

For the use only of a Registered Medical Practitioner, Hospital, Laboratories

This package insert is continually updated: Please read carefully before using a new pack

Fexofenadine HCl and Pseudoephedrine HCl ER Tablets U.S.P. Allegra® D

1. Generic Name

Fexofenadine HCl 60mg + Pseudoephedrine HCl 120mg Extended Release Tablets U.S.P.

2. Qualitative and quantitative composition

Each extended release tablet contains:

Fexofenadine Hydrochloride IP 60 mg

Pseudoephedrine Hydrochloride IP 120mg

3. Dosage form and strength

Extended release tablets - 60mg/120mg

4. Clinical particulars

4.1 Therapeutic indication

Allegra® D is indicated for the relief of symptoms associated with 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 (refer section *Pharmacological properties*).

4.2 Posology and method of 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. (refer section *Pharmacological properties and Precautions*).

4.3 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 (refer section *Drug Interactions*). 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 component, 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.

4.4 Special warnings and precautions for use

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 (refer section *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 (refer section *Warning 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 (refer section *Pharmacological properties & Posology and Method of Administration*).

4.5 Drugs interactions

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

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 pharmacokinetic findings of these studies are summarized in the following table.

The mechanisms of these interactions are unknown, and the potential for interaction with other azole antifungal or macrolide agents has not been studied. 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.

Administration of an antacid containing aluminum and magnesium hydroxide gels 15 minutes prior to fexofenadine hydrochloride caused a reduction in bioavailability. It is advisable to leave 2 hours between administration of fexofenadine hydrochloride and aluminum and magnesium containing antacids.

No interaction between fexofenadine and omeprazole was observed.

P-gp inducers (such as apalutamide) may reduce the exposure of fexofenadine.

A clinical drug-drug interaction study showed that co-administration of apalutamide and a single oral dose of 30 mg fexofenadine resulted in a 30 % decrease in AUC and 7 % in C_{max} of fexofenadine. Clinical impact on the pharmacodynamics and efficacy has not been studied.

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, methyl dopa, mecamlamine and reserpine), may reduce their anti-hypertensive 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 (refer section *Warnings*).

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} (0-12h) (extent of systemic Exposure)
Erythromycin (500 mg every 8 hrs)	+ 82%	+ 109%
Ketoconazole (400 mg once daily)	+ 135%	+ 164%

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

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 was 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 In-vitro (Bacterial Reverse Mutation, CHO/HGPRT Forward Mutation, and Rat Lymphocyte Chromosomal Aberration assays) and in vivo (Mouse Bone Marrow Micronucleus assay) 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 on 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 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 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 caution should be used when fexofenadine hydrochloride is administered to a nursing woman.

It is 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.

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

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 the 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 Experience Reported

In One Active-Controlled Allergic Rhinitis Clinical Trial at Rates of Greater than 1%			
Adverse Experience	60 mg Fexofenadine Hydrochloride/120mg 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.

Events that have been reported during controlled trials involving seasonal allergic rhinitis and chronic idiopathic urticaria patients with incidences less than 1% and similar to placebo and have been reported rarely during post marketing surveillance include : fatigue, insomnia, nervousness, and sleep disorders or paroniria. In rare cases, rash, urticaria, pruritus and hypersensitivity reactions with manifestations such as angioedema, chest tightness, dyspnea, flushing and systemic anaphylaxis have been reported. (In fexofenadine monotherapy studies) adverse events reported in placebo-controlled chronic idiopathic urticaria studies were similar to those reported in placebo-controlled seasonal allergic rhinitis studies.

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, ischemic colitis and acute generalized exanthematous pustulosis (AGEP) 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, urinary retention and cardiovascular collapse. Manic symptoms such as insomnia, high or irritable mood, inflated self-esteem, increased activity or restlessness, racing thoughts, talking fast, and distractibility have been reported.

4.9 Overdose

Information regarding acute overdosage is limited to experience from clinical trials conducted during the development of Allegra® D and 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).

5. Pharmacological properties

5.1 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 alpha-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.

5.2 Pharmacodynamic properties

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 QTc. In dogs, (10 mg/kg/day, orally for 5 days) and rabbits (10 mg/kg, intravenously over one hour) fexofenadine hydrochloride 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 1×10^{-5} M of fexofenadine. This concentration was at least 32 times the therapeutic plasma concentration in man (based on 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.

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 QTc 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 QTc 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 reduction 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 the 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.

5.3 Pharmacokinetic properties

The pharmacokinetics of fexofenadine hydrochloride and pseudoephedrine hydrochloride when administered separately has been well characterized. Fexofenadine pharmacokinetics was 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 faeces and urine, respectively. Approximately 5% of the total dose were 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 was 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. Co-administration 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 post-dose. Pseudoephedrine hydrochloride produced a mean single-dose pseudoephedrine peak plasma concentration of 206 ng/mL, which occurred 6 hours post dose. Following multiple dosing to steady state, a fexofenadine peak concentration of 255 ng/mL was observed 2 hours post dose. Following multiple dosing to steady state, a pseudoephedrine peak concentration of 411 ng/mL was observed 5 hours post dose. Co-administration 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. (refer section *Posology and Method of 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 (refer section *Posology and Method of 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.

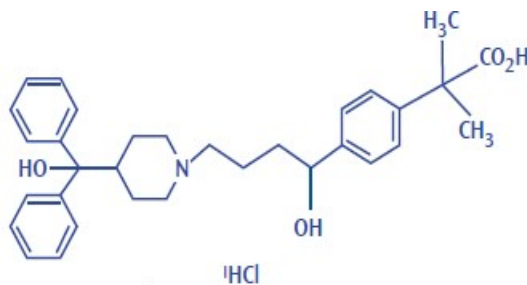
6 Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Not Applicable

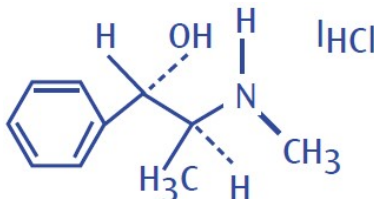
7. Description

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-receptor antagonist with the chemical name (±)-4-[1-hydroxy - 4 - [4 - (hydroxy di phenylmethyl) - 1 - piperidiny] - butyl] - α , α - dimethyl benzeneacetic acid hydrochloride and the following chemical structure:



The molecular weight is 538.13 and the empirical formula is $C_{32}H_{39}NO_4 \cdot HCl$. 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 zwitter ion 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-(methyl-amino)ethyl]- benzene-methanol hydrochloride and the following chemical structure:



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

8. Pharmaceutical particulars

8.1 Incompatibilities

Not Applicable

8.2 Shelf-life

Refer outer carton

8.3 Packaging information

Presentation

Box contains 5 blisters x 10 tablets.

8.4 Storage and handing instructions

STORAGE

Store below 30°C

Expiry date

Do not use later than the date of expiry.

Keep all medicine out of the reach of children.

ON MEDICAL PRESCRIPTION ONLY**9. Patient Counselling Information**

Patients taking Allegra® D tablets should receive the following information: Allegra® D tablets are prescribed for the relief of symptoms of 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 justified the potential risk to the fetus or nursing infants.

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.

10. Details of manufacturer**Manufactured by:**

Opella Healthcare International SAS, 56 Route de Choisy 60200 Compiègne, France.

Packaged by:

PT Kalventis Sinergi Farma, Jl. Jenderal Ahmad Yani No. 2, Pulo Mas, Kelurahan Kayu Putih, Jakarta Timur, DKI Jakarta, (Indonesia) - 13210

Imported in India by:

Sanofi India Limited, Building no. B-4, Gala No.1A, First Floor, Citylink Warehousing Complex, Mumbai Nashi Highway, Village Vadape Bhiwandi, Tal: Mumbai Nashik Highway (NH3) (THANE-Zone 2) Pin:421302.

11. Details of permission or licence number with date

New drug permission no.: IMP-42/2021

12. Date of revision

Updated: April 2024

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