For the use only of a Registered Medical Practitioner or hospital or a laboratory.

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

Fexofenadine Hydrochloride Tablets I.P.
ALLEGRA®

Fexofenadine Hydrochloride Suspension
ALLEGRA® Suspension

Therapeutic or Pharmacological Class
Fexofenadine is a non-sedating antihistamine, Histamine H_1 -receptor antagonist.

Pharmaceutical Form
Tablets and Oral Suspension

COMPOSITION
Fexofenadine Hydrochloride Suspension
Each 5ml contains:
Fexofenadine hydrochloride I.P. 30 mg
Colors: Titanium dioxide IP
In flavoured syrup base

Fexofenadine Hydrochloride Tablets IP 120mg
Each film-coated tablet contains:
Fexofenadine Hydrochloride I.P. 120 mg
Excipients: q.s.
Colors: Yellow Iron Oxide, Red Iron Oxide and Titanium dioxide IP

Fexofenadine Hydrochloride Tablets IP 180mg
Each film-coated tablet contains:
Fexofenadine Hydrochloride I.P. 180 mg
Excipients: q.s.
Colors: Yellow Iron Oxide, Red Iron Oxide and Titanium dioxide IP

INDICATIONS
1. Allegra is indicated for relief of symptoms associated with allergic rhinitis and chronic idiopathic urticaria.

2. Allegra oral suspension is indicated for relief of symptoms associated with allergic rhinitis in children 2-11 years of age and uncomplicated skin manifestations of chronic idiopathic urticaria in children 6 months to 11 years of age.

DOSAGE AND ADMINISTRATION

Allergic rhinitis:
Children 2-11 years of age
The recommended dose is 30mg twice daily (5ml in case of Allegra Suspension) in patients 2 to 11 years of age.

Adults and children aged 12 years and older
The recommended dose of fexofenadine hydrochloride is 120mg once daily or 180mg once daily for patients 12 years of age or older.

Allergic skin conditions, e.g. chronic idiopathic urticaria
Children 6 months-11years
The recommended dose is 30mg (5ml in case of Allegra suspension) twice daily for patients 2 to 11 years of age and 15mg (2.5ml) twice daily for patients 6 months to less than 2 years of age.

Adults and children aged 12 years and over
The recommended dose of fexofenadine hydrochloride is 180mg once daily for patients 12 years and over.

Special Populations
Studies in special risk groups (elderly, renally or hepatically impaired patients) indicate that it is not necessary to adjust the dose of fexofenadine hydrochloride in these patients.

CONTRA-INDICATIONS
The product is contraindicated in patients with known hypersensitivity to any of its ingredients.

PRECAUTIONS
Patients should be advised to shake the ALLEGRA suspension bottle well, before each use.

INTERACTIONS
The co administration of Fexofenadine with erythromycin or ketoconazole resulted in no significant increases in QTc. No differences in adverse effects were reported whether these agents were administered alone or in combination.

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 a gap of 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 Cmax of fexofenadine. Clinical impact on the pharmacodynamics and efficacy has not been studied.

PREGNANCY
There are no studies of Allegra in pregnant women. Allegra should be used in pregnancy only if the potential benefit outweighs the potential risk to the fetus.

In a comprehensive reproductive toxicity study in mice, fexofenadine did not impair fertility, was not teratogenic, and did not impair pre- or postnatal development.

LACTATION
There are no studies of Allegra in lactating women. Fexofenadine should be used in nursing women only if the potential benefit outweighs the potential risk to the infant.

ADVERSE REACTIONS

The following CIOMS frequency rating is used, when applicable:

Very common ≥ 10%; Common ≥ 1 and < 10%; Uncommon ≥ 0.1 and < 1%;

Rare ≥ 0.01 and < 0.1%; Very rare < 0.01%; Not known (cannot be estimated from available data).

In placebo-controlled trials involving seasonal allergic rhinitis and chronic idiopathic urticaria patients, adverse events were comparable in fexofenadine and placebo treated patients.

The most frequent adverse events reported with fexofenadine include:
>3%: headache
1-3%: drowsiness, dizziness and nausea.

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.

Adverse events reported in placebo-controlled chronic idiopathic urticaria studies were similar to those reported in placebo-controlled seasonal allergic rhinitis studies.

In placebo-controlled trials involving pediatric seasonal allergic rhinitis patients (6-11years of age), adverse events were similar to those observed in trials involving seasonal allergic rhinitis patients 12 years and older.

In controlled clinical trials involving pediatric patients 6 months to 5 years of age, there were no unexpected adverse events in patients treated with fexofenadine hydrochloride.

OVERDOSE
Human Experience:
Most reports of fexofenadine hydrochloride overdose contain limited information.
However, dizziness, drowsiness, and dry mouth have been reported. Single doses up to 800 mg and doses up to 690 mg BID for 1 month or 240 mg QD for 1 year were studied in healthy subjects without the development of clinically significant adverse events as compared to placebo. The maximum tolerated dose of Allegra was not established.

Management:
Consider standard measures to remove any unabsorbed drug. Symptomatic and supportive treatment is recommended.

Hemodialysis did not effectively remove fexofenadine from blood.

PHARMACODYNAMICS
Fexofenadine is an antihistamine with selective peripheral H1-receptor antagonist activity. Fexofenadine inhibited antigen-induced bronchospasm in sensitized guinea pigs and histamine release from peritoneal mast cells in rats. In laboratory animals, no anticholinergic or 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. Fexofenadine hydrochloride inhibits skin wheal and flare responses produced by histamine injection. Following single and twice daily oral dose administration, antihistaminic effects occurred within 1 hour, achieved a maximum of 2-3 hours, and lasted a minimum of 12 hours. Maximum inhibition in skin wheal and flare areas were greater than 80%. There is no evidence of tolerance to these effects after 28 days of dosing. Using reflective total symptom score assessments as the primary endpoint, clinical studies conducted in seasonal allergic rhinitis have shown that a dose of 120 mg is sufficient for 24 hour efficacy. In children aged 6 to 11 years, the suppressive effects of fexofenadine on histamine – induced wheal and flare were comparable to that in adults at similar exposure. In an integrated analysis of placebo-controlled double-blind phase III studies, involving 1369 children with seasonal allergic rhinitis aged 6 to 11 years, fexofenadine hydrochloride at 30 mg twice daily was significantly better than placebo in reducing total symptom score (p=0.0001). All

individual component symptoms including rhinorrhea, sneezing, itchy/ watery/red eyes, itchy nose/ palate and throat, and nasal congestion were significantly (p=0.0334 to p=0.0001) improved by fexofenadine hydrochloride.

The effectiveness of fexofenadine hydrochloride 30 mg twice daily for the treatment of seasonal allergic rhinitis in patients 2 to 5 years of age is based on the pharmacokinetic comparisons in adult and pediatric subjects and an extrapolation of the demonstrated efficacy of fexofenadine hydrochloride in adult and older pediatric subjects with this condition and the likelihood that the disease course, pathophysiology, and the drug's effect are substantially similar in pediatric patients to those in adult patients. The effectiveness of Allegra for the treatment of chronic idiopathic urticaria in patients 6 months to 11 years of age is based on the pharmacokinetic comparisons in adults and children and an extrapolation of the demonstrated efficacy of Allegra in adults with this condition and the likelihood that the disease course, pathophysiology and the drug's effect are substantially similar in children to that of adult patients. Administration of a 15 mg dose of fexofenadine hydrochloride to pediatric subjects 6 months to less than 2 years of age and a 30 mg dose to pediatric subjects 2 to 11 years of age produced exposures comparable to those seen with a dose of 60 mg administered to adults. The onset of action for the reduction in total symptom scores was observed at 60 minutes compared to placebo following a single 60 mg dose administered to seasonal allergic rhinitis patients who were exposed to ragweed pollen in an environmental exposure unit. No effect on QTc intervals was observed in seasonal allergic rhinitis patients given fexofenadine hydrochloride up to 240 mg twice daily for 2 weeks when compared to placebo. Also, no effect on QTc intervals was observed in healthy subjects given fexofenadine hydrochloride up to 400 mg twice daily for 6.5 days and 240 mg once daily for 1 year when compared to placebo. In children aged 6 to 11 years, no significant differences in QTc were observed following up to 60mg fexofenadine hydrochloride twice daily compare to placebo for two weeks. Fexofenadine at concentrations 32 times greater than the therapeutic concentration in man had no effect on the delayed potassium rectifier K+ channel cloned from human heart.

CLINICAL EFFICACY/CLINICAL STUDIES

A phase 3, single-center, sequential and parallel-group, double-blind, randomized study (NCT03664882) was conducted in 266 allergic rhinitis subjects (251 in the modified-ITT population) to demonstrate the aggravation of allergic rhinitis (AR) symptoms in presence of pollutants [Diesel Exhaust Particulate (DEP)] and to evaluate the efficacy of fexofenadine HCl in AR subjects with symptoms aggravated in presence of DEP.

The study was performed using an Environmental Exposure Unit in three sequential-exposure, three-hour periods [1. Ragweed pollen, 2. Ragweed pollen plus DEP, 3. Ragweed pollen plus DEP].

The first primary endpoint was the change from baseline in the Area Under the Curve (AUC) for the Total Nasal Symptom Score (TNSS, the sum of rhinorrhea, nasal itching and sneezing scores) from Hours 0-12 between Period 2 and Period 1. Mean TNSS AUC_{0-12} was significantly higher in Period 2 compared to Period 1 (41.22 vs 36.25 respectively). The Least-Square (LS) mean difference (95% CI) between the two periods was 0.13 [95% CI: 0.081; 0.182 ($p<0.0001$)], indicating an aggravation of pollen-induced AR symptoms in the presence of DEP.

The second primary endpoint was the comparison of AUC_{2-12} for TNSS between placebo- and fexofenadine-treated groups during Period 3. AUC_{2-12} for TNSS during Period 3 was significantly lower in the fexofenadine-treated subjects compared to placebo-treated subjects (18.53 vs 26.34 respectively). The LS-mean difference (95% CI) between the two groups was 0.24 (-0.425 to -0.047) [p=0.0148)], demonstrating that fexofenadine 180 mg was effective in reducing DEP-aggravated AR symptoms induced by ragweed pollen.

In addition, secondary efficacy endpoints included changes from baseline in Total Symptom Score (TSS) for individual AR symptoms. The mean (SD) AUC_{2-12} for individual symptom scores was lower in the fexofenadine HCl group vs placebo:

Symptom	AUC_{2-12} for individual symptom scores*	
	Mean (SD) SE	
	Placebo	Fexofenadine
Rhinorrhea	10.59 (6.50) 0.581	7.54 (5.96) 0.531
Sneezing	7.01 (6.49) 0.580	4.26 (4.75) 0.423
Nasal Itching	8.74 (6.03) 0.539	6.73 (5.63) 0.502
Nasal Congestion	11.27 (6.98) 0.624	8.48 (5.81) 0.517
Itchy eyes	5.92 (5.53) 0.495	4.56 (4.95) 0.441
Watery eyes	4.44 (5.61) 0.501	3.22 (4.00) 0.56
Red or burning eyes	5.13 (6.14) 0.549	3.86 (5.13) 0.457
Ear itching or palate or throat itching	6.13 (5.75) 0.515	4.99 (5.88) 0.524
Proportional mean symptom reduction with fexofenadine, compared to placebo, was: rhinorrhea (28.8%); sneezing (39.2%); nasal		

itching (23.0%); nasal congestion (24.8%); itchy eyes (23.0%); watery eyes (27.5%); red or burning eyes (24.8%); and ear, palate, or throat itching (18.6%; all data were cumulative, from treatment intake up to 10 hours post treatment).

* Individual symptom scores are presented for descriptive purposes only as TSS scores were not significantly different between fexofenadine and placebo treatments.
SD: Standard Deviation
SE: Standard Error

NONCLINICAL SAFETY DATA

Single dose toxicity

No clinical signs of toxicity and no effects on body weight or food consumption were observed in acute toxicity studies in several animal species administered fexofenadine hydrochloride by oral gavage at doses of 2,000 mg/kg. No treatment-related gross findings were observed in rodents following necropsy.

Repeat Dose toxicity

Dogs tolerated 450 mg/kg administered twice daily for 6 months and showed no toxicity other than occasional emesis.

Genotoxicity

Fexofenadine was found to be nonmutagenic in various in vitro and in vivo mutagenicity tests.

Carcinogenicity

The carcinogenic potential of fexofenadine hydrochloride was assessed using terfenadine studies with supporting pharmacokinetic studies showing adequate fexofenadine exposure (via plasma AUC values). No evidence of carcinogenicity was observed in rats and mice given terfenadine (up to 150 mg/kg) resulting in fexofenadine plasma exposure up to four times the human therapeutic value (based on 60 mg twice a daily fexofenadine hydrochloride).

PHARMACOKINETICS

Fexofenadine hydrochloride is rapidly absorbed following oral administration. Tmax occurred approximately 1-3 hours postdose. The mean Cmax was approximately 142ng/ml following the administration of a single 60 mg dose, approximately 289 ng/mL following a single 120 mg dose and approximately 494 ng/mL following a single 180 mg dose.

The plasma exposures produced by single doses of 15, 30, and 60 mg in children aged 2-11years are dose proportional and comparable to those produced by corresponding single doses of 30, 60, and 120 mg in adults, respectively. A dose of 30 mg BID was determined to provide plasma exposures (AUC) in pediatric patients which were comparable to plasma exposures achieved in adults following a total daily dose of 120mg. A 5 mL dose of suspension containing 30 mg of fexofenadine hydrochloride is bioequivalent to a 30 mg dose of fexofenadine hydrochloride tablets.

Fexofenadine is 60% to 70% bound to plasma proteins. Fexofenadine undergoes negligible metabolism.
Following a single 60 mg oral dose, 80% of the total fexofenadine hydrochloride dose was recovered in the feces and 11% was recovered in the urine. Following multiple dosing, fexofenadine has a mean terminal elimination half-life of 11 to 16 hours. The major route of elimination is believed to be biliary excretion while up to 10% of ingested dose is excreted unchanged through the urine.
The single and multiple dose pharmacokinetics of fexofenadine hydrochloride are linear from 20 mg to 120 mg doses. A dose of 240 mg BID produced slightly greater than proportional increase (8.8%) in steady state area under the curve.

EXPIRY DATE

Do not use later than the date of expiry.

Keep Medicine out of reach of children.

Manufactured by:

Allegra® 120 and 180 Tablets:
Sanofi India Limited,
Plot No. L-121, Phase III, Verna Industrial Estate, Verna, Salcete, Goa - 403 722

Allegra® Suspension 30mg/5ml:
Mistair Health & Hygiene Pvt. Ltd.
Plot No.3, MIDC, Shiroli, Kolhapur - 416122

Updated: December 2023

Source: CCDS Ver.7 dated September 2023