CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-786 /S003
20-625/S007

Trade Name: Allegra Tablets
Allegra Extended Release Tablets

Generic Name: fexofenadine hydrochloride
fexofenadine hydrochloride/pseudoephedrine

Sponsor: Hoechst Marion Roussel

Approval Date: December 22, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-786 /S003

20-625/S007

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-786 /S003

20-626/S007

APPROVAL LETTER

DEC 22 1998

NDA 20-625/S-007
NDA 20-786/S-007

Hoechst Marion Roussel
P.O. Box 9627
10236 Marion Park Drive
Kansas City, MO 64134-0627

Attention: Kim Leitzke
US Regulatory Affairs, Marketed Products

Dear Ms. Leitzke:

Please refer to your supplemental new drug applications dated June 19, 1998, received June 22, 1998, submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Allegra (fexofenadine HCl) Capsules, 60 mg and Allegra D (fexofenadine HCl and pseudoephedrine HCl, 120 mg) Extended Release Tablets.

These supplemental new drug applications provide for revisions to the DRUG INTERACTIONS (characterization of the metabolism of and the interactions between fexofenadine and ketoconazole and between fexofenadine and erythromycin) and OVERDOSAGE (inclusion of reports of dizziness, drowsiness and dry mouth following overdose of fexofenadine HCl) Sections of the Package Insert.

We have completed the review of these supplemental applications and they are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted June 1, 1998).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplements NDA 20-625/S-007 and NDA 20-786/S-007." Approval of these submissions by FDA is not required before the labeling is used.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Ms. Gretchen Trout, Project Manager, at (301) 827-1058.

Sincerely yours,

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDAs 20-625, 20-786
HFD-570/Div. Files
HFD-570/Dunn
HFD-570/Worobec/12-21-98
HFD-570/Bertha
HFD-570/Himmel/12-21-98
HFD-570/Poochikian
HFD-570/Sancilio
HFD-570/Sun
HFG-570/Trout
HF-2/MedWatch (with labeling)
HFD-102/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-21/ACS (with labeling) - for drug discussed at advisory committee meeting.
HFD-95/DDMS (with labeling)
DISTRICT OFFICE

12/22/98

Drafted by: KD/December 18, 1998
Initialed by: Schumaker/12-21-98
Uppoor/12-21-98
final: Campbell/12-22-98
filename: C:\mydocumets\NDAs\N20625_20786.AP.doc
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APPROVAL (AP)

12/22/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-786/S003

20-625/S007

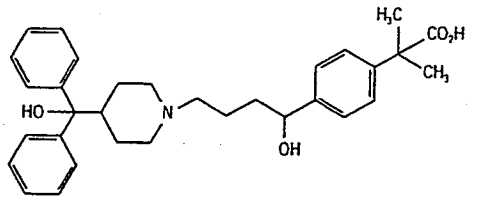
LABELING

Prescribing Information as of June 1998A

ALLEGRA®
(fexofenadine hydrochloride) Capsules
60 mg

DESCRIPTION

Fexofenadine hydrochloride, the active ingredient of ALLEGRA®, is a histamine H_1-receptor antagonist with the chemical name (±)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α,α-dimethyl benzeneacetic acid hydrochloride. It has the following chemical structure:



• HCl

The molecular weight is 538.13 and the empirical formula is $C_{32}H_{39}NO_4$•HCl. Fexofenadine hydrochloride is a white to off-white crystalline powder. It is freely soluble in methanol and ethanol, slightly soluble in chloroform and water, and insoluble in hexane. Fexofenadine hydrochloride is a racemate and exists as a zwitterion in aqueous media at physiological pH.

ALLEGRA is formulated as capsules for oral administration. Each capsule contains 60 mg fexofenadine hydrochloride and the following excipients: croscarmellose sodium, gelatin, lactose, microcrystalline cellulose, and pregelatinized starch. The printed capsule shell is made from gelatin, iron oxide, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and other ingredients.

CLINICAL PHARMACOLOGY

Mechanism of Action

Fexofenadine, a metabolite of terfenadine, is an antihistamine with selective peripheral H_1-receptor antagonist activity. Fexofenadine inhibited antigen-induced bronchospasm in sensitized guinea pigs and histamine release from peritoneal mast cells in rats. In laboratory animals, no anticholinergic or alpha$_1$-adrenergic-receptor blocking effects were observed. Moreover, no sedative or other central nervous system effects were observed. Radiolabeled tissue distribution studies in rats indicated that fexofenadine does not cross the blood-brain barrier.

Pharmacokinetics

Fexofenadine hydrochloride was rapidly absorbed following oral administration of a single dose of two 60-mg capsules to healthy male volunteers with a mean time to maximum plasma concentration occurring at 2.6 hours postdose. After administration of a single 60-mg dose as an oral solution to healthy subjects, the mean plasma concentration was 209 ng/mL. Mean steady-state peak plasma concentrations of 286 ng/mL were observed when healthy volunteers were administered multiple doses of fexofenadine hydrochloride (60 mg oral solution every 12 hours for 10 doses). Fexofenadine pharmacokinetics were linear for oral doses up to 120 mg twice daily. Although the absolute bioavailability of fexofenadine hydrochloride capsules is unknown, the capsules are bioequivalent to an oral solution. The mean elimination half-life of fexofenadine was 14.4 hours following administration of 60 mg, twice daily, to steady-state in normal volunteers.

Human mass balance studies documented a recovery of approximately 80% and 11% of the [^{14}C] fexofenadine hydrochloride dose in the feces and urine, respectively. Approximately 5% of the total dose was metabolized. Because the absolute bioavailability of fexofenadine hydrochloride has not been established, it is unknown if the fecal component represents unabsorbed drug or the result of biliary excretion.

The pharmacokinetics of fexofenadine hydrochloride in seasonal allergic rhinitis patients were similar to those in healthy subjects. Peak fexofenadine plasma concentrations were similar between adolescent (12-16 years of age) and adult patients.

Fexofenadine is 60% to 70% bound to plasma proteins, primarily albumin and α_1-acid glycoprotein.

Special Populations

Special population pharmacokinetics (for age and renal and hepatic impairment), obtained after a single dose of 80 mg fexofenadine hydrochloride, were compared to those from normal subjects in a separate study of similar design. While subject weights were relatively uniform between studies, these special population patients were substantially older than the healthy, young volunteers. Thus, an age effect may be confounding the pharmacokinetic differences observed in some of the special populations.

Effect of Age. In older subjects (≥65 years old), peak plasma levels of fexofenadine were 99% greater than those observed in normal volunteers (<65 years old). Mean elimination half-lives were similar to those observed in normal volunteers.

Renally Impaired. In patients with mild (creatinine clearance 41-80 mL/min) to severe (creatinine clearance 11-40 mL/min) renal impairment, peak plasma levels of fexofenadine were 87% and 111% greater, respectively, and mean elimination half-lives were 59% and 72% longer, respectively, than observed in normal volunteers. Peak plasma levels in patients on dialysis (creatinine clearance ≤ 10 mL/min) were 82% greater and half-life was 31% longer than observed in normal volunteers. Based on increases in bioavailability and half-life, a dose of 60 mg once daily is recommended as the starting dose in patients with decreased renal function. (See DOSAGE AND ADMINISTRATION.)

Hepatically Impaired. The pharmacokinetics of fexofenadine hydrochloride in patients with hepatic disease did not differ substantially from that observed in healthy subjects.

Effect of Gender. Across several trials, no clinically significant gender-related differences were observed in the pharmacokinetics of fexofenadine.

Pharmacodynamics

Wheal and Flare. Human histamine skin wheal and flare studies following single and twice daily doses of 20 mg and 40 mg fexofenadine hydrochloride demonstrated that the drug exhibits an antihistamine effect by 1 hour, achieves maximum effect at 2-3 hours, and an effect is still seen at 12 hours. There was no evidence of tolerance to these effects after 28 days of dosing.

Effects on QTc. In dogs, (10 mg/kg/day, orally for 5 days) and rabbits (10 mg/kg, intravenously over one hour) fexofenadine did not prolong QTc at plasma concentrations that were at least 28 and 63 times, respectively, the therapeutic plasma concentrations in man (based on a 60 mg twice daily fexofenadine hydrochloride dose). No effect was observed on calcium channel current, delayed K^+ channel current, or action potential duration in guinea pig myocytes, Na^+ current in rat neonatal myocytes, or on the delayed rectifier K^+ channel cloned from human heart at concentrations up to 1 x 10^{-5} M of fexofenadine. This concentration was at least 32 times the therapeutic plasma concentration in man (based on a 60-mg twice daily fexofenadine hydrochloride dose).

No statistically significant increase in mean QTc interval compared to placebo was observed in 714 seasonal allergic rhinitis patients given fexofenadine hydrochloride capsules in doses of 60 mg to 240 mg

twice daily for two weeks or in 40 healthy volunteers given fexofenadine hydrochloride as an oral solution at doses up to 400 mg twice daily for 6 days.

Clinical Studies

In three, 2-week, multi-center, randomized, double-blind, placebo-controlled trials in patients 12-68 years of age with seasonal allergic rhinitis (n=1634), fexofenadine hydrochloride 60 mg twice daily significantly reduced total symptom scores (the sum of the individual scores for sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes) compared to placebo. Statistically significant reductions in symptom scores were observed following the first 60-mg dose, with the effect maintained throughout the 12-hour interval. In general, there was no additional reduction in total symptom scores with higher doses of fexofenadine up to 240 mg twice daily. Although the number of subjects in some of the subgroups was small, there were no significant differences in the effect of fexofenadine hydrochloride across subgroups of patients defined by gender, age, and race. Onset of action for reduction in total symptom scores, excluding nasal congestion, was observed at 60 minutes compared to placebo following a single 60-mg fexofenadine hydrochloride dose administered to patients with seasonal allergic rhinitis who were exposed to ragweed pollen in an environmental exposure unit.

INDICATIONS AND USAGE

ALLEGRA is indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes.

CONTRAINDICATIONS

ALLEGRA is contraindicated in patients with known hypersensitivity to any of its ingredients.

PRECAUTIONS

Drug Interactions

Fexofenadine has been shown to exhibit minimal (ca. 5%) metabolism. However, co-administration of fexofenadine with ketoconazole and erythromycin led to increased plasma levels of fexofenadine. Fexofenadine had no effect on the pharmacokinetics of erythromycin and ketoconazole. In two separate studies, fexofenadine HCl 120 mg BID (twice the recommended dose) was co-administered with erythromycin 500 mg every 8 hours or ketoconazole 400 mg once daily under steady-state conditions to normal, healthy volunteers (n=24, each study). No differences in adverse events or QTc interval were observed when subjects were administered fexofenadine HCl alone or in combination with erythromycin or ketoconazole. The findings of these studies are summarized in the following table:

Effects on Steady-State Fexofenadine Pharmacokinetics After 7 Days of Co-Administration with Fexofenadine Hydrochloride 120 mg Every 12 Hours (twice recommended dose) in Normal Volunteers (n=24)

Concomitant Drug	$C_{max\ SS}$ *(Peak plasma concentration)*	$AUC_{SS(0\text{-}12\,h)}$ *(Extent of systemic exposure)*
Erythromycin (500 mg every 8 hrs)	+82%	+109%
Ketoconazole (400 mg once daily)	+135%	+164%

The changes in plasma levels were within the range of plasma levels achieved in adequate and well-controlled clinical trials.

1 The mechanism of these interactions has been evaluated in *in vitro, in situ* and *in vivo* animal models. These studies indicate that ketoconazole or erythromycin co-administration enhances fexofenadine gastrointestinal absorption. In vivo animal studies also suggest that in addition to enhancing absorption, ketoconazole decreases fexofenadine gastrointestinal secretion, while erythromycin may also decrease biliary excretion. 1

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential and reproductive toxicity of fexofenadine hydrochloride were assessed using terfenadine studies with adequate fexofenadine exposure (based on plasma area-under-the-curve [AUC] values). No evidence of carcinogenicity was observed when mice and rats were given daily oral doses of 50 and 150 mg/kg of terfenadine for 18 and 24 months, respectively; these doses resulted in plasma AUC values of fexofenadine that were up to four times the human therapeutic value (based on a 60-mg twice-daily fexofenadine hydrochloride dose).

In in-vitro (Bacterial Reverse Mutation, CHO/HGPRT Forward Mutation, and Rat Lymphocyte Chromosomal Aberration assays) and in-vivo (Mouse Bone Marrow Micronucleus assay) tests, fexofenadine hydrochloride revealed no evidence of mutagenicity.

In rat fertility studies, dose-related reductions in implants and increases in postimplantation losses were observed at oral doses equal to or greater than 150 mg/kg of terfenadine; these doses produced plasma AUC values of fexofenadine that were equal to or greater than three times the human therapeutic value (based on a 60-mg twice-daily fexofenadine hydrochloride dose).

Pregnancy

Teratogenic Effects: Category C. There was no evidence of teratogenicity in rats or rabbits at oral terfenadine doses up to 300 mg/kg; these doses produced fexofenadine plasma AUC values that were up to 4 and 37 times the human therapeutic value (based on a 60-mg twice-daily fexofenadine hydrochloride dose), respectively.

There are no adequate and well-controlled studies in pregnant women. Fexofenadine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects. Dose-related decreases in pup weight gain and survival were observed in rats exposed to oral doses equal to and greater than 150 mg/kg of terfenadine; at these doses the plasma AUC values of fexofenadine were equal to or greater than 3 times the human therapeutic values (based on a 60-mg twice-daily fexofenadine hydrochloride dose).

Nursing Mothers

There are no adequate and well-controlled studies in women during lactation. Because many drugs are excreted in human milk, caution should be exercised when fexofenadine hydrochloride is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of ALLEGRA in pediatric patients under the age of 12 years have not been established. Across well-controlled clinical trials in patients with seasonal allergic rhinitis, a total of 205 patients between the ages of 12 to 16 years received doses ranging from 20 mg to 240 mg twice daily for up to two weeks. Adverse events were similar in this group compared to patients above the age of 16 years.

Geriatric Use

In placebo-controlled trials, 42 patients, age 60 to 68 years, received doses of 20 mg to 240 mg of fexofenadine twice daily for up to two weeks. Adverse events were similar in this group to patients under age 60 years.

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1 See Reference No. 1

ADVERSE REACTIONS

In placebo-controlled clinical trials, which included 2461 patients receiving fexofenadine hydrochloride at doses of 20 mg to 240 mg twice daily, adverse events were similar in fexofenadine hydrochloride and placebo-treated patients. The incidence of adverse events, including drowsiness, was not dose related and was similar across subgroups defined by age, gender, and race. The percent of patients who withdrew prematurely because of adverse events was 2.2% with fexofenadine hydrochloride vs 3.3% with placebo. All adverse events that were reported by greater than 1% of patients who received the recommended daily dose of fexofenadine hydrochloride (60 mg twice-daily), and that were more common with fexofenadine than placebo, are listed in the following table.

Adverse Experiences Reported in Placebo-Controlled Seasonal Allergic Rhinitis Clinical Trials at Rates of Greater Than 1%

Adverse Experience	*Fexofenadine 60 mg Twice Daily (n=679)*	*Placebo Twice Daily (n=671)*
Viral Infection (cold, flu)	2.5%	1.5%
Nausea	1.6%	1.5%
Dysmenorrhea	1.5%	0.3%
Drowsiness	1.3%	0.9%
Dyspepsia	1.3%	0.6%
Fatigue	1.3%	0.9%

Adverse events occurring in greater than 1% of fexofenadine hydrochloride-treated patients (60 mg twice daily), but that were more common in the placebo-treated group, include headache and throat irritation.

The frequency and magnitude of laboratory abnormalities were similar in fexofenadine hydrochloride and placebo-treated patients.

OVERDOSAGE

Most reports of fexofenadine hydrochloride overdose contain limited information. However, dizziness, drowsiness, and dry mouth have been reported. Single doses of fexofenadine hydrochloride up to 800 mg (6 normal volunteers at this dose level), and doses up to 690 mg twice daily for one month (3 normal volunteers at this dose level), were administered without the development of clinically significant adverse events. — 2

In the event of overdose, consider standard measures to remove any unabsorbed drug. Symptomatic and supportive treatment is recommended.

Hemodialysis did not effectively remove fexofenadine from blood (up to 1.7% removed) following terfenadine administration.

No deaths occurred at oral doses of fexofenadine hydrochloride up to 5000 mg/kg in mice (170 times the maximum recommended human daily oral dose based on mg/m^2) and up to 5000 mg/kg in rats (330 times the maximum recommended human daily oral dose based on mg/m^2). Additionally, no clinical signs of toxicity or gross pathological findings were observed. In dogs, no evidence of toxicity was observed at oral doses up to 2000 mg/kg (450 times the maximum recommended human daily oral dose based on mg/m^2).

DOSAGE AND ADMINISTRATION

The recommended dose of ALLEGRA is 60 mg twice daily for adults and children 12 years of age and older.

A dose of 60 mg once daily is recommended as the starting dose in patients with decreased renal function. (See CLINICAL PHARMACOLOGY.)

HOW SUPPLIED

ALLEGRA 60-mg capsules are available in: high-density polyethylene (HDPE) bottles of 60 (NDC 0088-1102-41); HDPE bottles of 100 (NDC 0088-1102-47); HDPE bottles of 500 (NDC 0088-1102-55); and aluminum-foil blister packs of 100 (NDC 0088-1102-49).

ALLEGRA capsules have a white opaque cap and a pink opaque body. The capsules are imprinted in black ink, with "60 mg" on the cap, and "1102" on the body or "allegra" on the cap and "60 mg" on the body.

Store ALLEGRA capsules at controlled room temperature 20-25°C (68-77°F). Foil-backed blister packs should be protected from excessive moisture.

Prescribing Information as of June 1998A

Hoechst Marion Roussel, Inc.
Kansas City, MO 64137 USA

US Patents 4,254,129; 5,375,693; 5,578,610.

allp0698Ap

Hoechst Marion Roussel

The Pharmaceutical Company of Hoechst
Kansas City, MO 64134

Hoechst

2 See Reference No. 2-6

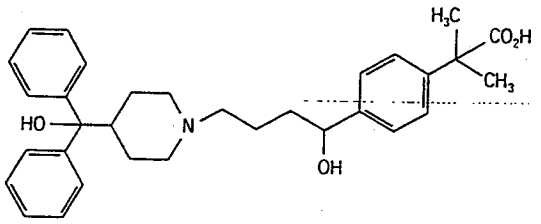
Prescribing Information as of June 1998A

ALLEGRA-D®
(fexofenadine HCl 60 mg and pseudoephedrine HCl 120 mg)
Extended-Release Tablets

DESCRIPTION

ALLEGRA-D® (fexofenadine hydrochloride and pseudoephedrine hydrochloride) Extended-Release Tablets for oral administration contain 60 mg fexofenadine hydrochloride for immediate-release and 120 mg pseudoephedrine hydrochloride for extended-release. Tablets also contain as excipients: microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, magnesium stearate, carnauba wax, stearic acid, silicon dioxide, hydroxypropyl methylcellulose and polyethylene glycol.

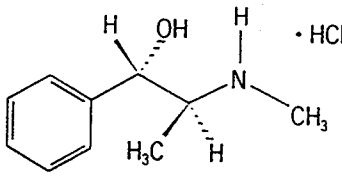
Fexofenadine hydrochloride, one of the active ingredients of ALLEGRA-D, is a histamine H_1-receptor antagonist with the chemical name (±)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α, α-dimethyl benzeneacetic acid hydrochloride and the following chemical structure:



• HCl

The molecular weight is 538.13 and the empirical formula is $C_{32}H_{39}NO_4$•HCl. Fexofenadine hydrochloride is a white to off-white crystalline powder. It is freely soluble in methanol and ethanol, slightly soluble in chloroform and water, and insoluble in hexane. Fexofenadine hydrochloride is a racemate and exists as a zwitterion in aqueous media at physiological pH.

Pseudoephedrine hydrochloride, the other active ingredient of ALLEGRA-D, is an adrenergic (vasoconstrictor) agent with the chemical name [S-(R*,R*)]-α-[1-(methylamino)ethyl]-benzene-methanol hydrochloride and the following chemical structure:



The molecular weight is 201.70. The molecular formula is $C_{10}H_{15}NO$•HCl. Pseudoephedrine hydrochloride occurs as fine, white to off-white crystals or powder, having a faint characteristic odor. It is very soluble in water, freely soluble in alcohol, and sparingly soluble in chloroform.

CLINICAL PHARMACOLOGY

Mechanism of Action

Fexofenadine hydrochloride, the major active metabolite of terfenadine, is an antihistamine with selective peripheral H_1-receptor antagonist activity. Fexofenadine hydrochloride inhibited antigen-induced bronchospasm in sensitized guinea pigs and histamine release from peritoneal mast cells in rats. In laboratory animals, no anticholinergic or alpha$_1$-adrenergic-receptor blocking effects were observed. Moreover, no sedative or other central nervous system effects were observed. Radiolabeled tissue distribution studies in rats indicated that fexofenadine does not cross the blood-brain barrier.

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. At the recommended oral dose, it has little or no pressor effect in normotensive adults.

Pharmacokinetics

The pharmacokinetics of fexofenadine hydrochloride and pseudoephedrine hydrochloride when administered separately have been well characterized. Fexofenadine pharmacokinetics were linear for oral doses of fexofenadine hydrochloride up to 120 mg twice daily. The mean elimination half-life of fexofenadine was 14.4 hours following administration of 60 mg fexofenadine hydrochloride, twice daily, to steady-state in normal volunteers. Human mass balance studies documented a recovery of approximately 80% and 11% of the [^{14}C] fexofenadine hydrochloride dose in the feces and urine, respectively. Approximately 5% of the total dose was metabolized. Because the absolute bioavailability of fexofenadine hydrochloride has not been established, it is unknown if the fecal component is unabsorbed drug or the result of biliary excretion. The pharmacokinetics of fexofenadine hydrochloride in seasonal allergic rhinitis patients were similar to those in healthy subjects. Peak fexofenadine plasma concentrations were similar between adolescent (12-16 years of age) and adult patients. Fexofenadine is 60% to 70% bound to plasma proteins, primarily albumin and α_1-acid glycoprotein.

Pseudoephedrine has been shown to have a mean elimination half-life of 4-6 hours which is dependent on urine pH. The elimination half-life is decreased at urine pH lower than 6 and may be increased at urine pH higher than 8.

The bioavailability of fexofenadine hydrochloride and pseudoephedrine hydrochloride from ALLEGRA-D Extended-Release Tablets is similar to that achieved with separate administration of the components. Coadministration of fexofenadine and pseudoephedrine does not significantly affect the bioavailability of either component.

Fexofenadine hydrochloride was rapidly absorbed following single-dose administration of the 60 mg fexofenadine hydrochloride/120 mg pseudoephedrine hydrochloride tablet with median time to mean maximum fexofenadine plasma concentration of 191 ng/mL occurring 2 hours postdose. Pseudoephedrine hydrochloride produced a mean single-dose pseudoephedrine peak plasma concentration of 206 ng/mL which occurred 6 hours postdose. Following multiple dosing to steady-state, a fexofenadine peak concentration of 255 ng/mL was observed 2 hours postdose. Following multiple dosing to steady-state, a pseudoephedrine peak concentration of 411 ng/mL was observed 5 hours postdose. Coadministration of ALLEGRA-D with a high-fat meal decreased fexofenadine plasma concentrations C_{max} (–46%) and AUC (–42%). Time to maximum concentration (T_{max}) was delayed by 50%. The rate or extent of pseudoephedrine absorption was not affected by food. It is recommended that the administration of ALLEGRA-D with food should be avoided. (See DOSAGE AND ADMINISTRATION).

Special Populations

Special population pharmacokinetics (for renal and hepatic impairment and age), obtained after a single dose of 80 mg fexofenadine hydrochloride, were compared to those from normal subjects in a separate study of similar design. While subject weights were relatively uniform between studies, these special population patients were substantially older than the healthy, young volunteers. Thus, an age effect may be confounding the pharmacokinetic differences observed in some of the special populations.

Effect of Age. In older subjects (≥65 years old), peak plasma levels of fexofenadine were 99% greater than those observed in younger subjects (<65 years old). Mean elimination half-lives were similar to those observed in younger subjects.

Renally Impaired. In patients with mild (creatinine clearance 41-80 mL/min) to severe (creatinine clearance 11-40 mL/min) renal impairment, peak plasma levels of fexofenadine were 87% and 111% greater, respectively, and mean elimination half-lives were 59% and 72% longer, respectively, than observed in normal volunteers. Peak plasma levels in patients on dialysis (creatinine clearance ≤10 mL/min) were 82% greater and half-life was 31% longer than observed in normal volunteers.

About 55-75% of an administered dose of pseudoephedrine hydrochloride is excreted unchanged in the urine; the remainder is apparently metabolized in the liver. Therefore, pseudoephedrine may accumulate in patients with renal insufficiency.

Based on increases in bioavailability and half-life of fexofenadine hydrochloride and pseudoephedrine hydrochloride, a dose of one tablet once daily is recommended as the starting dose in patients with decreased renal function (See DOSAGE AND ADMINISTRATION).

Hepatically Impaired. The pharmacokinetics of fexofenadine hydrochloride in patients with hepatic disease did not differ substantially from that observed in healthy subjects. The effect on pseudoephedrine pharmacokinetics is unknown.

Effect of Gender. Across several trials, no clinically significant gender-related differences were observed in the pharmacokinetics of fexofenadine hydrochloride.

Pharmacodynamics

Wheal and Flare. Human histamine skin wheal and flare studies following single and twice daily doses of 20 mg and 40 mg fexofenadine hydrochloride demonstrated that the drug exhibits an antihistamine effect by 1 hour, achieves maximum effect at 2-3 hours, and an effect is still seen at 12 hours. There was no evidence of tolerance to these effects after 28 days of dosing. The clinical significance of these observations is not known.

Effects on QT_C. In dogs, (10 mg/kg/day, orally for 5 days) and rabbits (10 mg/kg, intravenously over one hour) fexofenadine hydrochloride did not prolong QT_C at plasma concentrations that were at least 28 and 63 times, respectively, the therapeutic plasma concentrations in man (based on a 60 mg twice daily fexofenadine hydrochloride dose). No effect was observed on calcium channel current, delayed K^+ channel current, or action potential duration in guinea pig myocytes, Na^+ current in rat neonatal myocytes, or on the delayed rectifier K^+ channel cloned from human heart at concentrations up to 1×10^{-5} M of fexofenadine. This concentration was at least 32 times the therapeutic plasma concentration in man (based on a 60 mg twice daily fexofenadine hydrochloride dose).

No statistically significant increase in mean QT_C interval compared to placebo was observed in 714 seasonal allergic rhinitis patients given fexofenadine hydrochloride capsules in doses of 60 mg to 240 mg twice daily for two weeks or in 40 healthy volunteers given fexofenadine hydrochloride as an oral solution at doses up to 400 mg twice daily for 6 days.

A one year study designed to evaluate safety and tolerability of 240 mg of fexofenadine hydrochloride (n=240) compared to placebo (n=237) in healthy subjects, did not reveal a statistically significant increase in the mean QT_C interval for the fexofenadine hydrochloride treated group when evaluated pretreatment and after 1, 2, 3, 6, 9, and 12 months of treatment.

Administration of the 60 mg fexofenadine hydrochloride/120 mg pseudoephedrine hydrochloride combination tablet for approximately 2 weeks to 213 patients with seasonal allergic rhinitis demonstrated no statistically significant increase in the mean QT_C interval compared to fexofenadine hydrochloride administered alone (60 mg twice daily, n=215), or compared to pseudoephedrine hydrochloride (120 mg twice daily, n=215) administered alone.

Clinical Studies

In a 2-week, multicenter, randomized, double-blind, active-controlled trial in patients 12-65 years of age with seasonal allergic rhinitis due to ragweed allergy (n=651), the 60 mg fexofenadine hydrochloride/120 mg pseudoephedrine hydrochloride combination tablet administered twice daily significantly reduced the intensity of sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes, and nasal congestion.

In three, 2-week, multicenter, randomized, double-blind, placebo-controlled trials in patients 12-68 years of age with seasonal allergic rhinitis (n=1634), fexofenadine hydrochloride 60 mg twice daily significantly reduced total symptom scores (the sum of the individual scores for sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes) compared to placebo. Statistically significant reductions in symptom scores were observed following the first 60 mg dose, with the effect maintained throughout the 12-hour interval. In general, there was no additional reduction in total symptom scores with higher doses of fexofenadine hydrochloride up to 240 mg twice daily. Although the number of subjects in some of the subgroups was small, there were no significant differences in the effect of fexofenadine hydrochloride across subgroups of patients defined by gender, age, and race. Onset of action for reduction in total symptom scores, excluding nasal congestion, was observed at 60 minutes compared to placebo following a single 60 mg fexofenadine hydrochloride dose administered to patients with seasonal allergic rhinitis who were exposed to ragweed pollen in an environmental exposure unit.

INDICATIONS AND USAGE

ALLEGRA-D is indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, itchy nose/palate/ and/or throat, itchy/watery/red eyes, and nasal congestion. ALLEGRA-D should be administered when both the antihistaminic properties of fexofenadine hydrochloride and the nasal decongestant properties of pseudoephedrine hydrochloride are desired (see CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

ALLEGRA-D is contraindicated in patients with known hypersensitivity to any of its ingredients.

Due to its pseudoephedrine component, ALLEGRA-D is contraindicated in patients with narrow-angle glaucoma or urinary retention, and in patients receiving monoamine oxidase (MAO) inhibitor therapy or within fourteen (14) days of stopping such treatment (see Drug Interactions section). It is also contraindicated in patients with severe hypertension, or severe coronary artery disease, and in those who have shown hypersensitivity or idiosyncrasy to its components, to adrenergic agents, or to other drugs of similar chemical structures. Manifestations of patient idiosyncrasy to adrenergic agents include: insomnia, dizziness, weakness, tremor, or arrhythmias.

WARNINGS

Sympathomimetic amines should be used judiciously and sparingly in patients with hypertension, diabetes mellitus, ischemic heart disease, increased intraocular pressure, hyperthyroidism, renal impairment, or prostatic hypertrophy (see CONTRAINDICATIONS). Sympathomimetic amines may produce central nervous system stimulation with convulsions or cardiovascular collapse with accompanying hypotension.

PRECAUTIONS

General

Due to its pseudoephedrine component, ALLEGRA-D should be used with caution in patients with hypertension, diabetes mellitus, ischemic heart disease, increased intraocular pressure, hyperthyroidism, renal impairment, or prostatic hypertrophy (see WARNINGS and CONTRAINDICATIONS). Patients with decreased renal function should be given a lower initial dose (one tablet per day) because they have reduced elimination of fexofenadine and pseudoephedrine (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Information for Patients

Patients taking ALLEGRA-D tablets should receive the following information: ALLEGRA-D tablets are prescribed for the relief of symptoms of seasonal allergic rhinitis. Patients should be instructed to take ALLEGRA-D tablets only as prescribed. **Do not exceed the recommended dose.** If nervousness, dizziness, or sleeplessness occur, discontinue use and consult the doctor. Patients should also be advised against the concurrent use of ALLEGRA-D tablets with over-the-counter antihistamines and decongestants.

The product should not be used by patients who are hypersensitive to it or to any of its ingredients. Due to its pseudoephedrine component, this product should not be used by patients with narrow-angle glaucoma, urinary retention, or by patients receiving a monoamine oxidase (MAO) inhibitor or within 14 days of stopping use of MAO inhibitor. It also should not be used by patients with severe hypertension or severe coronary artery disease.

Patients should be told that this product should be used in pregnancy or lactation only if the potential benefit justifies the potential risk to the fetus or nursing infant. Patients should be cautioned not to break or chew the tablet. Patients should be directed to swallow the tablet whole. Patients should be instructed not to take the tablet with food. Patients should also be instructed to store the medication in a tightly closed container in a cool, dry place, away from children.

Drug Interactions

Fexofenadine hydrochloride and pseudoephedrine hydrochloride do not influence the pharmacokinetics of each other when administered concomitantly

Fexofenadine has been shown to exhibit minimal (ca. 5%) metabolism. However, co-administration of fexofenadine with ketoconazole and erythromycin led to increased plasma levels of fexofenadine. Fexofenadine had no effect on the pharmacokinetics of erythromycin and ketoconazole. In two separate studies, fexofenadine HCl 120 mg BID (twice the recommended dose) was co-administered with erythromycin 500 mg every 8 hours or ketoconazole 400 mg once daily under steady-state conditions to normal, healthy volunteers (n=24 each study). No differences in adverse events or QTc interval were observed when subjects were administered fexofenadine HCl alone or in combination with erythromycin or ketoconazole. The findings of these studies are summarized in the following table:

Effects on Steady-State Fexofenadine Pharmacokinetics After 7 Days of Co-Administration with Fexofenadine Hydrochloride 120 mg Every 12 Hours (twice recommended dose) in Normal Volunteers (n=24)

Concomitant Drug	$C_{max\ SS}$ *(Peak plasma concentration)*	$AUC_{SS(0\text{-}12h)}$ *(Extent of systemic exposure)*
Erythromycin (500 mg every 8 hrs)	+82%	+109%
Ketoconazole (400 mg once daily)	+135%	+164%

The changes in plasma levels were within the range of plasma levels achieved in adequate and well-controlled clinical trials.

The mechanism of these interactions has been evaluated in *in vitro*, *in situ* and *in vivo* animal models. These studies indicate that ketoconazole or erythromycin co-administration enhances fexofenadine gastrointestinal absorption. In vivo animal studies also suggest that in addition to enhancing absorption, ketoconazole decreases fexofenadine gastrointestinal secretion, while erythromycin may also decrease biliary excretion. [1]

ALLEGRA-D tablets (pseudoephedrine component) are contraindicated in patients taking monoamine oxidase inhibitors and for 14 days after stopping use of an MAO inhibitor. Concomitant use with antihypertensive drugs which interfere with sympathetic activity (eg, methyldopa, mecamylamine, and reserpine) may reduce their antihypertensive effects. Increased ectopic pacemaker activity can occur when pseudoephedrine is used concomitantly with digitalis.

Care should be taken in the administration of ALLEGRA-D concomitantly with other sympathomimetic amines because combined effects on the cardiovascular system may be harmful to the patient (see WARNINGS).

Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no animal or in vitro studies on the combination product fexofenadine hydrochloride and pseudoephedrine hydrochloride to evaluate carcinogenesis, mutagenesis, or impairment of fertility.

The carcinogenic potential and reproductive toxicity of fexofenadine hydrochloride were assessed using terfenadine studies with adequate fexofenadine exposure (area-under-the plasma concentration versus time curve [AUC]). No evidence of carcinogenicity was observed when mice and rats were given daily oral doses up to 150 mg/kg of terfenadine for 18 and 24 months, respectively. In both species, 150 mg/kg of terfenadine produced AUC values of fexofenadine that were approximately 3 times the human AUC at the maximum recommended daily oral dose in adults.

Two-year feeding studies in rats and mice conducted under the auspices of the National Toxicology Program (NTP) demonstrated no evidence of carcinogenic potential with ephedrine sulfate, a structurally related drug with pharmacological properties similar to pseudoephedrine, at doses up to 10 and 27 mg/kg, respectively (approximately 1/3 and 1/2, respectively, the maximum recommended daily oral dose of pseudoephedrine hydrochloride in adults on a mg/m^2 basis).

In in-vitro (Bacterial Reverse Mutation, CHO/HGPRT Forward Mutation, and Rat Lymphocyte Chromosomal Aberration assays) and in vivo (Mouse Bone Marrow Micronucleus assay) tests, fexofenadine hydrochloride revealed no evidence of mutagenicity.

Reproduction and fertility studies with terfenadine in rats produced no effect on male or female fertility at oral doses up to 300 mg/kg/day. However, reduced implants and post implantation losses were reported at 300 mg/kg. A reduction in implants was also observed at an oral dose of 150 mg/kg/day. Oral doses of 150 and 300 mg/kg of terfenadine produced AUC values of fexofenadine that were approximately 3 and 4 times, respectively, the human AUC at the maximum recommended daily oral dose in adults.

Pregnancy

Teratogenic Effects: Category C. Terfenadine alone was not teratogenic in rats and rabbits at oral doses up to 300 mg/kg; 300 mg/kg of terfenadine produced fexofenadine AUC values that were approximately 4 and 30 times, respectively, the human AUC at the maximum recommended daily oral dose in adults.

The combination of terfenadine and pseudoephedrine hydrochloride in a ratio of 1:2 by weight was studied in rats and rabbits. In rats, an oral combination dose of 150/300 mg/kg produced reduced fetal weight and delayed ossification with a finding of wavy ribs. The dose of 150 mg/kg of terfenadine in rats produced an AUC value of fexofenadine that was approximately 3 times the human AUC at the maximum recommended

[1] See Reference No. 1

daily oral dose in adults. The dose of 300 mg/kg of pseudoephedrine hydrochloride in rats was approximately 10 times the maximum recommended daily oral dose in adults on a mg/m^2 basis. In rabbits, an oral combination dose of 100/200 mg/kg produced decreased fetal weight. By extrapolation, the AUC of fexofenadine for 100 mg/kg orally of terfenadine was approximately 10 times the human AUC at the maximum recommended daily oral dose in adults. The dose of 200 mg/kg of pseudoephedrine hydrochloride was approximately 15 times the maximum recommended daily oral dose in adults on a mg/m^2 basis.

There are no adequate and well-controlled studies in pregnant women. ALLEGRA-D should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects. Dose-related decreases in pup weight gain and survival were observed in rats exposed to an oral dose of 150 mg/kg of terfenadine; this dose produced an AUC of fexofenadine that was approximately 3 times the human AUC at the maximum recommended daily oral dose in adults.

Nursing Mothers

It is not known if fexofenadine is excreted in human milk. Because many drugs are excreted in human milk, caution should be used when fexofenadine hydrochloride is administered to a nursing woman. Pseudoephedrine hydrochloride administered alone distributes into breast milk of lactating human females. Pseudoephedrine concentrations in milk are consistently higher than those in plasma. The total amount of drug in milk as judged by AUC is 2 to 3 times greater than the plasma AUC. The fraction of a pseudoephedrine dose excreted in milk is estimated to be 0.4% to 0.7%. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when ALLEGRA-D is administered to nursing women.

Pediatric Use

Safety and effectiveness of ALLEGRA-D in pediatric patients under the age of 12 years have not been established.

Geriatric Use

Clinical studies of ALLEGRA-D did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, although the elderly are more likely to have adverse reactions to sympathomimetic amines. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

The pseudoephedrine component of ALLEGRA-D is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

ALLEGRA-D

In one clinical trial (n=651) in which 215 patients with seasonal allergic rhinitis received the 60 mg fexofenadine hydrochloride/120 mg pseudoephedrine hydrochloride combination tablet twice daily for up to 2 weeks, adverse events were similar to those reported either in patients receiving fexofenadine hydrochloride 60 mg alone (n=218 patients) or in patients receiving pseudoephedrine hydrochloride 120 mg alone (n=218). A placebo group was not included in this study.

The percent of patients who withdrew prematurely because of adverse events was 3.7% for the fexofenadine hydrochloride/pseudoephedrine hydrochloride combination group, 0.5% for the fexofenadine hydrochloride group, and 4.1% for the pseudoephedrine hydrochloride group. All adverse events that were reported by greater than 1% of patients who received the recommended daily dose of the fexofenadine hydrochloride/pseudoephedrine hydrochloride combination are listed in the following table.

Adverse Experiences Reported in One Active-Controlled Seasonal Allergic Rhinitis Clinical Trial at Rates of Greater than 1%

Adverse Experience	60 mg Fexofenadine Hydrochloride/120 mg Pseudoephedrine Hydrochloride Combination Tablet Twice Daily (n=215)	Fexofenadine Hydrochloride 60 mg Twice Daily (n=218)	Pseudoephedrine Hydrochloride 120 mg Twice Daily (n=218)
Headache	13.0%	11.5%	17.4%
Insomnia	12.6%	3.2%	13.3%
Nausea	7.4%	0.5%	5.0%
Dry Mouth	2.8%	0.5%	5.5%
Dyspepsia	2.8%	0.5%	0.9%
Throat Irritation	2.3%	1.8%	0.5%
Dizziness	1.9%	0.0%	3.2%
Agitation	1.9%	0.0%	1.4%
Back Pain	1.9%	0.5%	0.5%
Palpitation	1.9%	0.0%	0.9%
Nervousness	1.4%	0.5%	1.8%
Anxiety	1.4%	0.0%	1.4%
Upper Respiratory Infection	1.4%	0.9%	0.9%
Abdominal Pain	1.4%	0.5%	0.5%

Many of the adverse events occurring in the fexofenadine hydrochloride/pseudoephedrine hydrochloride combination group were adverse events also reported predominately in the pseudoephedrine hydrochloride group, such as insomnia, headache, nausea, dry mouth, dizziness, agitation, nervousness, anxiety, and palpitation.

Fexofenadine Hydrochloride

In placebo-controlled clinical trials, which included 2461 patients receiving fexofenadine hydrochloride at doses of 20 mg to 240 mg twice daily, adverse events were similar in fexofenadine hydrochloride and placebo-treated patients. The incidence of adverse events, including drowsiness, was not dose related and was similar across subgroups defined by age, gender, and race. The percent of patients who withdrew prematurely because of adverse events was 2.2% with fexofenadine hydrochloride vs 3.3% with placebo.

Pseudoephedrine Hydrochloride

Pseudoephedrine hydrochloride may cause mild CNS stimulation in hypersensitive patients. Nervousness, excitability, restlessness, dizziness, weakness, or insomnia may occur. Headache, drowsiness, tachycardia, palpitation, pressor activity, and cardiac arrhythmias have been reported. Sympathomimetic drugs have also been associated with other untoward effects such as fear, anxiety, tenseness, tremor, hallucinations, seizures, pallor, respiratory difficulty, dysuria, and cardiovascular collapse.

OVERDOSAGE

Most reports of fexofenadine hydrochloride overdose contain limited information. However, dizziness, drowsiness, and dry mouth have been reported. For the pseudoephedrine hydrochloride component of ALLEGRA-D, information on acute overdose is limited to the marketing history of pseudoephedrine hydrochloride. Single doses of fexofenadine hydrochloride up to 800 mg (6 normal volunteers at this dose level), and doses up to 690 mg twice daily for one month (3 normal

2

[2] See Reference No. 2-6

volunteers at this dose level), were administered without the development of clinically significant adverse events.

In large doses, sympathomimetics may give rise to giddiness, headache, nausea, vomiting, sweating, thirst, tachycardia, precordial pain, palpitations, difficulty in micturition, muscular weakness and tenseness, anxiety, restlessness, and insomnia. Many patients can present a toxic psychosis with delusions and hallucinations. Some may develop cardiac arrhythmias, circulatory collapse, convulsions, coma, and respiratory failure.

In the event of overdose, consider standard measures to remove any unabsorbed drug. Symptomatic and supportive treatment is recommended.

Hemodialysis did not effectively remove fexofenadine from blood (up to 1.7% removed) following terfenadine administration.

The effect of hemodialysis on the removal of pseudoephedrine is unknown.

No deaths occurred in mature mice and rats at oral doses of fexofenadine hydrochloride up to 5000 mg/kg (approximately 170 and 340 times, respectively, the maximum recommended daily oral dose in adults on a mg/m^2 basis.) The median oral lethal dose in newborn rats was 438 mg/kg (approximately 30 times the maximum recommended daily oral dose in adults on a mg/m^2 basis). In dogs, no evidence of toxicity was observed at oral doses up to 2000 mg/kg (approximately 450 times the maximum recommended human daily oral dose in adults on a mg/m^2 basis). The oral median lethal dose of pseudoephedrine hydrochloride in rats was 1674 mg/kg (approximately 55 times the maximum recommended daily oral dose in adults on a mg/m^2 basis).

DOSAGE AND ADMINISTRATION

The recommended dose of ALLEGRA-D is one tablet twice daily for adults and children 12 years of age and older. It is recommended that the administration of ALLEGRA-D with food should be avoided. A dose of one tablet once daily is recommended as the starting dose in patients with decreased renal function. (See CLINICAL PHARMACOLOGY and PRECAUTIONS.)

HOW SUPPLIED

ALLEGRA-D (fexofenadine hydrochloride and pseudoephedrine hydrochloride) Extended-Release Tablets are available in: high-density polyethylene (HDPE) bottles of 60 (NDC 0088-1090-41) with a polypropylene child-resistant cap containing a pulp/wax liner with heat-sealed foil inner seal; HDPE bottles of 100 (NDC 0088-1090-47) with a polypropylene screw cap containing a pulp/wax liner with heat-sealed foil inner seal; HDPE bottles of 500 (NDC 0088-1090-55) with a polypropylene screw cap containing a pulp/wax liner with heat-sealed foil inner seal; and aluminum foil-backed clear blister packs of 100 (NDC 0088-1090-49).

ALLEGRA-D is a two-layer tablet, one white layer and one tan layer with a clear film coating on the tablet. The tablets are engraved with "Allegra-D" on the white layer.

Store ALLEGRA-D Extended-Release Tablets at 20-25°C (68-77°F). (See USP Controlled Room Temperature.)

Prescribing Information as of June 1998A

Hoechst Marion Roussel, Inc.
Kansas City, MO 64137 USA

US Patents 4,254,129; 5,375,693, 5,578,610.

alldp0698Ap

Hoechst Marion Roussel

The Pharmaceutical Company of Hoechst
Kansas City, MO 64134

Hoechst

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-786/S003

20-625/S007

MEDICAL REVIEW(S)

Memorandum

Date: November 30, 1998

From: Alexandra S. Worobec, M.D.
Medical Officer, HFD-570, Division of Pulmonary Drug Products

Subject: Labeling Review for NDA 20-625: ALLEGRA (fexofenadine HCL) capsules 60 mg and NDA 20-786: ALLEGRA D (fexofenadine HCL 60 mg and pseudoephedrine HCL 120 mg) Extended Release Tablets

To: Keary L. Dunn, Project Manager
Division of Pulmonary Drug Products, HFD-570

Thru: Martin H. Himmel, M.D., Deputy Director, HFD-570

Drug interactions section should be reviewed by Biopharm as well.
M Himmel
12/1/98

We have reviewed the proposed labeling revisions to the DRUG INTERACTIONS and OVERDOSAGE sections of the package inserts of ALLEGRA (fexofenadine HCL) capsules 60 mg and ALLEGRA D (fexofenadine HCL 60 mg and pseudoephedrine HCL 120 mg) Extended Release Tablets. The proposed revisions to the patient package inserts are identical for these 2 drug products and are summarized as follows:

In the DRUG INTERACTIONS section of the package insert of ALLEGRA (fexofenadine HCL) capsules 60 mg and ALLEGRA D (fexofenadine HCL 60 mg and pseudoephedrine HCL 120 mg) Extended Release Tablets the following additional information has been added:

Paragraph 1: "Fexofenadine has been shown to exhibit minimal (ca. 5%) metabolism. However, co-administration of fexofenadine with ketoconazole and erythromycin led to increased plasma levels of fexofenadine. Fexofenadine had no effect on the pharmacokinetics of erythromycin and ketoconazole."

Paragraph 2: "The mechanism of these interactions has been evaluated in *in vitro*, *in situ* and *in vivo* animal models. These studies indicate that ketoconazole or erythromycin co-administration enhances fexofenadine gastrointestinal absorption. In vivo animal studies also suggest that in addition to enhancing absorption, ketoconazole decreases fexofenadine gastrointestinal secretion, while erythromycin may also decrease biliary excretion."

Deleted from paragraph 2 in the DRUG INTERACTIONS section was the following: "The mechanisms of these interactions are unknown, and the potential for interaction with other azole antifungal or macrolide agents

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-786/S003

20-625/S007

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DEC 1 7 1998

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-625, 20-786

DRUG: Allegra, Allegra-D

SPONSOR: Hoechst Marion Roussel

REVIEWER: Young-Moon Choi, Ph.D.
SUBMISSION DATE: 6/22/98
ASSIGNED DATE: 11/25/98

REVIEW DATE: 12/16/98

TYPE OF SUBMISSION: SLR-007 (Labeling Supplement)

1. SYNOPSIS

The sponsor submitted the proposed labeling changes under the sections of "Drug Interactions" and "OVERDOSAGE" as prior approval supplements before implementation. It should be noted that the proposed labeling is identical to the previously approved final printed labeling except where changes are indicated in the annotated labeling section. (See Appendix: Proposed Labeling)

The present submission contains:
(1) Clinical data of drug interaction
(2) Nonclinical data to support the mechanism of interaction between fexofenadine and ketoconazole, and between fexofenadine and erythromycin.
(3) References for adverse event reports to support OVERDOSAGE revision.

The present review focused on the data (1) and (2). The references for adverse event report need to be separately reviewed by the reviewing medical officer.

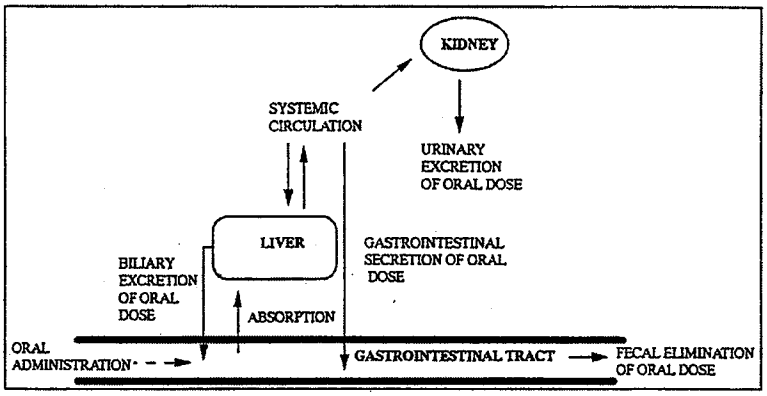
2. BACKGROUND INFORMATION

Terfenadine is eliminated by oxidative metabolism via CYP3A4. The concomitant administration of terfenadine with CYP3A4 inhibitors, e.g., ketoconazole and erythromycin, demonstrated clinically significant pharmacokinetic and pharmacodynamic drug –drug interactions. In addition, fexofenadine, an active metabolite of terfenadine, appeared significantly increased in plasma in those studies. In light of these previous experiences with terfenadine, the sponsor conducted human fexofenadine drug-drug interaction studies with ketoconazole and erythromycin.

The clinical data of fexofenadine demonstrated that:
(1) ketoconazole and erythromycin significantly increase fexofenadine AUC and decrease fexofenadine oral clearance. It should be noted that the changes in plasma levels were within the range of plasma levels achieved in adequate and well-controlled clinical trials. The two-fold and 2.6-fold increases in AUC have been observed during erythromycin and ketoconazole co-administration, respectively. It appeared that those increases have little clinical consequence. Therefore, the dosage adjustment has not been required;
(2) fexofenadine metabolism is not significant, and the fecal excretion is a major elimination route; and
(3) fecal elimination of oral fexofenadine may be attributed to biliary and/or gastrointestinal secretion.

In this context, the agency recommended a mechanistic study for fexofenadine drug interaction in the NDA 20-625 approval letter dated July 25, 1996. As per the agency's recommendation, the sponsor conducted non-clinical studies to understand the mechanism(s) of the fexofenadine-erythromycin and fexofenadine-ketoconazole drug interaction.

It should be noted that since fexofenadine is minimally metabolized and fecal excretion is the major elimination route (please see Figure: fexofenadine disposition model), the sponsor evaluated the drug-interaction mainly in terms of gastrointestinal absorption as well as excretion, and biliary excretion.



Fexofenadine Absorption & Disposition Model

3. SUMMARIZED EXPERIMENTAL METHODS and RESULTS

3-1. In vivo dog study

The sponsor conducted drug interaction studies using dog as an animal model in six different occasions:
(1) in vivo; fexofenadine intravenous injection ; no other drugs
(2) in vivo; fexofenadine intravenous injection ; with ketoconazole treatment
(3) in vivo; fexofenadine intravenous injection ; with erythromycin treatment
(4) in vivo; fexofenadine oral administration ; no other drugs
(5) in vivo; fexofenadine oral administration ; with ketoconazole treatment
(6) in vivo; fexofenadine oral administration ; with erythromycin treatment

To study biliary excretion, the sponsor also conducted drug interaction study in bile cannulated dogs in four different occasions:
(1) in vivo; fexofenadine intravenous injection ; with ketoconazole; bile collection
(2) in vivo; fexofenadine intravenous injection ; with ketoconazole; bile re-circulation
(3) in vivo; fexofenadine intravenous injection ; with erythromycin ; bile collection
(4) in vivo; fexofenadine intravenous injection ; with erythromycin ; bile re-circulation

In vivo dog study demonstrated that:
(1) both ketoconazole and erythromycin reduced the systemic oral clearance of fexofenadine;
(2) ketoconazole reduced the gastrointestinal excretion, while did not affect the renal and biliary excretion; and
(3) erythromycin significantly reduced the biliary excretion of fexofenadine, while did not affect the renal

and gastrointestinal excretion.

3-2. In vitro rat tissue study

To characterize the permeation of fexofenadine across rat intestine, the sponsor conducted in vitro diffusion studies using rat intestine and found that:

(1) Permeation of fexofenadine in the absorptive direction was concentration independent, while secretory direction was concentration dependent;
(2) Permeability coefficients in the secretory direction were approximately 1.5 to 5 fold greater than permeation in the absorptive direction;
(3) Ketoconazole increased permeation in the absorptive direction 2-8 fold while decreasing permeation in the secretory direction approximately 2 fold; and
(4) Erythromycin and verapamil produced significant decrease in secretory permeation in the ileal rat segment; however, the absorptive direction was not affected.

3-3. In situ rat intestinal perfusion study

To determine the effects of pretreatment or concomitant administration of ketoconazole or erythromycin on the in situ gastrointestinal absorption of fexofenadine, the sponsor performed in situ gastrointestinal absorption study using rat. Also the sponsor investigated the possible involvement of P-glycoprotein in the absorption process of fexofenadine using verapamil as a model inhibitor. The following methods were used:

Fexofenadine was perfused in rat in situ gastrointestinal segments in three different occasions:

(1) without any drug pretreatment and concomitant perfusion,
(2) with erythromycin, verapamil, or ketoconazole, and
(3) after oral pretreatment, the perfusion of either erythromycin or ketoconazole, respectively.

The above study showed that the fexofenadine gastrointestinal absorption appeared to be increased by concomitant perfusion of erythromycin or ketoconazole either with or without oral pretreatment.

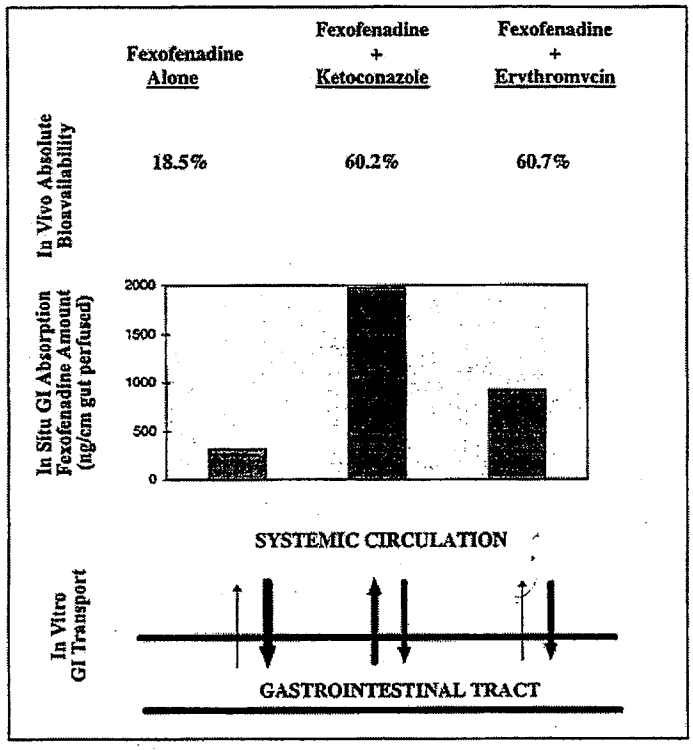
3-4. In vitro human Caco-2 cell study

The sponsor conducted in vitro absorption study using Caco-2 cell absorption model to determine the permeability of fexofenadine across the Caco-2 monolayer in both the apical to basolateral (absorptive) and basolateral to apical (secretory) directions. The effects of erythromycin or ketoconazole on the inherent permeability of fexofenadine in the Caco-2 cell system were also investigated. The possible involvement of a P-glycoprotein mechanism in the gastrointestinal transport of fexofenadine was investigated by transport inhibition with verapamil, a P-glycoprotein antibody, and decreased temperature.

The results demonstrated that:

(1) Fexofenadine had low in vitro permeability in the absorptive direction across the Caco-2 monolayer. Fexofenadine was secreted at a rate 1.5 to 5.2 fold greater than the absorptive transport rate;
(2) In the presence of either erythromycin or ketoconazole secretory net flux for fexofenadine was decreased approximately 3 and 2 fold respectively;
(3) Verapamil, a model P-glycoprotein inhibitor, increased fexofenadine permeability by a decrease in secretory permeability across the Caco-2 monolayer; and
(4) In the presence of mouse P-glycoprotein antibody, the absorptive and secretory transport rate were similar, indicating reduced secretory transport by antibody; and
(5) The secretory net flux of fexofenadine was six-fold decreased by decreasing the temperature to 4°C, indicating the active secretory process.

Overall results are summarized in the following figure.



Summary of Fexofenadine Bioavailability in *In Vitro*, *In Situ*, and *In Vivo* Systems

Above data appeared to adequately support the proposed labeling changes under the "Drug Interaction" section.

4. RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE-II) reviewed the present submission and found that the provided data appeared to appropriately support the proposed labeling change under the drug interaction section. Therefore, OCPB/DPE-II recommends that the labeling change under the drug interaction section be approved.

12/17/98

Young Moon Choi, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence

Uppoor 12/17/98

Venkata Ramana Uppoor, Ph.D.
Team Leader
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

CC:	HFD-570	NDA 20-625; NDA 20-786; DIV FILE; /CSO (1X);
	HFD-870	/OCPB/JHUNT (1x); /OCPB/MLCHEN (1X);/OCPB/CHOI/OCPB/UPPOOR;
	HFD-850	/OCPB/SHUANG
	CDR	Attn: Barbara Murphy

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-786/S003

20-625/S007

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEC 2 1 1998

PROJECT MANAGER LABELING REVIEW

NDA:	**20-625/SLR-007** / **20-786/SLR-007**
DATE:	11/24/98
DRUG:	**ALLEGRA (fexofenadine HCL) Capsules 60 mg ALLEGRA D (fexofenadine HCL and pseudoephedrine HCL 120 mg) Extended Release Tablets**
SPONSOR:	**Hoechst Marion Roussel**
PROJECT MANAGER:	Keary L. Dunn
SUBMISSION:	June 19, 1998

Background

These supplements provide for revisions to the DRUG INTERACTIONS and OVERDOSAGE sections of the package inserts. HMR submitted these labeling changes as PRIOR APPROVAL supplements before implementation, including additional clinical data and references (adverse event reports) to support the proposed labeling changes.

The proposed labeling is identical to the previously approved final printed labeling except where changes are indicated (highlighted) in the annotated draft labeling section.

Recommendation

Upon review and determination by the medical officer that the data and references provided support the proposed labeling changes, this labeling should be approved.

Keary L. Dunn
Project Manager

11/25/98
Date

cc:
Orig NDA # 20-625 and 20-786
HFD-570 Division File
HFD-570/ Worobec
HFD-570/Himmel
HFD-570/Bertha
HFD-570/Poochikian
HFD-570/Sancilio
HFD-57-/Sun
HFD-570/Trout
HFD-570/Dunn

12-21-98

R/D: Dunn/11-24-98
Initialed by: Schumaker/
C:\MyDocuments\N20625_20786.lr.doc

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-625/S-007
NDA 20-786/S-003

Aventis Pharmaceuticals
10236 Marion Park Drive
P.O. Box 9627
Kansas City, MO 64134-0627

Attention: Dan Henry, Pharm.D.
Assistant Director
US Regulatory Affairs, Marketed Products

Dear Dr. Henry:

We acknowledge the receipt of your April 30, 1999, submissions containing final printed labeling in response to our December 22, 1998, letter approving your supplemental new drug application for Allegra (fexofenadine hydrochloride) Capsules, 60 mg and Allegra-D (fexofenadine hydrochloride, 60 mg and pseudoephedrine hydrochloride, 120 mg) Extended Release Tablets.

We have reviewed the labeling that you submitted in accordance with our December 22, 1998 letter, and we find them acceptable.

If you have any questions, call Ms. Gretchen Trout, Project Manager, at (301) 827-1058.

Sincerely,

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/s/

Marianne Mann
11/24/00 03:08:29 PM

Project Manager's Labeling Review

NDA: 20-786/ SLR-003 FA

Product: Allegra-D (fexofenadine hydrochloride, 60 mg and pseudoephedrine hydrochloride, 120 mg) Extended Release Tablets

Sponsor: Aventis Pharmaceuticals (formerly Hoechst Marion Roussel, Inc.)

Submission dated: April 30, 1999

This submission contains Final Printed Labeling (FPL) as requested in the approval letter for the supplemental application S-003, dated December 22, 1998. The FPL submitted on April 30, 1999 is identical to the labeling text approved in the December 22, 1998 letter.

This labeling submission is acceptable. The labeling should be acknowledged and retained.

Craig Ostroff, Pharm.D. Date
Project Manager

/s/

Craig Ostroff
11/16/00 05:31:28 PM
CSO

Sandra Barnes
11/21/00 02:57:48 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-625/S-007

JUL - 7 1998

HOECHST MARION ROUSSEL
PO BOX 9627
KANSAS CITY, MO 64134-0627

Attention: KIM LEITZKE
US DRUG REGULATORY AFFAIRS
MARKETED PRODUCTS

Dear MS LEITZKE :

We acknowledge receipt of your supplemental application for the following:

Name of Drug: ALLEGRA

NDA Number: 20-625

Supplement Number: S-007

Date of Supplement: JUNE 19, 1998

Date of Receipt: JUNE 22, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on AUGUST 21, 1998 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Pulmonary Drug Products, HFD-570
Office of Drug Evaluation II
Attention: Document Control Room 10B-03
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

for Cathie Schumaker
Chief, Project Management Staff
Division of Pulmonary Drug Products, HFD-570
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-625/007
HFD-570/Div. Files
HFD-570/CSO/GRETCHEN TROUT

filename:

SUPPLEMENT ACKNOWLEDGEMENT

ORIGINAL

Hoechst Marion Roussel

NDA NO. 20-625 REF. NO. SLR-00

NDA SUPPL FOR Labeling

June 19, 1998

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive
Mail: P.O. Box 9627
Kansas City, MO 64134-0627
Telephone (816) 966-5000
U.S. Web site: www.hmri.com

John K. Jenkins, MD
Food and Drug Administration
Center for Drug Evaluation II
Division of Pulmonary Drug Products (HFD-570)
Document Control Room 10B-45
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 20-625 ALLEGRA® (fexofenadine hydrochloride) Capsules 60 mg**
NDA 20-786 ALLEGRA-D® (fexofenadine HCl 60 mg and pseudoephedrine HCl 120 mg) Extended Release Tablets

PRIOR APPROVAL SUPPLEMENT FOR AN APPROVED NDA

Dear Dr. Jenkins:

This supplement, submitted under 21 CFR 314.70(b), provides draft labeling submitted for PRIOR APPROVAL before implementation.

This supplemental application provides for revisions to the DRUG INTERACTIONS Section. Specifically, it characterizes the mechanism of interaction between fexofenadine and ketoconazole and between fexofenadine and erythromycin as encouraged by the Agency in the NDA 20-625 approval letter dated July 25, 1996. In addition, revisions to the OVERDOSAGE Section have also been made.

The following information is provided in support of these changes:

- Draft Labeling (June 1998a)
- Annotated Draft labeling (all changes are highlighted)
- Reference List
- References 1-6

If you have any questions, please contact Dan Henry, RPh at 816-966-7796.

Sincerely,

Kim Leitzke

Kim Leitzke
US Drug Regulatory Affairs
Marketed Products

Hoechst

Hoechst Marion Roussel
The Pharmaceutical Company of Hoechst

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Hoechst Marion Roussel, Inc.
PO Box 9627, F3-M3032
Kansas City, MO 64134-0627

2. TELEPHONE NUMBER *(Include Area Code)*

(816) 966-5215

3. PRODUCT NAME

ALLEGRA

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

6. LICENSE NUMBER / NDA NUMBER

NDA 20-625

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☐ NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
J. Matt Reilly	Vice President, North America Drug Regulatory Affairs	June 19, 1998

FORM FDA 3397 (5/98)

29.1

NDA # 20625 DOCUMENT ID/LETTER DATE SLR-007 6-19-98

APPLICANT NAME Hoechst Marion Roussel

PRODUCT NAME Allegra® (fexofenadine hydrochloride) capsules 60mg

FORM MUST BE COMPLETED ASAP

1. YES User Fee Cover Sheet Validated?

NOTE TO DOCUMENT ROOM:
PLEASE MAKE THE FOLLOWING CHANGES TO THE COMIS DATA ELEMENTS

2. YES NO **CLINICAL DATA?**
[Check YES if contains study reports or literature reports of what are explicitly or implicitly represented by the applicant to be adequate and well-controlled trials. *Clinical data do not include data used to modify the labelling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).]

REF **IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE *CROSS REFERENCED* IN ANOTHER SUBMISSION?**

3. YES NO **NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE** (OTHER THAN BUNDLING)? IF YES, list ALL NDA numbers, review divisions & indicate those for which application fees apply.

NDA #	DIVISION		
N_____	_____	FEE	NO FEE
N_____	_____	FEE	NO FEE

4. YES NO **BUNDLING POLICY APPLIED CORRECTLY? NO DATA ENTRY REQUIRED FOR ELEMENT**
[Check YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Check NO if application should be split into more than one application or submitted as an original instead of a supplement. IF NO, list resulting NDA numbers, and review divisions.]

NDA #	DIVISION	NDA #	DIVISION
N_____	_____	N_____	_____

5. P S **PRIORITY OR STANDARD?**

Christine Mount 7/2/98
6. CSO SIGNATURE/DATE

7/2/98
SCSO CONCURRENCE SIGNATURE/DATE

COPY DISTRIBUTION: ORIGINAL TO ARCHIVAL AFTER DATA ENTRY, ONE COPY EACH TO DIVISION FILE AND CDER, ASSOCIATE DIRECTOR FOR POLICY HFD-5