

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-786/S012

Trade Name: Allegra D Extended Release Tablets

Generic Name: (fexofenadine HCl 60 mg and pseudoephedrine HCl 120 mg)

Sponsor: Aventis Pharmaceuticals

Approval Date: November 1, 2002

Indication 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.

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RESEARCH**

APPLICATION NUMBER:

20-786/S012

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-786/S-012

Aventis Pharmaceuticals
399 Interpace Parkway
Parsippany NJ 07054

Attention: Alan Bergstrom
Senior Manager
US Drug Regulatory Affairs & Compliance

Dear Mr. Bergstrom:

Please refer to your supplemental new drug application dated March 1, 2001, received March 5, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Allegra-D (fexofenadine HCl 60 mg and pseudoephedrine HCl 120 mg) Extended-Release tablets.

This supplemental new drug application provides for the addition of a paragraph to the ADVERSE REACTIONS section describing adverse events reported during controlled clinical trial in fexofenadine, involving seasonal allergic rhinitis and chronic idiopathic urticaria.

We completed our review of this supplemental new drug application. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on March 1, 2001.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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, call Ms. Christine Yu, Regulatory Project Manager, at (301) 827-1051.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Acting Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Badrul Chowdhury
11/1/02 04:53:46 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-786/S012

LABELING

NDA 20-876
ALLEGRA-D® Extended-Release Tablets
 (fexofenadine HCl 60 mg and pseudoephedrine HCl 120 mg)

Intending: ORL SLR
 NDA No: 20786 Rct
 Reviewer: Sun R

"FINAL PRINTED LABELING"

Prescribing Information as of November 2000
Allegra-D®
fexofenadine HCl 60mg and
pseudoephedrine HCl 120mg
Extended-Release Tablets

†Aventis

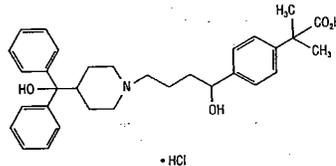
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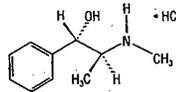
Prescribing Information as of November 2000
ALLEGRA-D®
 (fexofenadine HCl 60 mg and
 pseudoephedrine HCl 120 mg)
 Extended-Release Tablets

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 H₁-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:



The molecular weight is 538.13 and the empirical formula is C₃₂H₃₉NO₄·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 [5-(R*,R*)]-α-[1-(methylamino)ethyl]-benzenemethanol hydrochloride and the following chemical structure:



The molecular weight is 201.70. The molecular formula is C₁₀H₁₅NO·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 H₁-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 alpha₁-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 [¹⁴C] 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 α₁-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.

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Prescribing Information as of November 2000

Allegra-D®

fexofenadine HCl 60mg and
pseudoephedrine HCl 120mg
Extended-Release Tablets

✓Aventis

Prescribing Information as of November 2000

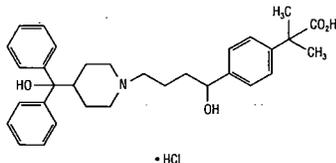
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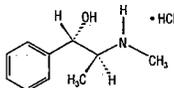
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Pseudoephedrine has been shown to have a mean elimination half-life of 4-6 hours which is dependent on urine pH. The elimination half-life is decreased at urine pH lower than 6 and may be increased at urine pH higher than 8.

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 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 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 QT_c 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 _{0-12h} (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.

ALLEGRA-D tablets (pseudoephedrine component) are contraindicated in patients taking monoamine oxidase inhibitors and for 14 days after stopping use of a 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/m² basis).

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 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/m² 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/m² 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%

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

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 predominantly 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.

Events that have been reported during controlled clinical trials involving seasonal allergic rhinitis and chronic idiopathic urticaria patients with incidences less than 1% and similar to placebo and have been rarely reported during postmarketing surveillance include: insomnia, nervousness, and sleep disorders or parosmia. In rare cases, rash, urticaria, pruritus and hypersensitivity reactions with manifestations such as angioedema, chest tightness, dyspnea, flushing and systemic anaphylaxis have been reported.

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 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/m² 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/m² 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/m² 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/m² basis).

DOSE 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 November 2000

Aventis Pharmaceuticals Inc.
Kansas City, MO 64137 USA
US Patents 4,254,129; 5,375,693; 5,578,610.
www.allegra.com

Best Possible Copy

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-786/S012

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



NDA 20-786

CBE-30/CBE-0 SUPPLEMENT

Aventis Pharmaceuticals, Inc.
399 Interpace Parkway
Parsippany, NJ 07054

Attention: Alan Bergstrom
Senior Manager
U.S. Drug Regulatory Affairs

Dear Mr. Bergstrom:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Allegra-D® Tablets (fexofenadine HCl 60 mg and pseudoephedrine HCl 120 mg) Extended-Release Tablets.

NDA Number: 20-786

Supplement number: S-012

Date of supplement: March 1, 2001

Date of receipt: March 5, 2001

This supplemental application, submitted as "Supplement - Changes Being Effected" proposes the following change: revision to the ADVERSE REACTIONS section of the package insert.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 4, 2001, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 5, 2001.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Pulmonary Drug Products, HFD-570
Attention: Division Document Room, 10B-03
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-786/S-012

Page 2

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary Drug Products
Attention: Document Room 10B-03
5600 Fishers Lane
Rockville, Maryland 20857 - 1706

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

Sincerely yours,

Sandra L. Barnes
Chief, Project Manager Staff
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/s/

Gretchen Trout
3/12/01 03:15:03 PM
for SBarnes

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

<p>1. APPLICANT'S NAME AND ADDRESS</p> <p>Aventis Pharmaceuticals, Inc. 399 Interpace Parkway Parsippany, NJ 07054</p>	<p>3. PRODUCT NAME</p> <p>Allegra-D Extended-Release Tablets</p>
<p>2. TELEPHONE NUMBER (Include Area Code)</p> <p>(973) 394-6738</p>	<p>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. No</p> <p>IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).</p>
<p>5. USER FEE I.D. NUMBER</p>	<p>6. LICENSE NUMBER / NDA NUMBER</p> <p>NDA 20-786</p>

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

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See Item 7, reverse side before checking box.)
<input type="checkbox"/> 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.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(b)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See Item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

FOR BIOLOGICAL PRODUCTS ONLY

<input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION	<input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT
<input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY	<input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT
<input type="checkbox"/> 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)

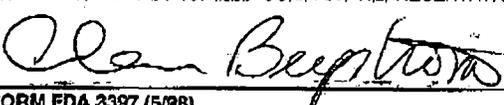
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

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.

<p>SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE</p> 	<p>TITLE Senior Manager US Drug Regulatory Affairs & Compliance</p>	<p>DATE 3/12/01</p>
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ORIGINAL



Aventis Pharmaceuticals

March 1, 2001

Robert Meyer, M.D. Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Division of Pulmonary Drug Products (HFD-570)
Document Room 10B-03
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-1706



NDA NO. 20786 REF NO. 012
NDA SUPPL FOR SUR-CBE

S.S - CBE
FPL

Subject: NDA 20-786 – Allegra- D® (fexofenadine HCl 60 mg and pseudoephedrine HCl 120 mg) Extended-Release Tablets

SPECIAL SUPPLEMENT: CHANGES BEING EFFECTED

Dear Dr. Meyer:

Reference is made to NDA 20-786 for Allegra-D (fexofenadine HCl 60 mg and pseudoephedrine HCl 120 mg) Extended-Release Tablets. This supplement is submitted in accordance with 21 CFR314.70(c) as Changes Being Effectuated for a labeling change which adds adverse reactions. Specifically, the following paragraph is added to ADVERSE REACTIONS:

“Events that have been reported during controlled clinical trials involving seasonal allergic rhinitis and chronic idiopathic urticaria patients with incidences less than 1% and similar to placebo and have been rarely reported during postmarketing surveillance include: insomnia, nervousness, and sleep disorders or paroniria. In rare cases, rash, urticaria, pruritus and hypersensitivity reactions with manifestations such as angiodema, chest tightness, dyspnea, flushing and systemic anaphylaxis have been reported.”

This addition is incorporated in the Allegra-D November 2000 Prescribing Information. A mocked-up label highlighting the addition is included in Attachment 1. Reasoned statements for the addition of the events are included in Attachments 2 – 7. Twenty copies of the Final Printed Labeling are enclosed (attachment 8). Ten copies are individually mounted on heavy weight paper.

The revised labeling will be used on or before May 12, 2001 in all packages sold or distributed from the company's facilities.

If you have any questions regarding this submission, please contact me at 973-394-6738.

Sincerely,

Alan Bergstrom
Senior Manager, U.S. Drug Regulatory Affairs

- Attachment 1 – Allegra-D November 2000 Prescribing Information (mocked-up)
- Attachment 2 – Reasoned statement for insomnia
- Attachment 3 – Reasoned statement for nervousness
- Attachment 4 – Reasoned statement for sleep disorders
- Attachment 5 – Reasoned statement for paroniria
- Attachment 6 – Reasoned statement for rash, urticaria, pruritus
- Attachment 7 – Reasoned statement for hypersensitivity reactions
- Attachment 8 – Final Printed Labeling