacy trial and 4 human pharmacokinetic studies.

In the single-dose bioequivalence study (n=48), bioequivalence was not demonstrated between the proposed tablet and reference treatment (ALLEGRA capsule and SUDAFED). While AUC and the plasma concentration at the end of the dosing interval were equivalent in both comparisons, C_{max} was significantly lower for pseudoephedrine (90% confidence interval: 0.78 - 0.83) and higher for fexofenadine (90% confidence interval: 1.04 - 1.34) (DDPR0005). This failure to demonstrate bioequivalence is offset by the results of the sponsor's clinical efficacy study (see Medical Officer Review). In the multiple-dose study, the combination product was bioequivalent to the reference products (DDPR0001). A food effect study demonstrated that when the combination product is given with food, a substantial decrease in fexofenadine bioavailability (C_{max} -46%, $AUC_{0-\infty}$ -42%) can be expected with no appreciable effect on the absorption of pseudoephedrine (DDPR0002). Study PJPR0043 demonstrated that there is no pharmacokinetic interaction between fexofenadine and pseudoephedrine when given at therapeutic doses in healthy, male subjects. Thus, these two compounds can be safely formulated into a combination product.

After administration of a single dose of the combination product, the mean fexofenadine C_{max} was 191.5 ng/mL (CV 52%), mean $AUC_{0-\infty}$: 1369 ng·hr/mL (CV 39%), median T_{max}: 2 (range: 0.5 - 7) hours, mean plasma elimination half-life: 16.48 hours (CV 47%) and oral clearance: 47.24 L/hr (CV 43%) (Study DDPR005). After multiple-dose administration (1 tablet every 12 hours for eleven doses) the mean fexofenadine $C_{max,ss}$ was 254.5 ng/mL (CV 48%), $AUC_{0-12hr,ss}$: 1525.1 ng·hr/mL (CV 41%) and $T_{max,ss}$: 2 (range: 1 - 6) hours (Study DDPR0001).

After administration of a single dose of the combination product, the mean pseudoephedrine C_{max} was: 206.4 ng/mL (CV 16%), mean $AUC_{0-\infty}$: 3576 ng·hr/mL (CV 23%), median T_{max}: 6 (range: 2 - 8) hours, mean plasma elimination half-life: 7.82 (CV 18%) and oral clearance:

28.51 L/hr (CV 24%) (Study DDPR 0005). After multiple-dose administration (1 tablet every 12 hours for eleven doses) the mean pseudoephedrine $C_{max,ss}$ was 410.8 ng/mL (CV 20%), $C_{min,ss}$: 224.5 (CV 27%), $AUC_{0-12hr,ss}$: 4060.5 ng·hr/mL (CV 20%) and $T_{max,ss}$: 5 (range: 3 - 6) hours (Study DDPR0001).

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Background Fexofenadine hydrochloride 60 mg capsules were approved on 7/25/96 for treatment of the symptoms associated with seasonal allergic rhinitis. Pseudoephedrine hydrochloride is generally recognized as an agent for the relief of nasal congestion. The sponsor has formulated a product (ALLEGRA-D) combining 60 mg of immediate release fexofenadine and 120 mg of sustained release pseudoephedrine.

In support of this program, the sponsor has submitted the results of one clinical efficacy trial and 4 human pharmacokinetics studies.

ALLEGRA-D's proposed indication is for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older. The proposed recommended dose is one tablet, twice daily.

Summary of Clinical Pharmacology & Biopharmaceutics

I. BIOAVAILABILITY/BIOEQUIVALENCE

A. Bioavailability: Absolute bioavailability was not determined for this product.

B. Bioequivalence: This combination product was compared to approved reference products (60 mg fexofenadine HCl capsule with a 120 mg sustained release SUDAFED tablet) in both single- and multiple-dose studies. In the single-dose trial (n=48), bioequivalence was not demonstrated between the proposed tablet and reference treatment (ALLEGRA capsule and SUDAFED). While AUC and the plasma concentration at the end of the dosing interval were equivalent in both comparisons, C_{max} was significantly lower for pseudoephedrine (90% confidence interval: 0.78 - 0.83) and higher for fexofenadine (90% confidence interval: 1.04 - 1.34) (DDPR0005). This failure to demonstrate bioequivalence is offset by the results of the sponsor's clinical efficacy study (see Medical Officer Review). In the multiple-dose study, the combination product was bioequivalent to the reference products (DDPR0001).

C. Food Effect: A food effect study demonstrated that when the combination product is given with food, a substantial decrease in fexofenadine bioavailability (C_{max} -46%, $AUC_{0-\infty}$ - 42%) can be expected with no appreciable effect on the absorption of pseudoephedrine. Thus, in order to ensure therapeutic fexofenadine plasma concentrations, this product should be labeled for dosing only in a fasted state (DDPR0002).

II. PHARMACOKINETICS

A. Single-Dose: After administration of a single dose of the combination product, the mean fexofenadine C_{max} was 191.5 ng/mL (CV 52%), mean $AUC_{0-\infty}$: 1369 ng·hr/mL (CV 39%), median T_{max}: 2 (range: hours, mean plasma elimination half-life: 16.48 hours (CV 47%) and oral clearance: 47.24 L/hr (CV 43%). Pseudoephedrine C_{max} was: 206.4 ng/mL (CV 16%), mean $AUC_{0-\infty}$: 3576 ng·hr/mL (CV 23%), median T_{max}: 6 (range:) hours, mean plasma elimination half-life: 7.82 (CV 18%) and oral clearance: 28.51 L/hr (CV 24%) (Study DDPR 0005).

B. Multiple-Dose: After multiple-dose administration of the combination product (1 tablet every 12 hours for eleven doses) the mean fexofenadine $C_{max,ss}$ was 254.5 ng/mL (CV 48%), $AUC_{0-12hr,ss}$: 1525.1 ng·hr/mL (CV 41%) and $T_{max,ss}$: 2 (range: hours. Pseudoephedrine $C_{max,ss}$ was 410.8 ng/mL (CV 20%), $C_{min,ss}$: 224.5 (CV 27%), $AUC_{0-12hr,ss}$: 4060.5 ng·hr/mL (CV 20%) and $T_{max,ss}$: 5 (range: hours (Study DDPR0001).

III. DRUG INTERACTIONS Study PJPR0043 demonstrated that there is no pharmacokinetic interaction between fexofenadine and pseudoephedrine when given at therapeutic doses in healthy, male subjects. Thus, these two compounds can be safely formulated into a combination product.

IV. FORMULATIONS With the exception of the pseudoephedrine-fexofenadine interaction study (Study PJPR0043), all trials used the same drug lot (RC9614), which is the to-be-marketed formulation. Study PJPR0043 used commercially available fexofenadine and pseudoephedrine.

V. DISSOLUTION The sponsor has conducted dissolution testing of the Biobatch (RC 9614)

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VI. ASSAY The sponsor contracted all of the assay work for this NDA to used the same methodology for all of the analytical testing. Assay validation data was satisfactory.

COMMENTS

Comments 1 - 2 are from Study DDPR0001

1) The sponsor has included terms in the ANOVA model to account for errors due to subject, period and treatment. The 1992 FDA guidance *Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design*, suggests the following factors be included in the model: sequence, subject (within sequence), period and treatment. Thus, this method does not test for a sequence effect.

2) This sampling schedule does not permit a characterization of pseudoephedrine or fexofenadine elimination.

Comment 3 is from Study DDPR0005

3) No details were provided for Subjects 41 and 47 who dropped out of the study for unexplained personal reasons prior to dosing in Period 2. The sponsor is requested to provide further information.

4) The dissolution method and specifications proposed by the sponsor are unacceptable.

The sponsor is requested to submit complete dissolution (individual tablet and mean) profiles on the next three production-scale batches using

Comments 5-6 refers to the proposed package insert

5) The sponsor should modify the pharmacokinetics section of the label by adding literature-based pseudoephedrine special population information.

6) *The Pharmacokinetics section of the proposed package insert is presented below. Required modifications are identified by redline and ~~strikeout~~ text. Explanations for selected modifications are provided as footnotes.*

---

[a]Study DDPR0005

[b]Pharmacokinetic parameters described in the label should be *non-log-transformed* estimates

[c]Time to maximum concentration (T_{max}) is best described as the *median*

2 pages
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Draft Labeling

Recommendation This submission has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics and has been found acceptable to support approval of this product provided that the sponsor provide an acceptable response to Comments 3 - 6. Comments 1 - 2 are for the sponsor's general reference and do not require a response.

Bradley K. Gillespie 10/17/97
Bradley K. Gillespie, PharmD
Division of Pharmaceutical Evaluation II

CP/B Briefing 10/17/97: Drs. Huang, Balian, Bashaw, Parekh, Conner, ChenM, Honig

FT 10/17/97
Dale P. Conner, PharmD, Team Leader

cc:
HFD-570 (NDA 20-786, Divisional File, Trout, Worobec)
HFD-870 (Chen, Conner, Hunt, Gillespie)
HFD-850 (Lesko, Huang)
CDR (Barbara Murphy)

Pivotal Bioequivalence of 60 mg Fexofenadine HCl/120 mg Pseudoephedrine HCl Combination Product

Study No. DDPR0001 **Volumes:** 1.18-1.19
Investigator:
Study Dates: 4/27/96 - 5/23/96
Analytical Facility:
Analysis Dates: 5/7/96 - 6/17/96

OBJECTIVES: (1) To establish the multiple-dose bioequivalence of a 60 mg fexofenadine HCl/120 mg pseudoephedrine HCl bilayer combination tablet compared to a 60 mg fexofenadine HCl capsule and Sudafed 12 hour 120 mg Caplet. (2) Characterize the multiple-dose pharmacokinetics of fexofenadine and pseudoephedrine when administered as the combination tablet.

FORMULATIONS

Treatment A: 60 mg commercially available fexofenadine HCL immediate release capsule (Allegra™); Lot No. RH9508

and

120 mg commercially available pseudoephedrine HCl extended release caplet (Sudafed® 12-Hour); Lot No. 5T1621

Treatment B: 60 mg immediate release fexofenadine HCl/120 mg pseudoephedrine HCl extended release bilayer tablet; Lot No. RC9614

STUDY DESIGN A total of 49 healthy, non-smoking adult males were included in this open-label, randomized, multiple-dose, 2-treatment, 2-period crossover study. All subjects received Treatment A and Treatment B, every 12 hours for 5.5 days (11 doses). Volunteers fasted 10 hours overnight before the morning dose on Day 6 (pharmacokinetic sampling day). Subjects remained fasting and ambulatory for 5 hours after study drug administration. After this time, regular meals were served. A washout interval of 8 days separated the dosing periods. Subjects were confined throughout each study phase and abstained from the consumption of xanthine containing foods and beverages. Blood samples were obtained for plasma fexofenadine and pseudoephedrine determinations just prior to (zero hour), 0.5, 1, 2, 3, 4, 5, 6, 8, 10 and12 hours after study drug administration on Day 6. Pre-dose (trough) samples were also collected on Days 1, 4 and 5.

ASSAY

RESULTS A total of 44 subjects completed both phases of the study. Four of the volunteers withdrew from the study due to personal reasons and one subject was dropped from the study due to a positive drug screen prior to dosing in period 2. The mean plasma trough concentrations and concentration versus time profiles for the 12 hours following the final dose are presented in Figures 1 and 2 for fexofenadine and pseudoephedrine, respectively. Pharmacokinetic parameters are presented and compared in Tables 1 and 2.

COMMENTS

1) The sponsor has included terms in the ANOVA model to account for errors due to subject, period and treatment. The 1992 FDA guidance *Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design*, suggests the following factors to be included: sequence, subjects (within sequences), period and treatment. Thus, this method does not test for a sequence (carryover) effect.

2) This sampling schedule does not permit a characterization of pseudoephedrine or fexofenadine elimination.

CONCLUSION The results of this study demonstrate the multiple-dose bioequivalence of the proposed fexofenadine/pseudoephedrine combination product to approved reference products with respect to fexofenadine and pseudoephedrine. This study did not assess the single-dose bioequivalence of these products.

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Figure 1. Mean Steady-State Plasma Fexofenadine Concentration versus Time Profiles After Administration of a 60 mg Fexofenadine HCl Capsule and a 120 mg Pseudoephedrine HCl Caplet (Treatment A) and After a Fexofenadine-D Combination Tablet (Treatment B)

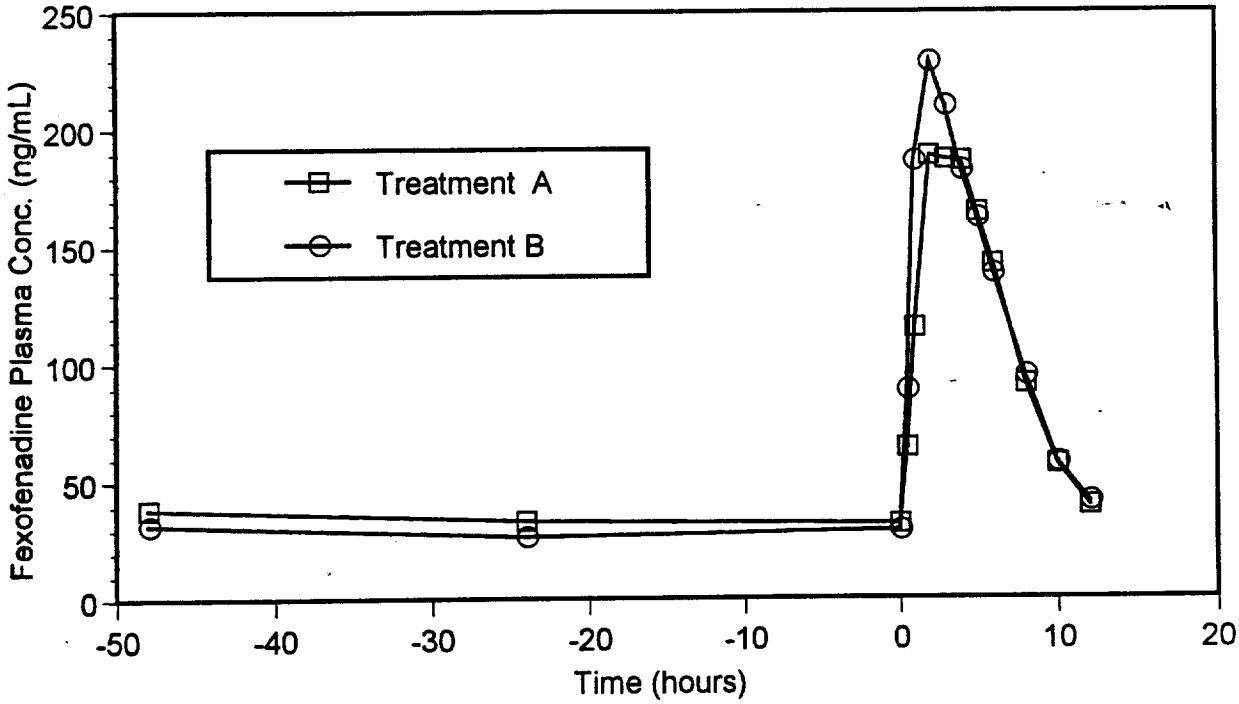

Table 1. Mean Fexofenadine Pharmacokinetic Parameters (%CV) After Administration of a 60 mg Fexofenadine HCl Capsule and a 120 mg Pseudoephedrine HCl Caplet (Treatment A) and After a Fexofenadine-D Combination Tablet (Treatment B)

Parameter		*Treatment A*	*Treatment B*	*Point Estimate*[1]	*90% CI*[1]
$C_{max,ss}$	(ng/mL)	227.88 (38)	254.54 (48)	1.11	0.98 - 1.25
$AUC_{0-12,ss}$	(ng·hr/mL)	1418.2 (36)	1525.1 (41)	1.08	0.98 - 1.20
$T_{max,ss}$ [2]	(hour)	3	2		

[1]Based on the two one-sided test procedure using natural log-transformed data

[2]Median (range)

Figure 2. Mean Steady-State Plasma Pseudoephedrine Concentration versus Time Profiles After Administration of a 60 mg Fexofenadine HCl Capsule and a 120 mg Pseudoephedrine HCl Caplet (Treatment A) and After a Fexofenadine-D Combination Tablet (Treatment B)

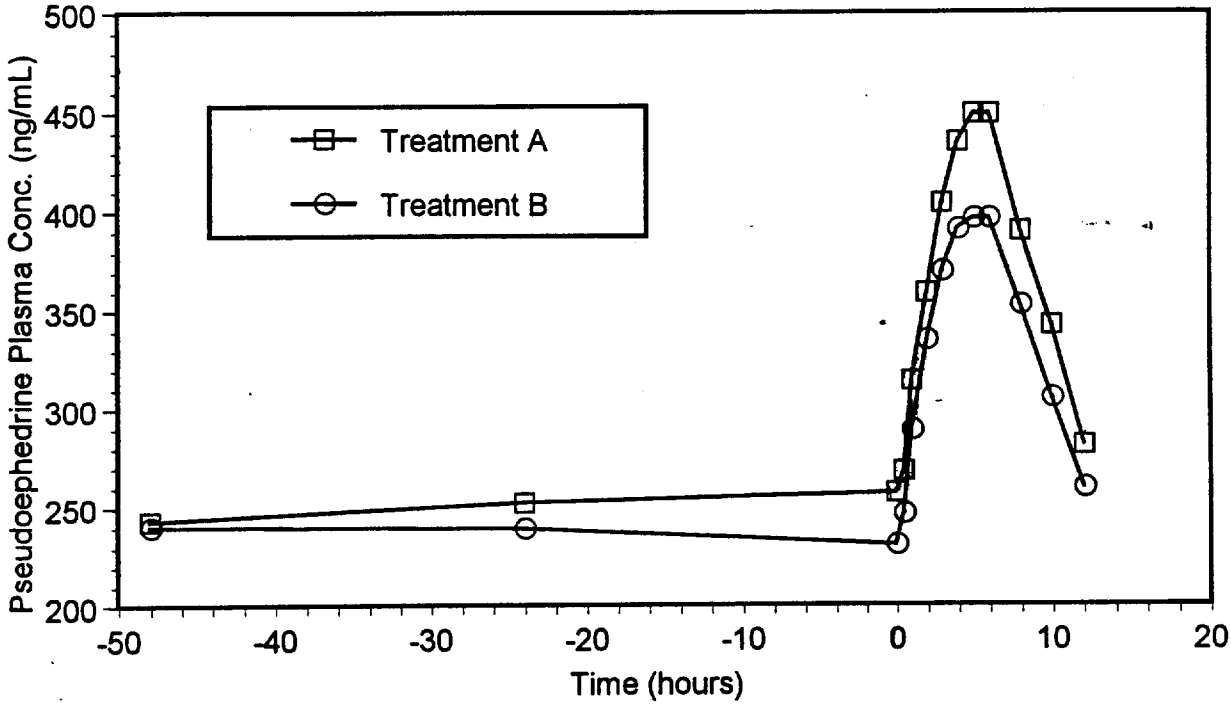

Table 2. Mean Pseudoephedrine Pharmacokinetic Parameters (%CV) After Administration of a 60 mg Fexofenadine HCl Capsule and a 120 mg Pseudoephedrine HCl Caplet (Treatment A) and After a Fexofenadine-D Combination Tablet (Treatment B)

Parameter		*Treatment A*	*Treatment B*	*Point Estimate*[3]	*90% CI*[3]
$C_{max,ss}$	(ng/mL)	460.26 (19)	410.77 (20)	0.89	0.86-0.93
$C_{min,ss}$	(ng/mL)	249.46 (28)	224.48 (27)	0.89	0.85-0.95
$AUC_{0-12,ss}$	(ng·hr/mL)	4501.5 (21)	4060.5 (20)	0.90	0.87-0.94
$T_{max,ss}$[4]	(hour)	5	5		

[3]Based on the two one-sided test procedure using natural log-transformed data

[4]Median (range)

The Effect of Food on the Pharmacokinetics of Fexofenadine/Pseudoephedrine Combination Product

Study No. DDPR0002 **Volumes:** 1.21-1.22
Investigator:

Study Dates: 4/27/96 - 5/6/96
Analytical Facility:
Analysis Dates: 5/2/96 - 5/17/96

OBJECTIVE: To characterize the single-dose pharmacokinetics and the effect of food on the rate and extent of absorption of the individual components of the combination product

FORMULATION 60 mg immediate release fexofenadine HCl/120 mg pseudoephedrine HCl extended release bilayer tablet; Lot No. RC9614

STUDY DESIGN A total of 22 healthy, non-smoking adult males were included in this open-label, randomized, single-dose, 2-treatment, 2-period crossover study. All volunteers fasted 10 hours overnight prior to the study's commencement. Subjects assigned to Treatment Group A continued fasting and then received the study drug while those in Group B received a high fat breakfast prior to dosing. A washout interval of 6 days separated the dosing periods. Subjects remained fasting and ambulatory for 5 hours after study drug administration. After this time, regular meals were served. Subjects were confined throughout each study phase and abstained from the consumption of xanthine or alcohol containing foods and beverages. Blood samples were obtained for plasma fexofenadine and pseudoephedrine determinations just prior to (zero hour), 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24, 36 and 48 hours after study drug administration.

ASSAY

DATA ANALYSIS

Pharmacokinetic: C_{max}, T_{max}, AUC_{0-z}, $AUC_{0-\infty}$, $t_{1/2}$, and CL_{po} were calculated for both analytes

RESULTS A total of 21 of 22 subjects completed both phases of the study. Subject 12 was dropped from the study due to a positive drug screen prior to dosing during period 2. The mean plasma concentration versus time profiles are presented in Figures 3 and 4 for fexofenadine and pseudoephedrine, respectively. Pharmacokinetic parameters are presented and compared in Tables 3 and 4.

CONCLUSION This study demonstrates that when this combination product is given with food, a substantial decrease in fexofenadine bioavailability can be expected with no appreciable effect on the absorption of pseudoephedrine. Thus, in order to ensure therapeutic fexofenadine plasma concentrations, this product should be labeled for dosing only in a fasted state.

Figure 3. Mean Plasma Fexofenadine Concentrations When the Combination Product is Administered in a Fed and Fasted State

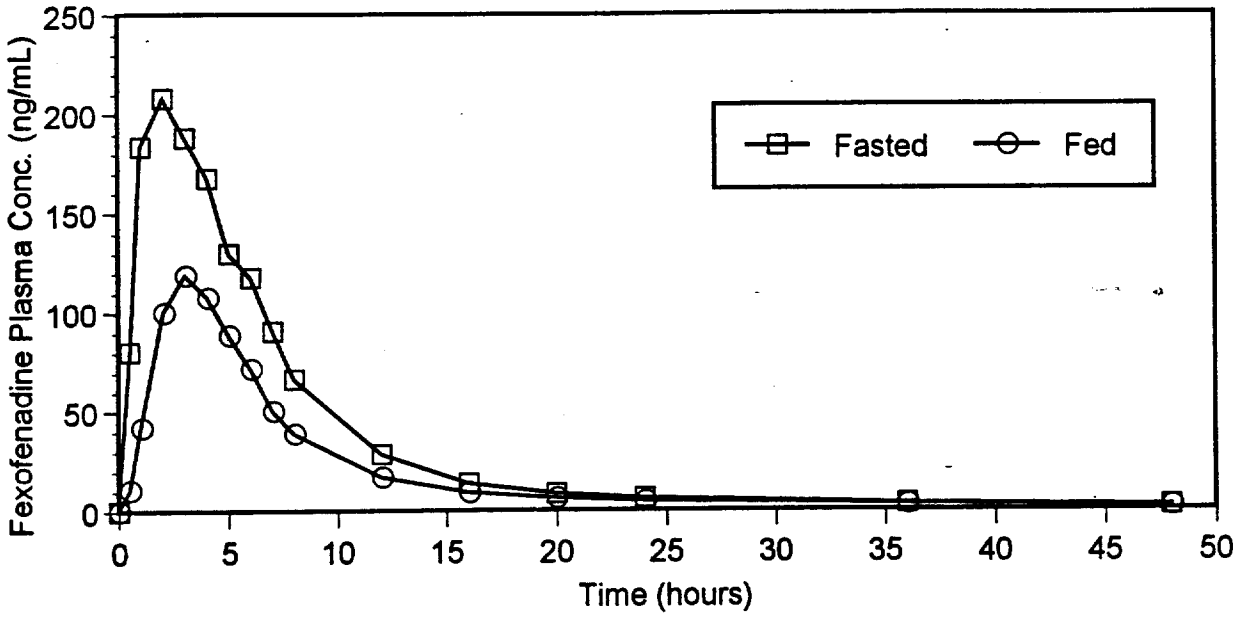

Table 3. Mean Fexofenadine Pharmacokinetic Parameters (%CV) After Administration of the Combination Product in a Fed and Fasted State

Parameter	(unit)	Fasted	Fed	% Difference
C_{max}	(ng/mL)	239.16 (33)	128.31 (35)	- 46%
T_{max}	(hours)[5]	2	3	+50%
AUC_{0-z}	(ng·hr/mL)	1532.5 (22)	868.49 (27)	- 43%
$AUC_{0-\infty}$	(ng·hr/mL)	1577.1 (21)	912.18 (28)	- 42%
CL_{po}	(L/hr)	37.22 (24)	66.21 (30)	+ 78%
$t_{1/2}$	(hours)	13.82 (33)	15.49 (22)	- 12%

[5]Median (range)

Figure 4. Mean Plasma Pseudoephedrine Concentrations When the Combination Product is Administered in a Fed and Fasted State

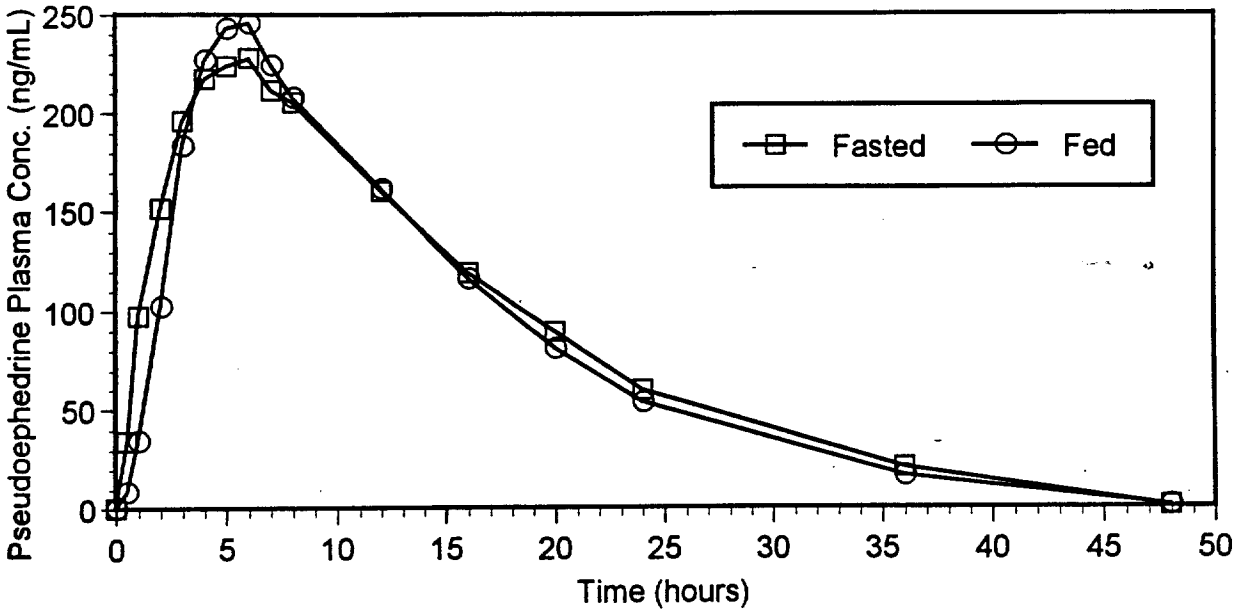

Table 4. Mean Pseudoephedrine Pharmacokinetic Parameters (%CV) After Administration of the Combination Product in a Fed and Fasted State

Parameter	(unit)	Fasted	Fed	% Difference
C_{max}	(ng/mL)	233.39 (14)	251.61 (15)	+ 8%
T_{max}	(hours)[6]	6	6	----
AUC_{0-z}	(ng·hr/mL)	3908.9 (25)	3705.4 (25)	- 5%
$AUC_{0-\infty}$	(ng·hr/mL)	4126.6 (24)	3935.2 (23)	- 5%
CL_{po}	(L/hr)	24.97 (21)	26.35 (24)	+ 5%
$t_{1/2}$	(hours)	7.70 (13)	7.39 (20)	- 4%

[6]Median (range)

Effect of Pseudoephedrine on the Pharmacokinetics of Fexofenadine

Study No. PJPR0043 **Volumes:** 1.23-1.24
Investigator:

Study Dates: 9/8/95 - 10/28/95
Analytical Facility:
Analysis Dates: 9/20/95 - 11/14/95

OBJECTIVE: To determine the pharmacokinetics of fexofenadine and pseudoephedrine administered alone and in combination.

FORMULATIONS Immediate Release 60 mg fexofenadine HCl Lot; No. RA 9543

Sudafed®12 Hour pseudoephedrine HCl extended release (120 mg); Lot No. 4X1968

STUDY DESIGN A total of 22 healthy, non-smoking adult males were included in this open-label, randomized, multiple-dose, 3-treatment, 3-period crossover study. All volunteers fasted overnight prior to the study's commencement. Subjects received each of the following three treatments separated by a 16 day washout period:

Treatment A)	Fexofenadine HCl 60 mg tablet administered bid for 4.5 days (9 doses)
Treatment B)	Pseudoephedrine HCl 120 mg caplet administered bid for 4.5 days (9 doses)
Treatment C)	Fexofenadine HCl 60 mg capsule and pseudoephedrine HCl 120 mg caplet given concurrently bid for 4.5 days (9 doses)

Subjects remained fasting and ambulatory for 5 hours after study drug administration. After this time, regular meals were served. Subjects were confined throughout each study phase and abstained from the consumption of xanthine or alcohol containing foods and beverages. Blood samples were obtained for plasma fexofenadine and pseudoephedrine determinations just prior to (zero hour), 1, 2, 3, 4, 5, 6, 8, 12, 18, 24, 30, 36, 48, and 72 hours after study drug administration on Day 5. Pre-dose (trough) samples were also collected on Days 1, 3 and 4.

ASSAY

RESULTS A total of 21 of 22 subjects completed both phases of the study. Subject 2 dropped out of the study due to personal reasons during period 2. The mean plasma concentration versus time profiles are presented in Figures 5 and 6 for fexofenadine and pseudoephedrine, respectively. Pharmacokinetic parameters are presented and compared in Tables 5 and 6.

CONCLUSION This study demonstrates that there is no pharmacokinetic interaction between fexofenadine and pseudoephedrine when given at therapeutic doses in healthy, male subjects. Thus, these two compounds can be safely formulated into a combination product.

Figure 5. Mean Steady-State Fexofenadine Plasma Concentrations When Administered Alone (Treatment A: 60 mg BID) and Concomitantly with Pseudoephedrine 120 mg BID (Treatment B)

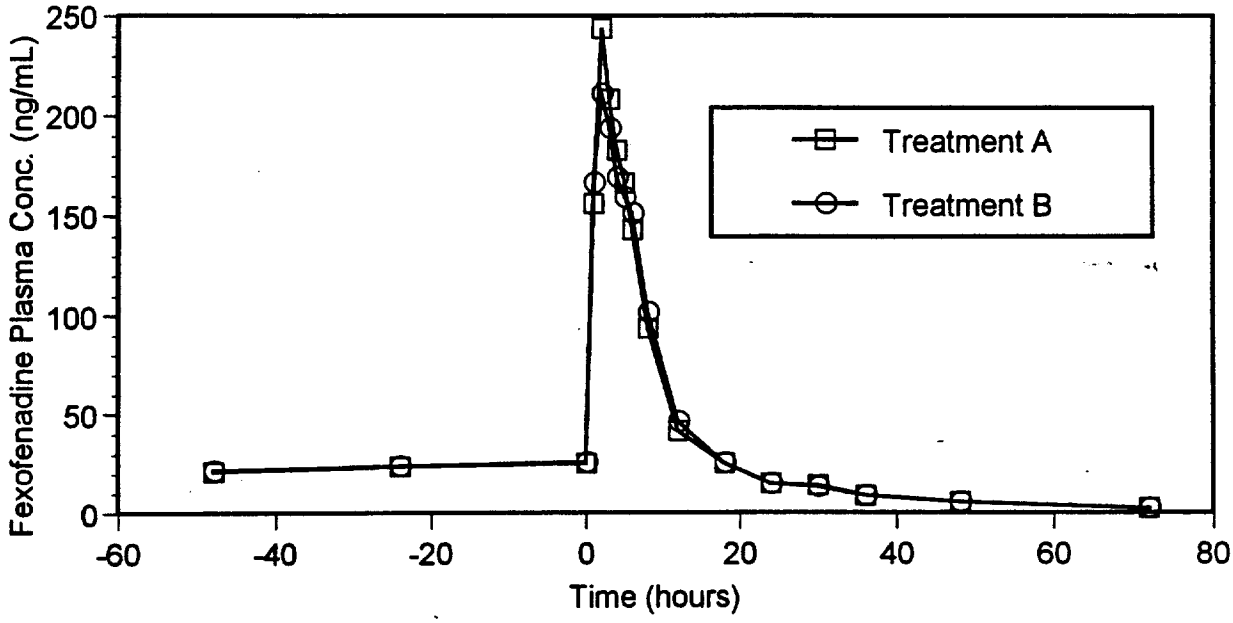

Table 5. Mean Steady-State Fexofenadine Pharmacokinetic Parameters (%CV) After Administration Alone (60 mg BID) and Concomitantly with Pseudoephedrine (120 mg BID)

Parameter	(unit)	Alone	With PSE	% Difference
$C_{max,\,ss}$	(ng/mL)	269.67 (56)	234.47 (39)	- 13%
$T_{max,ss}$	(hours)[7]	2	2	----
$AUC_{0-12,ss}$	(ng·hr/mL)	1544.0 (44)	1530.2 (33)	- 1%
$CL_{po,\,ss}$	(L/hr)	44.81 (53)	41.30 (40)	- 8%
$t_{1/2,ss}$	(hours)	16.53 (38)	17.49 (51)	+ 6%

[7]Median (range)

Figure 6. Mean Steady-State Pseudoephedrine Plasma Concentrations When Administered Alone (Treatment A: 60 mg BID) and Concomitantly with Fexofenadine 60 mg BID (Treatment B)

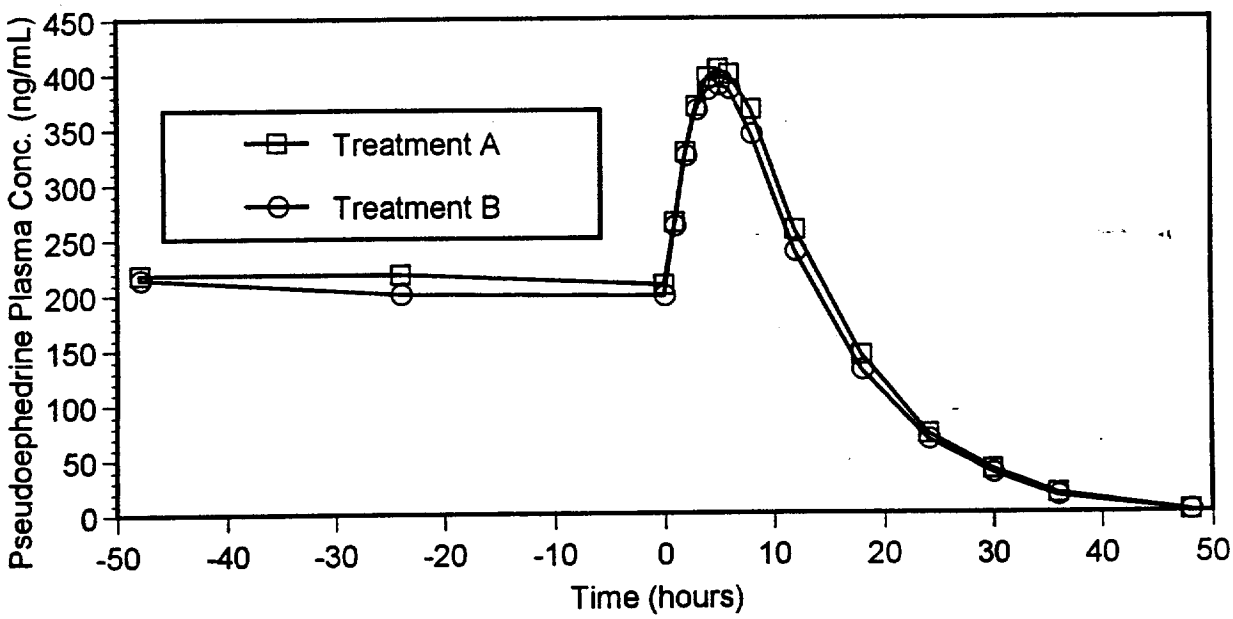

Table 6. Mean Steady-State Pseudoephedrine Pharmacokinetic Parameters (%CV) After Administration Alone (120 mg BID) and Concomitantly with Fexofenadine (60 mg BID)

Parameter	(unit)	Alone	With PSE	% Difference
$C_{max,ss}$	(ng/mL)	415.06 (22)	400.70 (18)	- 3%
$T_{max,ss}$	(hours)[8]	5 (	5 (	----
$AUC_{0-12,ss}$	(ng·hr/mL)	4077.7 (21)	3910.7 (19)	- 4%
$CL_{po,ss}$	(L/hr)	25.27 (23)	26.13 (22)	+ 3%
$t_{1/2,ss}$	(hours)	6.04 (14)	6.01 (20)	----

[8]Median (range)

Single-Dose Bioequivalence of 60 mg Fexofenadine HCl/120 mg Pseudoephedrine HCl Combination Product in Healthy Male Volunteers

Study No. DDPR0005 **Volumes:** 5.1 - 5.4
Investigator:
Study Dates: 2/22/97 - 3/3/97
Analytical Facility:
Analysis Dates: 2/26/97 - 3/13/97

OBJECTIVE: To establish the single-dose bioequivalence of a 60 mg fexofenadine HCl/120 mg pseudoephedrine HCl bilayer combination tablet compared to concomitantly dosed 60 mg fexofenadine HCl capsule and Sudafed 12 hour 120 mg Caplet

FORMULATIONS

Treatment A: 60 mg commercially available fexofenadine HCL immediate release capsule (Allegra™); Lot No. 98053501

120 mg commercially available pseudoephedrine HCl extended release caplet (Sudafed® 12-Hour); Lot No. 602530

Treatment B: 60 mg immediate release fexofenadine HCl/120 mg pseudoephedrine HCl extended release bilayer tablet; Lot No. RC9614

STUDY DESIGN A total of 50 healthy, non-smoking adult males were included in this open-label, randomized, single-dose, 2-treatment, 2-period crossover study. All subjects received both Treatments A and B, separated by a washout period of 6 days. Volunteers fasted 10 hours overnight before dosing, and continued fasting for 5 hours after study drug administration. After this time, regular, standardized meals were served. Subjects were confined throughout each study phase and abstained from the consumption of xanthine and alcohol-containing foods and beverages. Blood samples were obtained for plasma fexofenadine and pseudoephedrine determinations just prior to (zero hour), 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24, 36 and 48 hours after study drug administration.

ASSAY

RESULTS A total of 48 subjects completed both phases of the study. Subjects 41 and 47 dropped from the study for personal reasons prior to dosing in period 2, Treatments A and B, respectively. The mean plasma trough concentrations and concentration versus time profiles are presented in Figures 7 and 8 for fexofenadine and pseudoephedrine, respectively. Fexofenadine and pseudoephedrine pharmacokinetic parameters are presented and compared in Tables 7 and 8.

COMMENT

No details were provided for Subjects 41 and 47 who dropped out of the study for unexplained personal reasons prior to dosing in Period 2. The sponsor is requested to provide further information.

---

[9]Plasma concentration 12 hours after dosing (end of dosing interval)

[10]Area under the Plasma concentration versus time profile from time zero to the last quantifiable concentration

CONCLUSION With regard to fexofenadine, the combination product is not bioequivalent to the approved fexofenadine capsule dosed in combination with SUDAFED. While concentrations at the end of the dosing interval (C_{12}) and AUC are equivalent, peak plasma concentrations (C_{max}) are significantly higher for the combination product. Peak pseudoephedrine concentrations were significantly lower after administration of the combination product compared to the reference treatment. As with fexofenadine, AUC and plasma concentrations at the end of the dosing interval were equivalent.

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Figure 7. Mean Plasma Fexofenadine Concentration versus Time Profile After Single-Dose Administration of a 60 mg Fexofenadine Capsule with SUDAFED (TRT A) and Fexofenadine-D (TRT B)

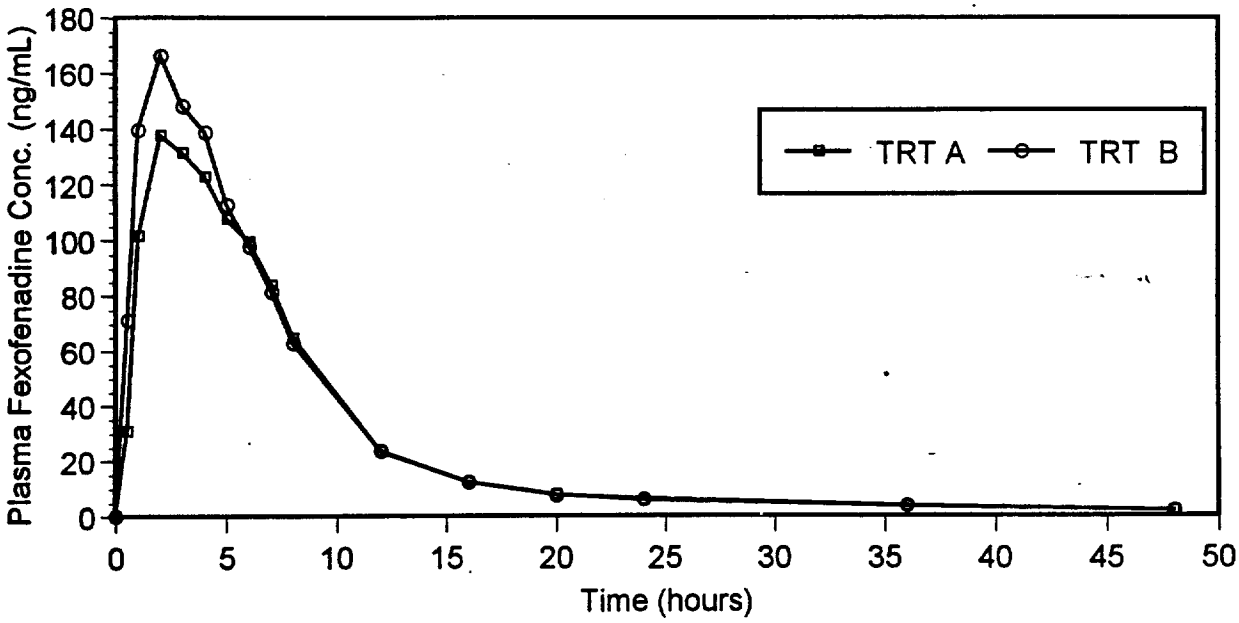

Table 7. Mean (%CV) Fexofenadine Pharmacokinetic Parameters (Excluding Subjects 41 and 47) After Single-Dose Administration of a 60 mg Fexofenadine Capsule with SUDAFED (TRT A) and Fexofenadine-D (TRT B)

Parameter (unit)	Treatment A	Treatment B	Ratio[11]	90% CI on Ratio[11]
C_{max} (ng/mL)	158.81 (45)	191.48 (52)	1.18	1.04 - 1.34
t_{max}[12] (hours)	2	2	---	---
C_{12} (ng/mL)	23.25 (42)	23.41 (39)	1.01	0.92 - 1.11
AUC_{0-z}[13] (ng·hr/mL)	1204.0 (38)	1308.3 (40)	---	---
$AUC_{0-\infty}$ (ng·hr/mL)	1258.3 (37)	1369.2 (39)	1.08	0.99 - 1.19
$t_{1/2}$ (hours)	15.99 (42)	16.48 (47)	1.04	---
CL_{po} (L/hr)	50.92 (41)	47.24 (43)	---	---

[11]Based on naturally log-transformed data

[12]Central tendency described as the *median* and variability as the *range*

[13]Area under the plasma concentration time curve to the last quantifiable timepoint

Figure 8. Mean Plasma Pseudoephedrine Concentration versus Time Profile After Single-Dose Administration of a 60 mg Fexofenadine Capsule with SUDAFED (TRT A) and Fexofenadine-D (TRT B)

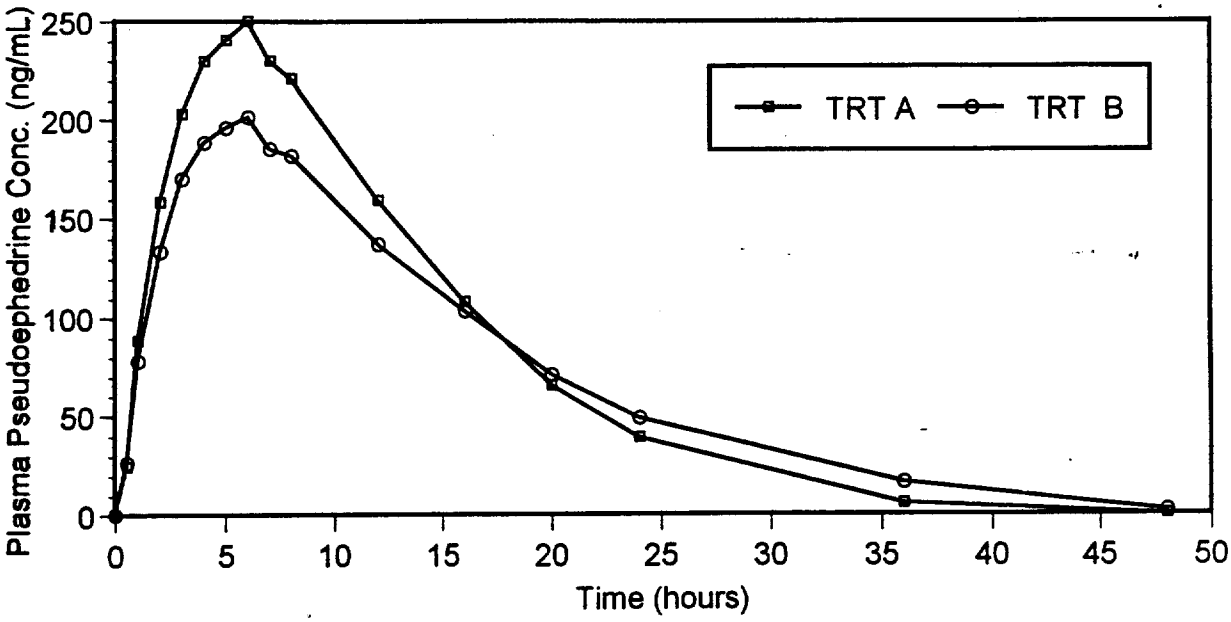

Table 8. Mean (%CV) Pseudoephedrine Pharmacokinetic Parameters (Excluding Subjects 41 and 47) After Single-Dose Administration of a 60 mg Fexofenadine Capsule with SUDAFED (TRT A) and Fexofenadine-D (TRT B)

Parameter (unit)	Treatment A	Treatment B	Ratio[14]	90% CI on Ratio[14]
C_{max} (ng/mL)	256.48 (16)	206.38 (16)	0.80	0.78 - 0.83
t_{max}[15] (hours)	6 [illegible]	6 ([illegible]	---	---
C_{12} (ng/mL)	159.59 (21)	137.79 (24)	0.86	0.82 - 0.90
AUC_{0-z}[16] (ng·hr/mL)	3513.7 (21)	3351.3 (24)	0.95	0.91 - 0.99
$AUC_{0-\infty}$ (ng·hr/mL)	3709.7 (20)	3576.3 (23)	0.96	0.92 - 1.00
$t_{1/2}$ (hours)	5.68 (12)	7.82 (18)	1.37	---
CL_{po} (L/hr)	26.56 (20)	28.51 (24)	---	--

[14]Based on naturally log-transformed data

[15]Central tendency described as the *median* and variability as the *range*

[16]Area under the plasma concentration time curve to the last quantifiable timepoint

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20786

ADMINISTRATIVE DOCUMENTS

13/14. Patent Information/Certification

Patent information relevant to Fexofenadine-D is defined in Attachments A, B, and C.

These attachments are copies of Patent Information Declarations issued separately to NDA 20-786. These declarations apply to:

1. United States Patent No. 4,254,129 (Attachment A).
2. United States Patent No. 5,375,693 (Attachment B).
3. United States Patent No. 5,578,610 (Attachment C).

December 20, 1996

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive
Mail: P.O. Box 9627
Kansas City, MO 64134-0627
Telephone (816) 966-5000

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Park Bldg., Room 2-14
12420 Parktown Drive
Rockville, MD 20857

Subject: Re: Original NDA Submission for Fexofenadine-D
Patent Information and Declaration

Dear Sir:

The undersigned submits the following patent information as relevant to Fexofenadine-D:

PATENT NUMBER: United States Patent No. 4,254,129

EXPIRATION DATE: April 10, 1999

PATENT OWNER: Merrell Pharmaceuticals Inc.
2110 E. Galbraith Road
Cincinnati, OH 45215

Hoechst Marion Roussel, Inc.
10236 Marion Park Drive
Kansas City, MO 64137

TYPE OF PATENT: Drug substance, Drug Product Composition and Method of Use.

The undersigned declares that United States Patent No. 4,254,129 covers Fexofenadine HCl, a drug substance contained in the drug product Fexofenadine-D for which the above-referenced NDA is being submitted for approval, even date herewith, as well as the drug product (composition) containing said drug substance and a method of using said drug substance in treating allergic reactions. Merrell Pharmaceuticals Inc. is a wholly owned subsidiary of Hoechst Marion Roussel, Inc. The patent is currently the subject of a pending application for patent term extension pursuant to 35 U.S.C. § 156.

Two copies of this declaration are submitted. Please list the above patent in the Orange Book Publication upon approval of the NDA.

Submitted by: Elaine Waller
Elaine Waller
Vice President
North American Drug Regulatory Affairs

December 20, 1996

Hoechst Marion Roussel, Inc.

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Center for Drug Evaluation and Research
Food and Drug Administration
Park Bldg., Room 2-14
12420 Parktown Drive
Rockville, MD 20857

Subject: Re: Original NDA Submission for Fexofenadine-D
Patent Information and Declaration

Dear Sir:

The undersigned submits the following patent information as relevant to Fexofenadine-D:

PATENT NUMBER: United States Patent No. 5,375,693

EXPIRATION DATE: August 3, 2012

PATENT OWNER: Sepracor Inc.
33 Locke Drive
Marlborough, MA 01752-1146

and

Georgetown University
Washington, D.C.

TYPE OF PATENT: Method of Use.

The undersigned declares that United States Patent No. 5,375,693 covers a method of using Fexofenadine HCl, a drug substance contained in the drug product Fexofenadine-D for which the above-referenced NDA is being submitted for approval, even date herewith, in treating allergic rhinitis. Hoechst Marion Roussel, Inc., is licensed under United States Patent No. 5,375,693, which has not been extended under 35 U.S.C. § 156.

Two copies of this declaration are submitted. Please list the above patent in the Orange Book Publication upon approval of the NDA.

Submitted by: Elaine Waller
Elaine Waller
Vice President
North American Drug Regulatory Affairs

December 20, 1996

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive
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Telephone (816) 966-5000

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Park Bldg., Room 2-14
12420 Parktown Drive
Rockville, MD 20857

Subject: Re: Original NDA Submission for Fexofenadine-D
Patent Information and Declaration

Dear Sir:

The undersigned submits the following patent information as relevant to Fexofenadine-D.

PATENT NUMBER: United States Patent No. 5,578,610

EXPIRATION DATE: November 26, 2013

PATENT OWNER: Albany Molecular Research, Inc.
21 Corporate Circle
Albany, New York 12203-5154

TYPE OF PATENT: Drug substance, Drug Product Composition and Method of Use.

The undersigned declares that United States Patent No. 5,578,610 covers Fexofenadine HCl, a drug substance contained in the drug product Fexofenadine-D for which the above-referenced NDA is being submitted for approval, even date herewith, as well as the drug product (composition) containing said drug substance and a method of using said drug substance in treating allergic reactions. Hoechst Marion Roussel, Inc. is licensed under U.S. Patent No. 5,578,610. The patent has not been extended under 35 U.S.C. § 156.

Two copies of this declaration are submitted. Please list the above patent in the Orange Book Publication upon approval of the NDA.

Submitted by: Elaine Waller
Elaine Waller
Vice President
North American Drug Regulatory Affairs

EXCLUSIVITY SUMMARY for NDA # 20-786 SUPPL #_____

Trade Name Allegra-D Extended Release Tablets
Generic Name fexofenadine 60 mg/pseudoephedrine 120 mg
Applicant Name Hoechst Marion Roussel HFD- 570

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA?
YES /_X__/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X__/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name_____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-625 Allegra (fexofenadine) Capsules

NDA # 17603 Novafed (psuedoephedrine)

NDA # 20021 Effidac (psuedoephedrine)

NDA # 73585 Sudafed (psuedoephedrine)

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____
_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_X__/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X__/

If yes, explain: _____
_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain: _____
_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # PR0035

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X__/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /_X__/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1_, Study # PR0035_____

Investigation #_, Study # _____

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # ____ YES /___/ ! NO /___/ Explain: _____
! _____

Investigation #2

IND # ____ YES /___/ ! NO /___/ Explain: _____
! _____

(b) - For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES /_X__/ Explain ____ ! NO /___/ Explain _____
! _____

The study was conducted by the applicant in Canada, therefore an IND was not needed. The applicant was the sponsor of the study ! _____

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____
! _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

_____

_____

Signature 12/16/97 Date

Title: Project Manager

Signature of Division Director 12/24/97 Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-786 Trade (generic) names Allegra-D (fexofenadine/pseudoephedrine

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

____ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children..

X 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

Gretchen Trout
Signature of Preparer

12/16/97
Date

cc: Orig NDA
HFD-570/Div File
NDA Action Package

Debarment Certification

Hoechst Marion Roussel, Inc. hereby certifies that we did not and will not use in any capacity the services of any person debarred under Section 306(a) or (b) in connection with this application.

Elaine Waller

Elaine Waller, PharmD
Vice President, North American
Drug Regulatory Affairs

30 Dec 96

Date

MEMORANDUM

DATE: December 24, 1997

TO: NDA 20-786

FROM: John K. Jenkins, M.D.
Director, Division of Pulmonary Drug Products HFD-570

12/24/97

SUBJECT: Overview of NDA Review Issues

Administrative

NDA 20-786 for Allegra-D (fexofenadine HCL 60 mg and pseudoephedrine HCL 120 mg) Extended Release Tablets was originally submitted by Hoechst Marion Roussel on December 20, 1996. The user fee payment for this application was received on January 2, 1997. The current user fee goal date for NDA 20-786 is January 2, 1998.

Clinical

Allegra-D contains the same dose of fexofenadine HCL (60 mg) as the currently approved Allegra and the same dose of pseudoephedrine HCL in an extended-release matrix (120 mg) as several other approved OTC and Rx extended-release PSE products. The proposed indication for Allegra-D is treatment of the symptoms of seasonal allergic rhinitis, including nasal congestion.

The development program for Allegra-D was based on a demonstration of bioequivalence between Allegra-D and Allegra for the fexofenadine HCL component and between Allegra-D and an approved reference PSE product for the PSE component. Such a program would be adequate to support the clinical approval of the combination of two previously approved active ingredients in these two pharmacologic classes (antihistamines and decongestants). The pivotal bioequivalence study, however, failed to demonstrate the bioequivalence of Allegra-D to the reference products (see Clinical Pharmacology and Biopharmaceutics review prepared by Dr. Gillespie). This study demonstrated a lower Cmax point estimate for the PSE component and a higher Cmax point estimate for the fexofenadine component for Allegra-D as compared to the reference products. The higher Cmax point estimate for fexofenadine with Allegra-D did not raise any issues with regard to approval from a clinical perspective; i.e., the efficacy of the fexofenadine HCL component of the product would not be in question (the fexofenadine levels observed were higher than those seen with Allegra) and there were no significant safety issues related to the higher plasma concentrations (levels of fexofenadine higher than those observed from Allegra-D were studied in the Allegra NDA database and found to be safe). The lower Cmax levels for the PSE component with Allegra-D did raise issues with regard to approval from a clinical perspective; i.e., while the lower levels of PSE with Allegra-D would not pose any safety concern the efficacy of the PSE component of the Allegra-D product would not be supported based on bioinequivalence to an approved PSE product.

In order to address the issues raised by the failed bioequivalence study, the sponsor submitted the results of a two-week, randomized, double-blind comparison of Allegra-D, Allegra, and a 120 mg extended-release PSE formulation in patients with seasonal allergic rhinitis. For more complete details of this study and the other components of the Allegra-D clinical program, please refer to the Medical Officer review prepared by Dr. Worobec and the Medical Team Leader Memorandum prepared by Dr. Himmel. The primary comparison of interest from a regulatory perspective from this trial was Allegra-D versus Allegra for relief of nasal congestion (the "PSE responsive" symptom). Allegra-D was statistically significantly more effective in reducing nasal congestion symptom scores than Allegra for both the reflective and instantaneous assessments. This finding confirms the efficacy of the PSE component of Allegra-D and obviates any concerns raised by the results of the bioequivalence trials. Of note, Allegra-D was also statistically significantly more effective in reducing the "antihistamine responsive" symptoms of allergic rhinitis than PSE; this finding reaffirms the efficacy of the fexofenadine HCL component of the Allegra-D combination.

No new safety issues were raised by any of the findings from the clinical trial program. In the above referenced 2-week trial, most of the adverse events reported with Allegra-D were adverse events commonly associated with the PSE component of the product. This was confirmed by the similar rates of reports of these adverse events in the PSE group.

There are no outstanding clinical issues and the NDA is approvable from a clinical perspective.

Preclinical

The sponsor did not submit any new preclinical studies in support of this NDA. This is appropriate and in keeping with division and agency precedent for the combination of two approved drug substances from these two pharmacologic classes (antihistamines and decongestants).

The NDA is approvable from a preclinical perspective.

CMC

Allegra-D is a bi-layer, coated tablet which contains 60 mg of fexofenadine HCL for immediate release and 120 mg of PSE for sustained release. All CMC deficiencies that must be resolved prior to approval have been satisfactorily addressed by the sponsor. For more complete details please refer to the CMC review prepared by Dr. Rogers. The sponsor has made several Phase 4 commitments and CMC agreements and these will be included in the action letter.

The application is approvable from a CMC perspective. The sponsor will be reminded of their Phase 4 commitments and CMC agreements in the action letter.

Clinical Pharmacology and Biopharmaceutics

As noted above, the primary basis of the development program of Allegra-D was demonstration of bioequivalence to approved formulations of fexofenadine HCL (Allegra) and

PSE. Please refer to the Clinical Pharmacology and Biopharmaceutics review prepared by Dr. Gillespie for complete details of this aspect of the review. In the single dose bioequivalence study, usual bioequivalence criteria were met for AUC and Cmin for both fexofenadine and HCL; however, Cmax failed for both comparisons (Cmax for PSE was lower with a 90% CI of 0.78-0.83 and Cmax for fexofenadine was higher with a 90% CI of 1.04-1.34). In the multiple-dose bioequivalence study, Allegra-D was bioequivalent to the reference products (NOTE: This finding confirms that the single-dose study is a more sensitive detector of differences between formulations.) No PK interaction was noted between fexofenadine HCL and PSE when administered concomitantly; however, administration of Allegra-D with food resulted in significant reduction in the bioavailability of the fexofenadine HCL component. This finding could impact on the efficacy of the product if taken with food and will be reflected in the labeling. With regard to dissolution, the Division does not feel that the current method proposed by the sponsor is sufficiently discriminating for this product. The sponsor and the Division have agreed to interim test methods and specifications for dissolution pending the sponsor's development of a new dissolution method and specification as a Phase 4 commitment.

There are no outstanding clinical pharmacology and biopharmaceutics issues and the application is approvable. The sponsor will be reminded in the action letter of their Phase 4 commitment with regard to

Data Verification

The Division of Scientific Investigations was not asked to audit any of the clinical investigations for this NDA.

Labeling

The package insert, carton, and container labeling as submitted by the sponsor on December 19, 1997, have been reviewed by the appropriate disciplines and is acceptable with minor modifications which will be communicated to the sponsor in the action letter. The trademark "Allegra-D" is acceptable to the Division and the Labeling and Nomenclature Committee.

Conclusion

There are no significant outstanding deficiencies, therefore, this NDA should be APPROVED. The sponsor will be instructed in the approval letter to make some minor editorial changes in the package insert. They will also be reminded of their Phase 4 commitments and CMC agreements in the letter.

cc:
NDA 20-786
HFD-570 Division Files
HFD-570/Jenkins
HFD-570/Schumaker
HFD-570/Trout