

# TILAST Tablets

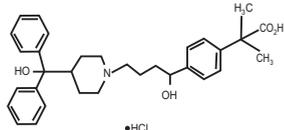
(Fexofenadine HCl)

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Tablets 60mg, 120mg, 180mg

## DESCRIPTION

Fexofenadine Hydrochloride, the active ingredient of Tilast, is a histamine H1-receptor antagonist with the chemical name (+)-4- [1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-a, a- dimethyl benzeneacetic acid hydrochloride, it has the following chemical structure:



The molecular weight is 538,13 and the empirical formula is  $C_{22}H_{29}NO_4 \cdot HCl$ .

## COMPOSITION

Tilast Tablet 60mg :  
Each film-coated tablet contains:  
Fexofenadine Hydrochloride....60mg.  
Tilast Tablet 120mg :  
Each film-coated tablet contains:  
Fexofenadine Hydrochloride....120mg.  
Tilast Tablet 180mg :  
Each film-coated tablet contains:  
Fexofenadine Hydrochloride....180mg.

## CLINICAL PHARMACOLOGY

### Mechanism of action

Fexofenadine, a metabolite of terfenadine, is an antihistamine with selective peripheral H<sub>1</sub>-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 alpha 1-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.

## Pharmacokinetics

Fexofenadine Hydrochloride was rapidly absorbed following oral administration of a single dose (2x60mg) to healthy male volunteers with a mean time to maximum plasma concentration occurring at 2.6 hours postdose. After administration of a single 60mg dose as an oral solution to healthy subjects, the mean plasma concentration was 209ng/ml. Fexofenadine pharmacokinetics were linear for oral doses up to 120mg twice daily. The mean elimination half-life of Fexofenadine was 14.4 hours following administration of 60mg, twice daily, to steady-state in normal volunteers.

Human mass balance studies documented a recovery of approximately 80% and 11% of the (<sup>14</sup>C) Fexofenadine Hydrochloride dose in the faeces and urine respectively. Approximately 5% of the total dose was metabolized. Because the absolute bioavailability of Fexofenadine Hydrochloride has not been established, it is unknown if the faecal component represents unabsorbed drug or the result of biliary excretion.

The pharmacokinetics of Fexofenadine Hydrochloride in allergic rhinitis patients were similar to those in healthy subjects. Peak Fexofenadine plasma concentrations were similar between adolescent (12-16 years of age) and adult patients.

Fexofenadine is 60% to 70% bound to plasma proteins, primarily albumin and  $\alpha_1$ -acid glycoprotein.

## Special Populations

Special population pharmacokinetics (for age and renal and hepatic impairment), obtained after a single dose of 80mg 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 ( $\geq 65$  years old), peak plasma levels of Fexofenadine were 99% greater than those observed in normal volunteers ( $\leq 65$  years old)- Mean elimination half-lives were similar to those observed

in normal volunteers.

**Renally Impaired:** In patients with mild (creatinine clearance 41- 80 ml/min.) to severe (creatinine clearance 11-40 ml/min.) renal impairment, peak plasma levels of Fexofenadine were 87% and 111% greater, respectively, and mean elimination half-lives were 59% and 72% longer, respectively, than observed in normal volunteers. Peak plasma levels in patients on dialysis (creatinine clearance < 10 ml/min.) were 82% greater and half-life was 31% longer than observed in normal volunteers. Based on increases in bioavailability and half-life, a dose of 60mg once daily is recommended as the starting dose in patients with decreased renal function-(See DOSAGE AND ADMINISTRATION)

**Hepatically Impaired:** The pharmacokinetics of Fexofenadine Hydrochloride in patients with hepatic disease did not differ substantially from that observed in healthy subjects.

**Effect of Gender:** Across several trials, no clinically significant gender - related differences were observed in the pharmacokinetics of Fexofenadine.

## Pharmacodynamics

**Wheal and flare:** Human histamine skin wheal and flare studies following single and twice daily doses of 20mg and 40mg 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.

**Effects on QTc:** In dogs, (10 mg/kg/day, orally for 5 days) and rabbits (10 mg/kg/day, intravenously over one hour) Fexofenadine 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 60mg twice daily Fexofenadine Hydrochloride dose). No effect was observed on calcium channel current, delayed K<sup>+</sup> channel current, or action potential duration in guinea pig myocytes, Na<sup>+</sup> current in rat neonatal myocytes or on the delayed rectifier K<sup>+</sup> channel cloned from human heart at concentrations up to  $1 \times 10^{-5}$  M of Fexofenadine. This concentration was at least 32 times the therapeutic plasma concentration in man (based on a 60mg twice daily Fexofenadine Hydrochloride dose).

No statistically significant increase in mean QTc interval compared to placebo was observed in 714 allergic rhinitis patients given Fexofenadine Hydrochloride tablets in doses of 60mg to 240mg twice daily for two weeks or in 40 healthy volunteers given Fexofenadine Hydrochloride as an oral solution at doses up to 400mg twice daily for 6 days.

## THERAPEUTIC INDICATIONS

### Tilast 60mg and Tilast 120mg

Tilast 60mg Tablet / Tilast 120mg Tablet is indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes.

### Tilast 180mg.

Tilast 180mg Tablet is indicated for the relief of symptoms associated with chronic idiopathic urticaria.

## Contraindications

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

## PRECAUTIONS

### Drug interactions

In two separate studies, Fexofenadine Hydrochloride 120mg twice daily (twice the recommended dose) was co-administered with erythromycin 500mg every 8 hours or ketoconazole 400mg once daily under steady state conditions to normal, healthy volunteers (n=24, each study). No differences in adverse events or QTc interval were observed when subjects were administered Fexofenadine Hydrochloride alone or in combination with erythromycin or ketoconazole. The findings of these studies are summarized in the following table:

**Effects on Steady-State Fexofenadine Pharmacokinetics After 7 days of Co-Administration with Fexofenadine Hydrochloride 120mg Every 12 hours (twice recommended dose) In Normal Volunteers (n=24)**

Concomitant Drug (Peak Plasma concentration exposure)	C max ss (+82%)	AUC ss (0-12h) (+109%)
Erythromycin (500mg every 8 hrs)	+82%	+109%
Ketoconazole (400mg once daily)	+135%	+164%

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

## Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential and reproductive toxicity of Fexofenadine Hydrochloride were assessed using terfenadine studies with adequate Fexofenadine exposure (based on plasma area - under-the- curve [AUC] values). No evidence of carcinogenicity was observed when mice and rats were given daily oral doses of 50 and 1 50 mg/kg of terfenadine for 18 and 4 months, respectively, these doses resulted in plasma AUC values of Fexofenadine that were up to four times the human therapeutic value (based on a 60-mg twice-daily Fexofenadine Hydrochloride dose). In vitro (bacterial Reserve Mutation, CHO/HGPRT Forward Mutation, and Rat Lymphocyte Chromosomal Aberration assays) and in-vivo (Mouse Bone marrow Micronucleus assay) tests, Fexofenadine Hydrochloride revealed no evidence of mutagenicity.

In rat fertility studies, dose related reductions in implants and increases in postimplantation losses were observed at oral doses equal to or greater than 150 mg/kg of terfenadine; these doses produced plasma AUC values of Fexofenadine that were equal to or greater than three times the human therapeutic value (based on a 60-mg twice daily Fexofenadine Hydrochloride dose).

## Pregnancy

**Teratogenic Effects :** Category C. There was no evidence of teratogenicity in rats or rabbits at oral terfenadine doses up to 300 mg/kg; these doses produced Fexofenadine plasma AUC values that were up to 4 and 37 times the human therapeutic value (based on a 60-mg twice daily Fexofenadine Hydrochloride dose), respectively.

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

**Non teratogenic effects :** Dose-related decreases in pup weight gain and survival were observed in rats exposed to oral doses equal to and greater than 150mg/kg of terfenadine; at these doses the plasma AUC values of Fexofenadine were equal to or greater than 3 times the human therapeutic values (based on a 60-mg twice daily Fexofenadine Hydrochloride dose).

## Nursing Mothers

There are no adequate and well-controlled studies in women during lactation. Because many drugs are excreted in human milk, caution should be exercised when Fexofenadine Hydrochloride is administered to a nursing woman.

## PediatricUse

Safety and effectiveness of Tilast in pediatric patients under the age of 12 years have not been established. Across well-controlled clinical trials in patients with allergic rhinitis, a total of 205 patients between the ages of 12 to 16 years received doses ranging from 20mg to 240mg twice daily for up to two weeks. Adverse events were similar in this group compared to patients above the age of 16 years.

## Geriatric Use

In placebo-controlled trials, 42 patients, age 60 to 68 years, received doses of 20mg to 240mg of Fexofenadine twice daily for up to two weeks. Adverse events were similar in this group compared to patients under age 60 years.

## ADVERSE REACTIONS

In placebo-controlled clinical trials, which included 2461 patients receiving Fexofenadine Hydrochloride at doses of 20mg to 240mg 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. All, adverse events that were reported by greater than

1% of patients who received the recommended daily dose of Fexofenadine Hydrochloride (60mg twice-daily), and that were more common with Fexofenadine than placebo, are listed in the following table.

Adverse Experience	Fexofenadine 60mg	
	Twice daily (n=679)	Placebo Twice daily (n=671)
Viral infection (Cold, flu)	2.5%	1.5%
Nausea	1.6%	1.5%
Dysmenorrhea	1.5%	0.3%
Drowsiness	1.3%	0.9%
Dyspepsia	1.3%	0.6%
Fatigue	1.3%	0.9%

Adverse events occurring in greater than 1% of Fexofenadine Hydrochloride-treated patients (60mg twice daily), but that were more common in the placebo-treated group, include headache and throat irritation.

The frequency and magnitude of laboratory abnormalities were similar in Fexofenadine Hydrochloride and placebo-treated patients.

## Overdosage

Information regarding acute overdosage is limited to experience from clinical trials conducted during the development of Fexofenadine. Single doses of Fexofenadine Hydrochloride up to 800mg (6 normal volunteers at this dose level), and doses up to 690mg twice daily for one month (3 normal volunteers at this dose level), were administered without the development of clinically significant adverse events.

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.

No deaths occurred at oral doses of Fexofenadine Hydrochloride up to 5000 mg/kg in mice (170 times the maximum recommended human daily oral dose based on mg/m<sup>2</sup>) and up to 5000 mg/kg in rats (330 times the maximum recommended human daily oral dose based on mg/m<sup>2</sup>).

Additionally, no clinical signs of toxicity or gross pathological findings were observed. In dogs, no evidence of toxicity was observed at oral doses up to 2000 mg/kg (450 times the maximum recommended human daily oral dose based on mg/m<sup>2</sup>).

## DOSAGE AND ADMINISTRATION

**Tilast 60mg:** The recommended dose of Tilast 60mg for adults & children aged 12 years or older is 60mg twice daily.

**Tilast 120mg:** The recommended dose of Tilast 120mg for adults & children aged 12 years and over is 120mg once daily.

**Tilast 180mg:** The recommended dose of Tilast 180mg for adults and children aged 12 years or older is 180mg once daily.

A dose of 60mg once daily is recommended as the starting dose in patients with decreased renal function. (See CLINICAL PHARMACOLOGY).

## STORAGE

Store below 30°C.  
Protect from heat, sunlight and moisture.  
The expiration date refers to the product correctly stored at the required conditions.

## HOW SUPPLIED

Tilast (Fexofenadine HCl) Tablets 60mg are available in blister pack of 10's  
Tilast (Fexofenadine HCl) Tablets 120mg are available in blister pack of 10's.  
Tilast (Fexofenadine HCl) Tablets 180mg are available in blister pack of 10's.



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