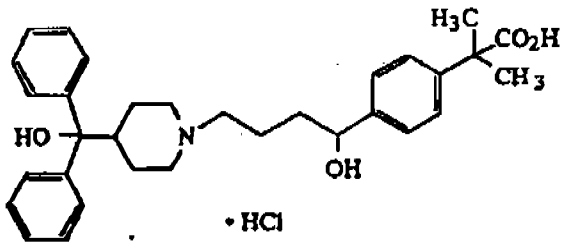
Prescribing Information as of July 1996

ALLEGRA™
(fexofenadine hydrochloride) Capsules
60 mg ~~capsules~~

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, (Refs. 3-9). It has the following chemical structure (Ref. 10):



The molecular weight is 538.13 (Ref. 11) and the empirical formula is $C_{32}H_{39}NO_4$•HCl (Ref. 12). Fexofenadine hydrochloride is a white to off-white crystalline powder (Ref. 13). It is freely soluble in methanol and ethanol, slightly soluble in chloroform and in water, and insoluble in hexane (Ref. 14). Fexofenadine hydrochloride is ~~provided as~~ a racemate and exists as a zwitterion in aqueous media at physiological pH (Refs. 15,16).

ALLEGRA™ is formulated as capsules for oral administration (Ref. 1). 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 (Ref. 2).

CLINICAL PHARMACOLOGY

Mechanism of Action

Fexofenadine, a metabolite of terfenadine, is an antihistamine with selective peripheral H_1-receptor antagonist activity (Refs. 3-8). Fexofenadine inhibited antigen-induced bronchospasm in sensitized guinea pigs and ~~inhibited~~ histamine release from peritoneal mast cells in rats (Refs. 17,18). In laboratory animals, no anticholinergic or alpha$_1$-adrenergic-receptor blocking effects were observed (Refs. 4,19,20). Moreover, no sedative or other central nervous system effects were observed (Refs. 3,21). Radiolabeled tissue distribution studies in rats indicated that fexofenadine does not cross the blood-brain barrier (Ref. 35).

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 (Ref. 31). After administration of a single dose of 60-mg as an oral solution to healthy subjects, the mean plasma concentration was 209 ng/mL (Ref. 32). 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) (Ref. 32). Fexofenadine pharmacokinetics were linear for oral doses up to 120 mg twice daily (Ref. 32). Although the absolute bioavailability of fexofenadine hydrochloride capsules is unknown, the capsules are bioequivalent to an oral solution (Ref. 31). The mean elimination half-life of fexofenadine was 14.4 hours following administration of 60 mg, twice daily, to steady-state in normal volunteers (Ref. 32).

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 (Refs. 33,34). 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 (Ref. 24).

Fexofenadine is 60% to 70% bound to plasma proteins, primarily albumin and α_1-acid glycoprotein (Refs. 36,37).

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 (Ref. 38). 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 (Refs. 38,41).

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.) (Refs. 38,40)

Hepatically Impaired. The pharmacokinetics of fexofenadine hydrochloride in patients with hepatic disease did not differ substantially from that observed in healthy subjects (Refs. 38,39).

Effect of Gender. Across several trials, no clinically significant gender-related differences were observed in the pharmacokinetics of fexofenadine (Refs. 38,74).

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 (Refs. 22,23). There was no evidence of tolerance to these effects after 28 days of dosing (Ref. 23).

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 ~~which~~ 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) (Refs. 24-26). 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) (Refs. 24,27).

No statistically significant increase in mean QTc interval compared to placebo was observed in 714 seasonal allergic rhinitis patients (Ref. 73) given fexofenadine hydrochloride capsules in doses of 60 mg to 240 mg twice daily for two weeks or in 40 healthy volunteers (Ref. 29) given fexofenadine hydrochloride as an oral solution at doses up to 400 mg twice daily for 6 days (Refs. 28,29).

Clinical Studies

In three, ~~two~~ 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 (Refs. 75,76). Statistically significant reduction in symptom scores was observed following the first 60 mg dose, with the effect maintained throughout the 12-hour interval (Ref. 77). In general, there was no additional reduction in total symptom scores with higher doses of fexofenadine up to 240 mg twice daily (Ref. 42). Although the number of subjects in some of the subgroups was small, there was no significant difference in the effect of fexofenadine hydrochloride across subgroups of patients defined by gender, age and race (Ref. 45). 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 (Ref. 43).

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 (Refs. 7,8,46,47).

CONTRAINDICATIONS

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

PRECAUTIONS

Drug Interactions

In two separate studies, fexofenadine hydrochloride 120 mg twice daily (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 hydrochloride 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} *(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 mechanisms of these interactions are unknown, and the potential for interaction with other azole antifungal or macrolide agents has not been studied (Refs. 48,49). These changes in plasma levels were within the range of plasma levels achieved in adequate and well-controlled clinical trials. Fexofenadine had no effect on the pharmacokinetics of erythromycin or ketoconazole (Refs. 48,49).

Carcinogenesis, Mutagenesis, Impairment of Fertility

~~Fexofenadine is an active acid metabolite of terfenadine.~~ 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) (Refs. 50,51).

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 (Refs. 53-56).

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) (Ref. 52).

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 (Refs. 57-59).

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) (Ref. 52).

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 (Ref. 72).

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 (Refs. 7,8,46,47).

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 (Refs. 75,78). 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 (Ref. 79,80). All adverse events 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 (Ref. 78).

The frequency and magnitude of laboratory abnormalities were similar in fexofenadine hydrochloride and placebo-treated patients (Ref. 63).

OVERDOSAGE

Information regarding acute overdosage is limited to experience from clinical trials conducted during the development of ALLEGRA™. 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 (Refs. 22,23).

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 (Ref. 64).

~~An oral lethal dose in rodents could not be determined for~~ fexofenadine hydrochloride ~~was~~ no deaths occurred at oral doses 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 Refs. 65,66). 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 Refs. 67,68).

DOSAGE AND ADMINISTRATION

The recommended dose of ALLEGRA™ is 60 mg twice daily for adults and children 12 years of age and older (Refs. 7,8).

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 (Ref. 69): 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 (Ref. 70).

Store ALLEGRA™ capsules at controlled room temperature 20-25°C (68-77°F) (Ref. 71). Foil-backed blister packs should be protected from excessive moisture (Ref. 81).

Prescribing Information as of July 1996

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