

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

ALLEGRA[®] 12 Hour and
Fexofenadine hydrochloride tablets
Tablets, 60 mg, Oral
Manufacturer's Standard

ALLEGRA[®] 24 Hour
Fexofenadine hydrochloride tablets
Tablets, 120 mg, Oral
Manufacturer's Standard

ALLEGRA[®] HIVES
Fexofenadine hydrochloride tablets
Tablets, 60 mg, Oral
Manufacturer's Standard

Histamine H₁ Receptor Antagonist

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RECENT MAJOR LABEL CHANGES

Patient Medication Information	04/2021
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ALLEGRA[®] (fexofenadine hydrochloride) is indicated for:

Allergic rhinitis: ALLEGRA[®] (fexofenadine hydrochloride) is indicated for: the relief of symptoms associated with seasonal (ALLEGRA[®] 12 Hour, ALLEGRA[®] 24 Hour) and perennial (ALLEGRA[®] 12 Hour) allergic rhinitis, in adults and children 12 years of age and over.

Symptoms treated effectively include sneezing, rhinorrhea, lacrimation, itchy, red eyes and itchy nose/palate/throat. ALLEGRA[®] improves health-related quality of life and work/activity productivity.

Chronic idiopathic urticaria: ALLEGRA[®] 12 Hour and ALLEGRA[®] HIVES are indicated for the relief of symptoms associated with chronic idiopathic urticaria in adults and children 12 years of age and older. ALLEGRA[®] 12 Hour and ALLEGRA[®] HIVES significantly reduces the signs and symptoms of chronic idiopathic urticaria, the number of wheals, and pruritus.

ALLEGRA[®] 12 Hour and ALLEGRA[®] HIVES improves health-related quality of life and, work/activity productivity.

1.1 Pediatrics

The safety and effectiveness of fexofenadine hydrochloride in children under the age of 12 have not been established.

1.2 Geriatrics

Refer to WARNINGS AND PRECAUTIONS.

2 CONTRAINDICATIONS

ALLEGRA[®] (fexofenadine hydrochloride) is contraindicated in patients with a known hypersensitivity to this drug or to any ingredients in the formulation, including any non-medicinal ingredient or any component of the container. For a complete listing see *DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING*.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

A dose of 60 mg once daily is recommended as the starting dose in patients with decreased renal function.

It is recommended to not take with fruit juices.

The safety and effectiveness of fexofenadine hydrochloride in children under the age of 12 have not been established.

4.2 Recommended Dose and Dosage Adjustment

Adults and Children, 12 years of age and older:

Seasonal Allergic Rhinitis:

ALLEGRA® 12 Hour

The recommended dose is 1 tablet (60 mg) every 12 hours with a glass (250 ml) of water. Do not take more than 2 tablets in 24 hours.

ALLEGRA® 24 Hour

The recommended dose 1 tablet (120 mg) once daily with a glass (250 ml) of water.

Perennial Allergic Rhinitis:

ALLEGRA® 12 Hour

The recommended dose is 60 mg every 12 hours with a glass (250 ml) of water. Do not take more than 2 tablets in 24 hours.

Chronic Idiopathic Urticaria (allergic skin condition):

ALLEGRA® 12 Hour:

The recommended dose is 1 tablet (60 mg) every 12 hours with a glass (250 mL) of water. Do not take more than 2 tablets in 24 hours.

ALLEGRA® HIVES:

The recommended dose is 1 tablet (60 mg) every 12 hours with a glass (250 mL) of water. Do not take more than 2 tablets in 24 hours.

4.3 Administration

For oral use only.

5 OVERDOSAGE

Most reports of fexofenadine hydrochloride overdose have been infrequent and contain limited information. However, dizziness, drowsiness, and dry mouth have been reported. Single doses of fexofenadine hydrochloride up to 800 mg, and doses up to 690 mg BID for one month or 240 mg once daily for 1 year were investigated without the development of clinically significant adverse events as compared to placebo. The maximum tolerated dose of fexofenadine hydrochloride was not established. Overall, there was no evidence of QT_c prolongation at doses 11 times the recommended therapeutic dose.

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

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Each ALLEGRA® 12 Hour tablet contains 60 mg fexofenadine hydrochloride.

Each ALLEGRA® 24 Hour tablet contains 120 mg fexofenadine hydrochloride.

Each ALLEGRA® HIVES tablet contains 60 mg fexofenadine hydrochloride.

Table – Dosage Forms, Strengths, Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet, 60 mg, fexofenadine hydrochloride	colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, pregelatinized starch, titanium dioxide
Oral	Tablet, 120 mg, fexofenadine hydrochloride	colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, pregelatinized starch, titanium dioxide

Lactose-free

ALLEGRA® 12 Hour 60 mg tablets are available in blister packs of 12 and 36 tablets. Each peach, oval, double convex tablet is engraved on one side and scripted “e” and with “06” on the other side.

ALLEGRA® 24 Hour 120 mg tablets are available in blister packs of 2,6,12, 18 and 30 tablets. Each peach, oblong, double convex tablet is engraved on one side with a scripted “e” and engraved on the other side with “012”

ALLEGRA® HIVES 60 mg tablets are available in blister packs of 12, 36, and 48 tablets. Each peach, oval, double convex tablets is engraved on one side and scripted “e” and with “06” on the other side.

7 WARNINGS AND PRECAUTIONS

General

Do not take with fruit juices.

Gastrointestinal

In surgically manipulated intestinal tissue (e.g., bowel resection) as well as in inflamed intestinal tissue, p-glycoprotein expression is actually increased. Thus, the oral bioavailability of fexofenadine could possibly be reduced in these disease states.

Renal

The pharmacokinetics of fexofenadine HCl are altered in individuals with renal impairment (see Pharmacokinetics section under **CLINICAL PHARMACOLOGY**). 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.

Hepatic/Biliary/Pancreatic

Moderate to severe hepatic disease does not affect the pharmacokinetics of fexofenadine HCl substantially.

Reproductive Health: Female and Male Potential

- **Teratogenic Risk**

There was no evidence of teratogenicity in rats or rabbits at fexofenadine plasma AUC values four and 37 times the human therapeutic value, respectively (see table under Long Term Toxicity in **NON-CLINICAL TOXICOLOGY** section). Dose-related decreases in pup weight gain and survival were observed in rats exposed to fexofenadine plasma AUC values equal to or greater than three times the human therapeutic value (obtained at steady state with 60 mg bid dosing).

7.1 Special Populations

7.1.1 Pregnant Women

The reproduction toxicology data for fexofenadine HCl rely solely upon those that have been obtained with terfenadine (Seldane) and linked by appropriate bridging pharmacokinetic studies.

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

7.1.2 Pregnancy and Breast-feeding

There are no adequate and well controlled studies in pregnant women or during lactation. However, when terfenadine was administered to nursing mothers, fexofenadine was found to cross into human breast milk. Therefore, fexofenadine HCl is not recommended for breast-feeding women.

7.1.3 Pediatrics

The safety and effectiveness of fexofenadine hydrochloride in children under-12 years of age have not been established. In a randomized, controlled, clinical trial setting, a total of 205 subjects between the ages of 12 to 16 years were administered doses of fexofenadine HCl

ranging from 20 to 240 mg bid for two weeks. Adverse events were similar in this group compared to subjects above 16 years of age.

7.1.3 Geriatrics

In placebo-controlled trials 35 patients aged 65 to 74 years received fexofenadine HCl doses of 20 to 240 mg bid, and 4 patients 75 years and over received fexofenadine HCl doses of 60 to 180 mg once daily. Adverse events were similar in this group compared to patients under 65 years of age. Nevertheless, the pharmacokinetics of fexofenadine HCl are altered (increased bioavailability) in individuals over 65 years of age (see Pharmacokinetics section under **CLINICAL PHARMACOLOGY**).

8 ADVERSE REACTIONS

8.1 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adults

In four, two-week, placebo-controlled seasonal allergic rhinitis trials with doses of 20 mg to 240 mg twice daily adverse events were similar in ALLEGRA® (fexofenadine hydrochloride) and placebo-treated patients. There was no dose-related increase in adverse events, including drowsiness, when administered up to four times the recommended therapeutic dose. Adverse event rates were similar among subgroups defined by age, gender, and race. The rate of premature withdrawal because of adverse events was 2.0% (48/2346) with ALLEGRA® vs 3.2% (22/685) with placebo.

Table 1: Percentage of Patients Reporting Adverse Events (≥1%) in Placebo-Controlled Seasonal Allergic Rhinitis Clinical Trials (bid dosing)			
Adverse Event	Placebo (n=671)	ALLEGRA 60 mg bid (n=679)	Total ALLEGRA 20-240 mg bid (n=2319)
headache	3.1	3.1	2.9
nausea	1.0	1.3	0.8
drowsiness	0.9	1.3	0.8
fatigue	0.9	1.0	1.0

One 2-week, placebo-controlled trial evaluated once daily ALLEGRA[®] doses of 120 mg and 180 mg. Table 2 lists all adverse reactions reported by $\geq 1\%$ of fexofenadine treated patients. The rate of premature withdrawal because of adverse events was 1.2% (7/570) with ALLEGRA[®] vs 1.4% (4/293) with placebo.

Table 2: Percentage of Patients Reporting Adverse Reactions ($\geq 1\%$) in Placebo-Controlled Seasonal Allergic Rhinitis Clinical Trial (qd dosing)				
Adverse Event	Placebo <i>(n=293)</i>	ALLEGRA 120 mg qd <i>(n=287)</i>	ALLEGRA 180 mg qd <i>(n=283)</i>	Total ALLEGRA 120-180 mg qd <i>(n=570)</i>
headache	1.4	1.7	3.9	2.8
epistaxis	0.0	0.3	1.1	0.7
abdominal pain	0.3	0.7	1.1	0.9

In a four-week trial conducted in perennial allergic rhinitis, the nature and incidence of adverse events observed were comparable for ALLEGRA[®] (60 mg BID, 120 mg QD) and placebo, and similar to those observed in the seasonal allergic rhinitis trials.

In two, four-week, placebo-controlled chronic idiopathic urticaria clinical trials evaluating doses of 20 mg to 240 mg twice daily, adverse reactions were similar in ALLEGRA[®] and placebo-treated patients, with no dose-related increase. Table 3 lists all adverse reactions reported by at least 1% of patients. The proportion of patients who withdrew prematurely because of adverse reactions was 3.6% (26/713) with ALLEGRA[®] vs 3.9% (7/178) with placebo.

Table 3: Percentage of Patients Reporting Adverse Reactions ($\geq 1\%$) in Placebo-Controlled Chronic Idiopathic Urticaria Clinical Trials			
Adverse Event	Placebo <i>(n=178)</i>	ALLEGRA 60 mg bid <i>(n=186)</i>	Total ALLEGRA 20-240 mg bid <i>(n=713)</i>
headache	11.2	10.2	10.5
diarrhea	0.6	1.6	0.8
dyspepsia	2.2	1.6	2.0
somnolence	0	1.6	1.5
abdominal pain	2.2	1.1	1.3
dizziness	0.6	1.1	0.8
dry eyes	0.0	1.1	0.6
insomnia	0.6	1.1	1.8
nausea	3.9	1.1	3.1

Two double-blind, placebo-controlled, parallel group, long-term safety studies were conducted in healthy volunteers. In one study, 217 subjects received 60 mg fexofenadine HCl bid for 6 months, and in the other, 234 subjects received 240 mg fexofenadine HCl once daily for 12 months. The nature and incidence of adverse events observed were similar for fexofenadine and placebo, and the types of adverse events reported in these two long-term studies were not different from those observed in the Phase III clinical trials. There were no particular patterns observed in the occurrence of treatment related adverse events in demographic subgroups with respect to gender, age and race. There were no statistically significant changes in measured ECG parameters or vital signs from baseline to the last visit in subjects treated with fexofenadine versus placebo.

8.2 Less Common Clinical Trial Adverse Reactions

In addition to Table 1, the following infrequent ($\geq 0.1\%$ to $<1\%$) adverse events were reported at rates similar to placebo in the controlled seasonal allergic rhinitis (SAR) studies with doses from 20 to 240 mg bid and have been reported rarely during post-marketing surveillance:

Central and Peripheral Nervous Systems: Insomnia, dizziness

Gastrointestinal: Diarrhea, dyspepsia, abdominal pain, flatulence, vomiting

Respiratory: Epistaxis, throat irritation

Metabolic and Nutritional: Thirst

Psychiatric: Appetite increase, nervousness, agitation, sleep disorders or paroniria

Autonomic Nervous System: Dry mouth, dryness of mucous membranes

Skin and Appendages: Pruritus, rash, urticaria

Urinary: Urinary frequency

Cardiovascular System: Tachycardia, palpitation

Infectious Disease: Viral infection

Vision: Blurred vision

Hearing and Vestibular: Earache

Body as a Whole: In rare cases, rash, urticaria pruritis, and hypersensitivity reactions with manifestations such as angioedema, chest tightness, dyspnea, flushing and systemic anaphylaxis.

8.3 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

In all studies, the frequency and magnitude of laboratory abnormalities were similar with ALLEGRA[®] and placebo.

8.4 Post-Market Adverse Reactions

In United States post-marketing surveillance, one case of congestive heart failure has been reported. One case of atrial fibrillation has been reported in clinical studies. A definite cause and effect relationship has not been established.

9 DRUG INTERACTIONS

9.1 Drug Interactions Overview

Since fexofenadine HCl does not undergo hepatic biotransformation, it is unlikely to interact with drugs that rely upon hepatic metabolism.

9.2 Drug-Drug Interactions

During multiple dose co-administration (fexofenadine HCl 120 mg bid for 6.5 days plus erythromycin 500 mg tid for 6.33 days) erythromycin increased $AUC_{ss(0-12\text{ h})}$ of fexofenadine from 2422 to 5055 ng/mL·h (109%), reduced oral clearance by 51%, extended t_{max} from 2.2 to 3.7 hours and increased C_{max} from 410 to 744 ng/mL (80%) in 20 healthy volunteers. Renal clearance was increased from 3.6 to 4.0 L/h. Fexofenadine HCl had no effect on the pharmacokinetics of erythromycin.

Ketoconazole co-administration (fexofenadine HCl 120 mg bid plus ketoconazole 400 mg daily for 7 days) increased $AUC_{ss(0-12\text{ h})}$ of fexofenadine from 2100 to 5547 ng/mL·h (164%), reduced oral clearance by 61% and increased C_{max} from 388 to 914 ng/mL (136%) in 24 healthy volunteers. Fexofenadine had no effect on the pharmacokinetics of ketoconazole.

ALLEGRA® 12 Hour (fexofenadine hydrochloride) at twice the recommended dose (120 mg bid), have been safely coadministered with erythromycin (500 mg q8h) and ketoconazole (400 mg qd) under steady-state conditions in healthy volunteers. No differences in adverse events were reported whether ALLEGRA® was administered alone or in combination. The co-administration of fexofenadine hydrochloride with erythromycin or ketoconazole resulted in no significant increases in daily mean or maximum QT_c interval when analyzed by machine or a cardiologist.

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.

The increased systemic exposure to fexofenadine as a result of erythromycin or ketoconazole co-administration is below that observed with 240 or 400 mg bid doses (AUC_{ss} of 6935 and 13578 ng/mL·h, (respectively) of fexofenadine HCl, neither of which was associated with any adverse effects.

The administration of a single 20 mL dose of Maalox[®] suspension followed 15 min later by a single oral dose of 120 mg fexofenadine HCl resulted in a significant reduction in fexofenadine bioavailability (41% reduction in AUC_(0-30h); 43% reduction in C_{max}). This interaction has been explained on the basis that up to 27.8% of fexofenadine is physically bound to Maalox in the stomach at pH of 4 or greater.

Pretreatment with omeprazole (20 mg 10 hours prior to and 40 mg one hour prior to a single dose of 120 mg fexofenadine) did not alter the bioavailability of fexofenadine.

9.3 Drug-Food Interactions

Do not take with fruit juices. (see *Dosage and Administration*)

9.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

Animal Pharmacology

Fexofenadine hydrochloride inhibited antigen-induced bronchospasm in sensitized guinea pigs and inhibited histamine release from peritoneal mast cells of the rat. In laboratory animals, no anticholinergic or α_1 -adrenergic-receptor blocking effects were observed. Moreover, no sedative or other central nervous system effects were observed. Radiolabelled tissue distribution studies in rats indicated that fexofenadine did not cross the blood-brain barrier.

Fexofenadine had no effects on general behaviour until doses approaching toxic levels were reached (mice: > 200 mg/kg i.p.; rats: > 100 mg/kg, i.p.).

Fexofenadine's activity in a battery of miscellaneous tests was unremarkable. It had no effect on prothrombin time, platelet aggregation, electrolyte excretion, or gastric/intestinal motility; lack of effect on gastric acid secretion indicates no H₂-receptor antagonist activity.

Fexofenadine HCl had no blocking effect on delayed rectifier K⁺ current in adult guinea pig myocytes (10⁻⁵M) and only a very weak blocking effect on cloned delayed rectifier K⁺ channel from human heart (583 fold less potent than terfenadine); these concentrations of fexofenadine are approximately 32 times greater than the therapeutic concentration in man. Similarly, concentrations 32 times greater than the therapeutic concentration in man had no effect on

calcium channel currents, or action potential duration in guinea pig myocytes, or Na⁺ channel current in rat neonatal myocytes.

Doses of fexofenadine HCl ten times greater than doses of terfenadine that were associated with prolongation of QTc intervals did not prolong QTc intervals in anesthetized rabbits and conscious dogs. Fexofenadine levels that were shown to have no effect on QTc in conscious dogs following 30 mg/kg bid for five days were associated with plasma concentrations 15 times higher than the maximum plasma concentrations achieved in man at steady state with the recommended clinical dose (4,382 vs 299 ng/mL).

10.1 Mechanism of Action

Fexofenadine, the predominant human and animal active metabolite of terfenadine, is a selective histamine H₁ - receptor antagonist. Both enantiomers of fexofenadine display approximately equipotent antihistaminic effects. In laboratory animals, there is no evidence of local anesthetic, analgesic, anticonvulsant, antidepressant, antidopaminergic, antiserotonergic, anticholinergic, sedative, H₂-receptor antagonist, α₁-adrenergic receptor or β-adrenergic receptor blocking activity. Fexofenadine HCl inhibits antigen-induced bronchospasm in sensitized guinea pigs and histamine release from peritoneal mast cells of the rat. It does not cross the blood-brain barrier in the rat.

Fexofenadine hydrochloride inhibits histamine induced skin wheal and flare responses. Following single and twice daily oral dose administration, antihistaminic effects occur within one hour, achieve a maximum at two to three hours, and last a minimum of 12 hours. There is no evidence of tolerance to these effects after 28 days of dosing.

At steady state with 60 mg bid dosing in adults, the average percent inhibition of skin wheal was 45.8% and 53.6% for fexofenadine hydrochloride and terfenadine, respectively. The average maximum inhibition and average area under effect curve was similar for both drugs at equivalent doses. Although higher doses, i.e., 180 mg bid produced somewhat greater inhibition, the average difference was only 10-12%. At 12 hours post dose, the average percent inhibition was approximately 30%. Similar results were observed with the skin flare response, although the average percent inhibition was somewhat higher - 69% and 75%, for 60 mg bid fexofenadine hydrochloride and terfenadine, respectively. Equivalent doses of both drugs produced comparable maximum inhibition and area under effect curve. The flare area was inhibited greater than 55% at 12 hours post-dose.

There was no clear relationship between plasma concentrations of fexofenadine and dose of either fexofenadine hydrochloride or terfenadine. Maximum inhibition was achieved at plasma fexofenadine concentrations of 200 ng/mL.

In randomized, double-blind, placebo-controlled trials, a daily dose of fexofenadine hydrochloride 60 mg bid and 120 mg qd were shown to be effective in relieving the symptoms of seasonal allergic rhinitis (trees and grasses in the spring or ragweed pollen in the fall) and perennial allergic rhinitis (animal dander, dust mites and moulds). These symptoms consisted of sneezing, rhinorrhea, itchy nose/palate/throat and itchy, watery, red eyes. Fexofenadine hydrochloride also effectively relieved the signs and symptoms of chronic idiopathic urticaria, including pruritus and number of wheals (see **Indications**).

There was no direct comparison with terfenadine. However, in studies with similar trial design, the effectiveness of fexofenadine appears to be comparable to that of the parent compound.

Preclinical and clinical evidence indicates that fexofenadine HCl does not prolong the QT_c interval (the mechanism underlying the arrhythmias associated with elevated levels of terfenadine). The evidence is derived from *in vitro* electrophysiological studies, *in vivo* preclinical studies in dogs and rabbits and a number of clinical trials consisting of two definitive QT_c studies (n = 24 and 40), two dose escalation studies (n = 24 and 66), two drug interaction studies investigating the effects of erythromycin and ketoconazole (n = 24 for each study), two randomized Phase III clinical trials in patients with fall allergic rhinitis (n = 870 subjects treated with fexofenadine HCl), two long term safety studies (n = 234 and 217 subjects treated with fexofenadine HCl), and single dose (80 mg) studies in special populations (individuals over 65 years of age, patients with various degrees of renal and hepatic impairment).

10.1 Pharmacodynamics

Fexofenadine HCl was shown to inhibit the H₁-mediated effect of injected histamine in producing skin wheal and flare in a dose dependent manner, with the 40 mg bid dose being the minimum effective dose. Both 60 and 180 mg bid doses significantly diminished the ability of histamine to induce wheals and flares, with the effect appearing within 2 hours of drug ingestion and lasting for at least 12 hours. Treatment for 7 days demonstrated no reduction in effect. Elderly subjects showed a similar pattern of histamine wheal suppression compared to young adults. There was no evidence of tolerance to these effects after 28 days of dosing. The percent inhibition in flare and wheal area reaches a maximum, despite continuing increase in plasma fexofenadine concentration beyond 200 ng/mL. Studies attempting to correlate plasma levels of fexofenadine with histamine wheal inhibition are inconclusive.

10.2 Pharmacokinetics

Fexofenadine hydrochloride is rapidly absorbed following oral administration. The single and multiple dose pharmacokinetics of fexofenadine hydrochloride were linear for oral daily doses from 20 mg to 120 mg bid. Following oral administration of a single dose of two 60 mg capsules to healthy, male volunteers, T_{max} occurred at approximately 2.6 hours. Following single dose oral administration of the 60 mg, 120 mg and 180 mg tablet to healthy, male volunteers, mean maximum plasma concentrations were 142, 289 and 494 ng/mL, respectively. Following multiple dosing, fexofenadine has an apparent elimination half-life of 11 to 16 hours. Steady state pharmacokinetic parameters following 60 mg bid dosing are: AUC_{ss} (0-12h) = 1367 ng/mL·h, C_{max} = 299 ng/mL, C_{min} = 29 ng/mL, t_{max} = 1 h.

The pharmacokinetics of fexofenadine HCl in seasonal allergic rhinitis patients and chronic idiopathic urticaria patients are similar to that of otherwise healthy subjects. Peak fexofenadine plasma concentrations were similar between adolescent (12-16 years of age) and adult patients.

The following table summarizes the pharmacokinetic properties of fexofenadine HCl in man, rat, and dog.

Table 4: Comparison of Single Dose Pharmacokinetic Parameters Between Humans and Various Animal Species				
Parameters	Human (60 mg, 0.78 mg/kg; n=27)	Human (240 mg, 3.12 mg/kg; n=23)	Rat (30 mg/kg; n=3) ↓	Dog (8.7 mg/kg; n=3)
Absolute Bioavailability (%)	33*	33*	2.9	57 (15%)
Extent of Absorption (%)	Unknown	Unknown	25	Unknown
AUC ₍₀₋₄₎ (ng/mL ·h)	1348 (41%)	6571 (35%)	436	45197 (29%)
C _{max} (ng/mL)	209 (45%)	1119 (49%)	457	10563 (24%)
t _{max} (h)	1.42 (50%)	1.52 (41%)	0.5	1.2 (66%)
Oral Clearance (L/h/kg)	0.658 (53%) ◇	0.493 (38%)	62.0 '	0.186 (25%) '
Half-life (h)	13.05 (30%)	14.03 (46%)	4.8	13.2 (14%)
Renal Clearance (L/h/kg)	0.0561 (25%) ◇	0.0545 (24%)	N/A	0.0114 (54%)
Recovery of fexofenadine in Urine (% Dose)	9.54 (40%)	11.4 (27%)	0.63 (25%)	5.63 (32%)
Recovery of fexofenadine in Feces (% Dose)	66.7 (4.12%)	N/A	87.2 (0.6%) &	78.1 (0.3%) &
Protein Binding (% Bound)	69.4	N/A	89%	94%
() Coefficient of variation in % N/A Not available * Indirect estimate ↓ 1 sample/rat; n=3 rats/data point in construction of AUC ◇ Converted from L/hr by dividing by a mean body weight of 77 kg ' Calculated for CL _s /F and converted from mL/min/kg to L/h/kg Converted from mL/min/kg & [¹⁴ C] radioactivities				

On a mg dose per kg body weight basis, systemic exposure of fexofenadine in dogs is 2.47 times higher than in humans, and in rats is 145 times less than that in humans.

Absorption

The absolute bioavailability of fexofenadine has not been established but is estimated to be approximately 33%. The 60 mg capsule and tablet formulations are considered to be bioequivalent but the tablet formulation exhibits a greater food effect. The AUC and C_{\max} of the 60 mg tablet formulation in the presence of food was reduced to 76% (83% for the capsule) and 75% (89% for the capsule) of the fasted values. The AUC and C_{\max} of the 120 mg tablets in the presence of food were reduced to 85% (AUC) and 86% (C_{\max}).

Current theory suggests that fexofenadine absorption is incomplete due to the “gate-keeping” function of the p-glycoprotein transport system in the intestinal epithelium which reduces both fexofenadine absorption, explaining the low bioavailability, as well as secretes absorbed drug back into the gastrointestinal tract. Since approximately 80% of an orally administered dose is recovered in the feces, primarily as unchanged drug, rather than 67% (100%-33%), this difference is believed to represent fexofenadine secretion from the systemic circulation into the gastrointestinal lumen.

Distribution

Fexofenadine is 60% to 80% bound to plasma proteins, including serum albumin and α -acid glycoprotein. Protein binding is decreased to 56-68% and 56-75% in renally and hepatically impaired patients, respectively.

Metabolism

Metabolism of fexofenadine is negligible. The methyl ester of fexofenadine (3.6% of the dose) and MDL 4829 (1.5% of the dose) were the only potential metabolites of fexofenadine detected.

Elimination

Following a single 60 mg oral dose, 80% and 11% of the total [^{14}C] fexofenadine hydrochloride dose is recovered in the feces and urine, respectively. The principal elimination pathways of fexofenadine are biliary and renal. Fecal excretion of fexofenadine is comprised of biliary excretion and gastrointestinal secretion processes as well as nonabsorbed drug. The contribution of each component is unknown.

Special Populations and Conditions

Pharmacokinetics in special populations were determined following a single 80 mg oral dose of fexofenadine HCl. The pharmacokinetics were compared to those from normal subjects in a separate study of similar design. While subjects' weights were relatively uniform between the studies, the special population patients were older than the healthy, young volunteers. Thus, an age effect may be confounding the pharmacokinetic differences observed. There was no

statistically significant difference in the treatment effect in subgroups defined by age, gender, race.

- **Geriatrics:** The pharmacokinetics of fexofenadine in healthy elderly individuals (>65 years old, n = 20) were different from those observed in healthy younger individuals following a single oral dose of 80 mg fexofenadine HCl. Mean AUC was 63% higher (control value = 1788 ng/mL·h), oral clearance 30% lower (control value = 48 L/h), renal clearance 24% less (control value = 3.6 L/h), C_{max} 68% higher (control value = 248.7 ng/mL) and half-life 10% longer (15.2 h).
- **Sex:** The steady state AUC and C_{max} values in female subjects (n=20) were 33% and 46% higher, respectively, than those observed in male subjects (n=20). Renal clearance was equivalent. There was no indication of any difference in safety or efficacy.
- **Breast-feeding:** There are no adequate and well controlled studies in women during lactation. However, when terfenadine was administered to nursing mothers, fexofenadine was found to cross into human breast milk. Therefore, fexofenadine HCl is not recommended for breast-feeding women.
- **Hepatic Insufficiency:** The pharmacokinetics of fexofenadine in 14 patients with hepatic disease (moderate, n=9; moderate to severe, n=5), did not differ substantially from that observed in healthy subjects. The lack of effect may be explained by the fact that none of the patients investigated suffered from complete biliary obstruction, as biliary excretion is one the major elimination pathways for fexofenadine.
- **Renal Insufficiency:** Following a single 80 mg oral dose, renal clearance is decreased to 68, 15 and 3% of the control value (3.63 L/h) in patients with mild to moderate impairment (creatinine clearance 41-80 mL/min; n = 9), moderate to severe impairment (creatinine clearance 11-40 mL/min; n = 10) and dialysis patients (creatinine clearance <10 mL/min; n = 10). The corresponding AUC_{0-∞} and C_{max} were increased by 80, 154 and 88%, respectively (control value = 1788.1 ng/mL·h), and by 58, 78 and 54%, respectively (control value = 248.7 ng/mL). The half-life increased from 13.7 hours to 22.8, 24.8 and 18.9 hours, respectively. Based on these 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.

11 STORAGE, STABILITY AND DISPOSAL

ALLEGRA® (fexofenadine hydrochloride) tablets should be stored at 15°-30°C in a dry place.

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

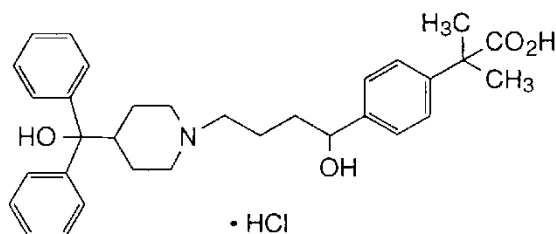
Drug Substance

Proper Name: Fexofenadine hydrochloride

Chemical Name: \pm (4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidiny]-butyl]- α ,
 α -dimethyl, benzeacetic acid hydrochloride

Molecular formula and molecular mass: C₃₂H₃₉NO₄ HCl, 538.13

Structural formula:



Physicochemical properties: A white to off-white crystalline powder, 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, with a pK₁ and a pK₂ = 9.53. The pH of a 1mg/mL solution of fexofenadine HCl is 3.618.

13 CLINICAL TRIALS

13.1 Trial Design and Study Demographics

Seasonal allergic rhinitis: Four randomized, double-blind, placebo-controlled multicentre studies were conducted in subjects with seasonal allergic rhinitis. Two studies each were conducted during the spring and fall allergy seasons. These data were based on 3157 subjects broken down into the following treatment groups: placebo - 689, 20 mg bid - 400, 40 mg bid - 546, 60 mg bid - 685, 80 mg bid - 400, 120 mg bid - 291 and 240 mg bid - 146. Forty-three percent were female and 57% male. Eighty-three percent were Caucasian, 8% black and 9% other. Ages ranged from 11 - 68 years (mean of 33 years); weights from 30 - 178 kg (mean of 73 kg). Years since first episode occurred and successive years of seasonal allergy ranged from 2 - 62 years, with means of 18 and 17 years, respectively.

Perennial allergic rhinitis: A four week, multicentre, randomized, double-blind, placebo-controlled trial in patients 12-78 years of age with perennial allergic rhinitis (n=668).

Chronic idiopathic urticaria: Two 4-week multicentre, randomized, double-blind, placebo-controlled clinical trials compared four fexofenadine HCl doses (20 mg, 60 mg, 120 mg and 240 mg twice daily) to placebo in patients age 12-70 years with chronic idiopathic urticaria (n=726). Additionally, one six-week multicentre, randomized, double-blind, placebo-controlled clinical trial compared four once daily doses of fexofenadine HCl (60 mg, 120 mg, 180 mg and 240 mg QD) in 222 patients with chronic idiopathic urticaria.

13.2 Study Results

Seasonal allergic rhinitis: In three trials, 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 was observed following the first 60 mg dose, with the effect maintained throughout the 12 hour interval.

There appeared to be no clinically significant differences between the 40 and 60 mg bid dosage regimens, although the 60 mg dose had a more rapid onset of action. There were no marked increases in response when the dosage was increased to 240 mg bid. Therefore, there appears to be no correlation between plasma concentrations and pharmacological effect over the dosage range investigated. Since, in general, significant reduction in symptom severity was observed in both the morning and evening, the studies support a twice daily dosing regimen.

In a four-week multicentre, randomized, double-blind, placebo-controlled trial in patients 12-78 years of age with perennial allergic rhinitis (n=668), fexofenadine 60 mg bid significantly reduced total symptom score (the sum of the individual scores for sneezing, rhinorrhea, itchy nose/palate/throat, and itchy/watery/red eyes) compared to placebo. Statistically significant efficacy was maintained throughout the 12-hour treatment interval.

The onset of action in the Phase III clinical trials at doses of 60 mg fexofenadine HCl and higher was within three hours (approximately the time when blood levels of fexofenadine would be at their peak).

Onset of action for reduction in total symptom scores, excluding nasal congestion, was observed at 60 minutes following a single 60 mg or 120 mg dose of fexofenadine HCl administered to subjects suffering from ragweed pollen allergy, compared to 100 minutes for placebo when exposed to this allergen in an environmental exposure unit (n = approximately 33 per group).

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.

Perennial allergic rhinitis: In a four week, multicentre, randomized, double-blind, placebo-controlled trial in patients 12-78 years of age with perennial allergic rhinitis (n=668), fexofenadine 60 mg bid significantly reduced total symptom score (the sum of the individual scores for sneezing, rhinorrhea, itchy nose/palate/throat, and itchy/watery/red eyes) compared to placebo. Statistically significant efficacy was maintained throughout the 12 hour treatment

interval. 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.

Chronic idiopathic urticaria: Two 4-week multicentre, randomized, double-blind, placebo-controlled clinical trials compared four fexofenadine HCl doses (20 mg, 60 mg, 120 mg and 240 mg twice daily) to placebo in patients age 12-70 years with chronic idiopathic urticaria (n=726). Efficacy was demonstrated by a significant reduction in mean pruritus scores (MPS), mean number of wheals (MNW), and mean total symptom scores (MTSS). Although all four doses were significantly superior to placebo in the management of chronic idiopathic urticaria, symptom reduction was greater and efficacy was maintained over the entire 4 week treatment period with fexofenadine HCl doses of ≥ 60 mg twice daily. Treatment effect was also demonstrated in health-related quality of life and work/activity productivity. Improvements in quality of life were demonstrated by a statistically significant reduction for 60 mg twice daily in the following parameters: overall quality of life, symptoms/feelings, daily activities, work/school and personal relations domains. The domains of leisure and treatment were not statistically significant. Improvement in percent of work productivity was statistically significant; improvement in percent of productivity in regular activity was also significant for 60 mg twice daily.

Additionally, one six-week multicentre, randomized, double-blind, placebo-controlled clinical trial compared four once daily doses of fexofenadine HCl (60 mg, 120 mg, 180 mg and 240 mg QD) in 222 patients with chronic idiopathic urticaria. Both the 180 mg and 240 mg QD doses demonstrated statistically significant efficacy in reducing the total symptom score (composite of pruritus score and mean wheals score).

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. **QTc Interval:** In human dose tolerance studies, no evidence of increased QTc was observed with fexofenadine at single doses up to 800 mg or twice daily doses up to 690 mg for 28.5 days. No statistically significant increase in mean QTc interval compared to placebo was observed in 714 seasonal allergic rhinitis patients given fexofenadine HCl in doses of 60 mg to 240 mg twice daily for two weeks. In contrast to the dose-related changes in QTc observed with terfenadine, there were no dose-related increases in QTc with fexofenadine doses up to 240 mg bid. There were no significant increases in QTc interval or differences from placebo with fexofenadine at doses up to 400 mg bid for 6.5 days and 240 mg once daily for 1 year in healthy volunteers.

In the majority of cases, there was good consistency between ECG data read by machine (average of 12 leads using a variable number of intervals) and those obtained by a cardiologist, who visually identified three R-R intervals to be digitized, with the average of these three intervals used to compute the QTc. It was taken into consideration that there may be a subset of patients with an inherent or acquired propensity to develop Torsades de Pointes (an atypical rapid ventricular tachycardia) who are identified by pause-accentuated U waves and/or T wave abnormalities. No such changes were found on visual inspection. Overall there was no correlation between the levels of fexofenadine in the plasma and the QTc interval.

One study (PJPR0004) compared the change in QTc with fexofenadine and terfenadine. The machine read data showed a small, statistically significant increase (mean 4.3 msec) versus pretreatment baseline for fexofenadine 180 mg bid (2 to 3 times the recommended dosage) and a larger statistically significant increase (mean 23 msec) for terfenadine 180 mg bid (3 times the recommended dose) versus baseline. The effect on QTc with terfenadine was statistically significantly greater than that with fexofenadine. The machine read ECG data also showed a borderline statistically significant increase on the average maximum QTc with 180 mg bid fexofenadine versus baseline (6.3 msec, $p=0.05$). Cardiologist read data revealed no statistically significant increases in QTc with fexofenadine. The true effect of fexofenadine and terfenadine alone cannot be derived from this study since a placebo treatment group was not included.

In the other definitive QTc study (PJPR0007), the majority of the machine read data for daily maximum QTc interval did not meet predefined criteria for equivalence to placebo (± 12 msec) although none of the doses (40, 200 and 400 mg bid) were associated with daily maximum QTc intervals that were significantly different from placebo. In this study, an abnormally high proportion of study participants (50%) had at least one QTc outlier. However, there was no consistent trend with respect to dose or time and the proportion of subjects having outlier QTc values was similar for all treatments, including placebo.

In the study on patients with renal impairment, QTc prolongation was reported as an adverse event in one subject: the 2-hour post dose QTc was 494 msec, 23 msec higher than the pre dose value of 471 msec; 4 hours post dose, the QTc interval was 463 msec. This increase is within the range of intra-individual variability in QTc.

In the erythromycin interaction study, there was no significant effect on daily mean or maximum QT, HR, PR or QRS (machine data). There were no QRS outliers. For QTc and PR, the frequency of outliers was the same for the combination as for erythromycin alone while the frequency of outliers for fexofenadine alone was less than that for erythromycin alone. This test had 80% power to detect an increase from baseline of 6.5 msec.

In the ketoconazole interaction study, there were no significant changes in mean or maximum QT, HR (maximum HR was statistically increased when fexofenadine was given in combination with ketoconazole but a change of 5.4 bpm is not considered to be clinically relevant), or QRS. Mean and maximum PR were increased with ketoconazole alone but not with fexofenadine alone or when the two drugs are administered concurrently. There were no QRS or PR interval outliers. Nine subjects had outlier QTc intervals. The number of subjects with QTc outliers was the same for the combination as for fexofenadine alone while there were no QTc outliers observed during the ketoconazole alone phase. This test had 80% power to detect an increase from baseline of 6 msec.

14 NON-CLINICAL TOXICOLOGY

Acute Toxicity

The approximate LD₅₀ in the mouse, rat and dog is provided below.

Table 5: LD ₅₀ Values for Fexofenadine HCl		
Species	Route	LD ₅₀ (mg/kg)
Mouse	Oral (gavage)	>5146
Rat	Oral (gavage)	>5146
Dog	Oral (gavage)	>2000

For the 14 day duration of study in each of these species, no clinical signs of toxicity were observed. No effects on body weight or food consumption were observed in any species. In rodent species there were no treatment related findings noted at necropsy. Necropsy results indicated a high incidence of gross uterine lesions (dilated/fluid filled/congested) in female rats but these were not related to dose. No necropsy data is available for dogs, as all were returned to stock at study end.

The C_{max} and AUC_{0-24h}, determined in a single male dog receiving 2 g/kg were 66,998 ng/mL and 816,343 ng/mL·h, respectively. Mean C_{max} and AUC_{0-96h} in three fasted female dogs dosed with 500 mg/kg fexofenadine HCl were 58,381 ng/mL and 358,457 ng/mL·h, respectively.

Subchronic Toxicity Studies

Multidose toxicity studies with fexofenadine HCl for up to 1 month duration were undertaken in Beagle dogs.

An oral tolerance study at daily oral doses of fexofenadine HCl of 10 and 30 mg/kg x 10 days and 100 and 300 mg/kg x 15 days indicated that fexofenadine HCl was well tolerated with the exception of sporadic episodes of diarrhea and emesis. A sex difference in the plasma levels of fexofenadine was observed, with females having higher plasma concentrations than males (100 mg/kg dose x 15 days gave 1 hour plasma concentrations of 53,504 and 12,171 ng/mL, respectively). Similar sex differences were reflected in the AUC.

A one month oral toxicity study in Beagle dogs dosed tid at 90, 300 and 900 mg/kg/day showed sporadic and reversible episodes of emesis and salivation at the high dose level. There were no drug-related changes in the ECG, body weight, food consumption, hematology, clinical chemistry, urinalysis parameters, organ weights, gross or histopathology findings. A reversible vehicle-related anemia was observed in all groups including controls. Again, plasma concentrations tended to be higher in females as compared to males and increased as dose increased. The AUC_{0-8h} also tended to be higher for females than for males, particularly at the highest dose.

The highest mean C_{max} and AUC observed (female dogs, 900 mg/kg/day) was 100,403 \pm 16,289 ng/mL (day 1) and 72,885 \pm 31,599 ng/mL (day 29) with corresponding AUC_{0-8h} of 355,667 \pm 121,259 and 372,096 \pm 133,125 ng/mL·h.

Mean peak steady state plasma concentrations of fexofenadine on Day 29 after a 300 mg/kg tid regimen were 65,000 ng/mL in males and 73,000 ng/mL in females. The mean steady state AUC_{0-8h} of fexofenadine on Day 29 after the 300 mg/kg tid regimen was 238,000 ng·hr/mL in males and 372,000 ng·hr/mL in females.

In the one month pharmacokinetic study bridging to the chronic terfenadine study in dogs, the toxicity observed in the terfenadine dog studies was not observed in the one month fexofenadine HCl study (with the exception of trembling at weeks 2 and 3 in all three female dogs) although fexofenadine exposure (AUC and C_{max}) was much greater in the fexofenadine HCl study (see table below). Effects in the terfenadine studies were seen at fexofenadine AUCs in the 23,000 to 47,000 ng·hr/mL range and C_{max} in the 3,000 to 5,000 ng/mL range. However, in the one month fexofenadine HCl dog study, fexofenadine AUCs in the 714,000 to 1,116,000 ng·hr/mL range and C_{max} in the 65,000 to 73,000 ng/mL range were achieved with only emesis and salivation as compound related effects. These data demonstrate a better safety profile for fexofenadine than terfenadine.

Long Term Toxicity Studies

The carcinogenic potential and the chronic and reproductive toxicity of fexofenadine hydrochloride were based upon carcinogenicity and reproductive toxicity studies conducted with terfenadine, with appropriate pharmacokinetic bridging studies to demonstrate that there was adequate fexofenadine exposure (based on plasma area-under-the-curve [AUC] values).

In rats, the bioavailability of fexofenadine HCl is extremely low (approximately 3%) because of poor absorption and high first pass extraction. Hence, administration of terfenadine results in higher systemic levels of fexofenadine metabolite than the administration of fexofenadine HCl. Therefore, all of the toxicity data generated in this species with terfenadine adequately characterize the toxicological profile of fexofenadine HCl, since systemic exposure to fexofenadine in the preclinical studies with terfenadine was greater after oral administration of terfenadine than after the oral administration of fexofenadine HCl.

In contrast to the rat, systemic levels of fexofenadine were 3 x higher after the oral administration of fexofenadine HCl in the dog as compared to an equimolar dose of terfenadine. Systemic exposure in the dog toxicity studies was over 200 times that achieved at steady state in humans with 60 mg bid dosing of fexofenadine HCl.

In the bridging studies, the experimental conditions (doses, dosing vehicle, dosing regimen, etc.) employed were identical to those used in the terfenadine chronic toxicity, carcinogenicity, and reproductive studies. Doses selected were equal to the high dose in the original terfenadine studies. Systemic levels of fexofenadine, as assessed by plasma AUC data, exceeded that observed in man following 60 mg terfenadine bid by 3 to 26 fold and, following 60 mg bid fexofenadine HCl, by 4 to 37 fold, depending on the dose and species (see table below).

Table 6: Exposure to Fexofenadine in Chronic Terfenadine Toxicity Studies and the Relationship to Human Exposure at Therapeutic Doses of Terfenadine and Fexofenadine HCl (both at 60 mg bid)					
New Studies Bridging	To Original Terfenadine Studies	Species	Bioavailability of Fexofenadine	AUC Ratio* Animal/Man After Doses of Terfenadine	AUC Ratio* Animal/Man After Doses of Fexofenadine HCl
One month terfenadine 80 mg/kg/day (capsule)	Two year oral Capsule	Dog	C _{max} 4,986 ng/mL AUC ₀₋₂₄ 46,644 ng·hr/mL	12	17
One month terfenadine 150 mg/kg/day (diet)	18 month dietary carcinogenicity study	Mouse	C _{max} 689 ng/mL AUC ₀₋₂₄ 11,444 ng·hr/mL	2.9	4.2
One month terfenadine 150 mg/kg/day (diet)	Two year dietary carcinogenicity study	Rat	C _{max} 675 ng/mL AUC ₀₋₂₄ 11,618 ng·hr/mL	2.9	4.2
Terfenadine 300 mg/kg/day (gavage)	Teratology	Rat	C _{max} 946 ng/mL AUC ₀₋₂₄ 11,927 ng·hr/mL	3.0	4.4
Terfenadine 300 mg/kg/day (gavage)	Teratology	Rabbit	C _{max} 9,313 ng/mL AUC ₀₋₂₄ 101,631 ng·hr/mL	26	37
<p>* Based on a 60 mg bid dose in man</p> <p>[C_{max} = 341 ng/mL and AUC₀₋₂₄ = 3,944 ng·h/mL (2 x AUC₀₋₁₂ of 1,972 ng·h/mL)]</p> <p>↓ Based on 60 mg bid dose of fexofenadine HCl in man.</p> <p>[C_{max} = 299 ng/mL and AUC₀₋₂₄ = 2,734 ng·h/mL (2 x AUC₀₋₁₂ of 1,367 ng·h/mL)]</p>					

Carcinogenicity: No evidence of carcinogenicity was observed when mice and rats were exposed to fexofenadine plasma AUC values four times the human therapeutic value (based on 60 mg fexofenadine hydrochloride bid dose) for 18 and 24 months, respectively.

In the terfenadine mouse chronic toxicity/carcinogenicity study doses of 50 and 150 mg/kg/day did not enhance tumour development. Mice receiving 150 mg/kg/day in the diet exhibited a 5% decrease in weight gain compared to controls, indicating that this dose approached the maximum tolerated dose.

In the terfenadine rat chronic toxicity/carcinogenicity study, doses up to 150 mg/kg/day administered via the diet for two years showed no apparent carcinogenic effects. Rats receiving 150 mg/kg/day in the diet exhibited a 10% decrease in body weight gain, and an increase in relative liver weights compared to controls.

Genotoxicity: All tests for mutagenic activity of terfenadine, both directly or in the presence of activated rat liver microsomal enzyme systems, were negative. Additional genetic toxicity studies have been performed which demonstrate that fexofenadine hydrochloride shows no evidence of mutagenicity.

Fexofenadine HCl was tested in the *in vitro* *Salmonella* - *Escherichia coli* / mammalian microsome reverse mutation assay, the Chinese hamster ovary cell/hypoxanthine-guanine-phosphoribosyl transferase (CHO/HGPRT) forward mutation assay and the *in vitro* chromosome aberration assay utilizing rat lymphocytes. In all tests, fexofenadine HCl was found to be negative. Fexofenadine HCl was also negative in the *in vivo* mouse bone marrow micronucleus test which determines the potential for chromosome aberrations and spindle malfunction.

Reproductive and Developmental Toxicology: The data generated in the Segment I, II, and III reproduction studies for terfenadine support the safety of fexofenadine HCl as well.

Oral doses of 50-300 mg/kg/day terfenadine did not produce any embryo lethality or teratogenicity in the mouse nor did terfenadine exhibit any teratogenic potential or delay in fetal development in the rat.

In rat reproduction and fertility studies, dose-related reductions in implants and increases in post implantation losses were observed at fexofenadine plasma AUC values greater than or equal to three times human therapeutic value (based on a 60 mg twice daily fexofenadine hydrochloride dose). These effects occurred at maternally toxic doses.

No evidence of teratogenicity was observed in the rabbit at doses of 0, 30, 100 or 300 mg/kg/day.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

ALLEGRA® 12 Hour

fexofenadine hydrochloride tablets, Manufacturer's standard

Read this carefully before you start taking **ALLEGRA® 12 Hour** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ALLEGRA® 12 Hour**.

What is ALLEGRA® 12 Hour used for?

For the relief of symptoms associated with year-round and seasonal allergies, including sneezing, runny nose, itchy, watery, red eyes and itchy nose/palate/throat. To control allergy symptoms. Multi-symptom relief.

For the relief of hives and skin itch due to allergic skin reactions.

ALLEGRA® 12 Hour improves health-related quality of life and, work/activity related productivity.

How does ALLEGRA® 12 Hour work?

ALLEGRA® 12 Hour blocks the natural substance, known as histamine (a chemical released by your immune system) that the cells from your body makes during an allergic reaction.

What are the ingredients in ALLEGRA® 12 Hour?

Medicinal ingredients: fexofenadine hydrochloride

Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, pregelatinized starch and titanium dioxide.

Lactose-free

ALLEGRA® 12 Hour comes in the following dosage forms:

Tablets, 60 mg

Do not use ALLEGRA® 12 Hour if:

You have ever had an allergic reaction to this product or any of its ingredients.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ALLEGRA® 12 Hour. Talk about any health conditions or problems you may have, including if you:

- Are pregnant or breastfeeding
- Have kidney disease
- Are 65 years of age or older

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ALLEGRA® 12 Hour:

- Antacids that contains aluminum or magnesium hydroxide, as they may alter the effectiveness of ALLEGRA® 12 Hour
- Do not take within 2 hours of taking an antacid
- Do not take with fruit juices

Usual dose:

Adults and children 12 years of age or older: take 1 tablet (60 mg) every 12 hours with a glass (250 ml) of water. Do not use for a long period of time unless advised by a doctor. Do not take more than 2 tablets in 24 hours.

Overdose:

Reports of overdose with ALLEGRA® 12 Hour have been infrequent, and symptoms include lightheadedness, sleepiness and dry mouth.

If you think you, or a person you are caring for, have taken too much ALLEGRA® 12 Hour, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using ALLEGRA® 12 Hour?

Like all medicines ALLEGRA® 12 Hour can cause unwanted side effects. These are not all the possible side effects you may have when taking ALLEGRA® 12 Hour. If you experience any side effects not listed here, tell your healthcare professional.

Common side effects that may occur include headache, nausea, sleepiness, fatigue, diarrhea, stomach discomfort, abdominal pain, lightheadedness, dry eye and sleeplessness.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE			
Allergic reaction: rash, redness, swelling, difficulty in breathing			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store between 15° and 30°C, in a dry place.

Keep out of reach and sight of children.

If you want more information about ALLEGRA® 12 Hour:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website www.sanofi.ca or by calling **1-800-636-3664**.

This leaflet was prepared by Sanofi Consumer Health Inc.

Last Revised: October 5th, 2021.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

ALLEGRA® 24 Hour

fexofenadine hydrochloride tablets, Manufacturer's standard

Read this carefully before you start taking **ALLEGRA® 24 Hour** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ALLEGRA® 24 Hour**.

What is ALLEGRA® 24 Hour used for?

For the relief of symptoms associated with seasonal allergies, including sneezing, runny nose, itchy, watery, red eyes and itchy nose/palate/throat. To control allergy symptoms. Multi-symptom relief. ALLEGRA® 24 Hour once-daily significantly improves symptoms of seasonal allergy during the day and through the night.

How does ALLEGRA® 24 Hour work?

ALLEGRA® 24 Hour blocks the natural substance, known as histamine (a chemical released by your immune system) that the cells from your body makes during an allergic reaction.

What are the ingredients in ALLEGRA® 24 Hour?

Medicinal ingredients: fexofenadine hydrochloride

Non-medicinal ingredients: colloidal silicon dioxide croscarmellose sodium, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, pregelatinized starch and titanium dioxide.

Lactose-free

ALLEGRA® 24 Hour comes in the following dosage forms:

Tablets, 120 mg

Do not use ALLEGRA® 24 Hour if:

You have ever had an allergic reaction to this product or any of its ingredients.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ALLEGRA® 24 Hour. Talk about any health conditions or problems you may have, including if you:

- Are pregnant or breastfeeding
- Have kidney disease
- Are 65 years of age or older

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ALLEGRA® 24 Hour:

- Antacids that contains aluminum or magnesium hydroxide, as they may alter the effectiveness of ALLEGRA® 24 Hour
- Do not take within 2 hours of taking an antacid
- Do not take with fruit juices

Usual dose: Adults and children 12 years of age or older: take 1 tablet (120 mg) once daily with a glass (250 ml) of water. Do not use for a long period of time unless advised by a doctor.

Overdose:

Reports of overdose with ALLEGRA® 24 Hour have been infrequent, and symptoms include lightheadedness, sleepiness and dry mouth.

If you think you, or a person you are caring for, have taken too much ALLEGRA® 24 Hour, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using ALLEGRA® 24 Hour?

Like all medicines, ALLEGRA® 24 Hour can cause unwanted effects. These are not all the possible side effects you may have when taking ALLEGRA® 24 Hour. If you experience any side effects not listed here, tell your healthcare professional.

Common side effects that may occur include headache, nausea, sleepiness, fatigue, diarrhea, stomach discomfort, abdominal pain, lightheadedness, dry eye, nosebleed and sleeplessness.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE			
Allergic reaction: rash, redness, swelling, difficulty in breathing			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store between 15° and 30°C, in a dry place.

Keep out of reach and sight of children.

If you want more information about ALLEGRA® 24 Hour:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website www.sanofi.ca or by calling **1-800-636-3664**.

This leaflet was prepared by Sanofi Consumer Health Inc.

Last Revised: October 5th, 2021

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

ALLEGRA® HIVES

fexofenadine hydrochloride tablets, Manufacturer's standard

Read this carefully before you start taking **ALLEGRA® HIVES** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ALLEGRA® HIVES**.

What is ALLEGRA® HIVES used for?

For the relief of hives and skin itch due to allergic skin reactions.

ALLEGRA® HIVES improves health-related quality of life and, work/activity related productivity.

How does ALLEGRA® HIVES work?

ALLEGRA® HIVES blocks the natural substance, known as histamine (a chemical released by your immune system) that the cells from your body makes during an allergic reaction.

What are the ingredients in ALLEGRA® HIVES?

Medicinal ingredients: fexofenadine hydrochloride

Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, pregelatinized starch and titanium dioxide.

Lactose-free

ALLEGRA® HIVES comes in the following dosage forms:

Tablets, 60 mg

Do not use ALLEGRA® HIVES if:

You have ever had an allergic reaction to this product or any of its ingredients.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ALLEGRA® HIVES. Talk about any health conditions or problems you may have, including if you:

- Are pregnant or breastfeeding
- Have kidney disease
- Are 65 years of age or older

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ALLEGRA® HIVES:

- Antacids that contains aluminum or magnesium hydroxide, as they may alter the effectiveness of ALLEGRA® HIVES
- Do not take within 2 hours of taking an antacid
- Do not take with fruit juices

Usual dose: Adults and children 12 years of age or older: take 1 tablet (60 mg) every 12 hours with a glass (250 ml) of water. Do not use for a long period of time unless advised by a doctor. Do not take more than 2 tablets in 24 hours.

Overdose:

Reports of overdose with ALLEGRA® HIVES have been infrequent, and symptoms include light-headedness, sleepiness and dry mouth.

If you think you, or a person you are caring for, have taken too much ALLEGRA® HIVES, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using ALLEGRA® HIVES?

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Serious side effects and what to do about them			
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