PRODUCT INFORMATION
TELFAST®

NAME OF THE MEDICINE

Non-proprietary Name
Fexofenadine (as hydrochloride).

Chemical Structure
Fexofenadine HCl is an equimolar mixture of two enantiomers. It has the following structure:

![Chemical Structure Diagram]

The molecular formula is C_{32}H_{39}NO_{4}.HCl and the molecular weight is 538.13.

DESCRIPTION
Fexofenadine is the carboxylic acid metabolite of terfenadine. It is an orally-active non-sedating histamine H₁-receptor antagonist that is administered as the hydrochloride salt in Telfast. The chemical name is benzeneacetic acid, 4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]-α,α-dimethyl-, hydrochloride.

Fexofenadine occurs as a fine white to off-white powder. It is freely soluble in methanol, soluble in ethanol, slightly soluble in water (3.6 mg/mL) and only very slightly soluble in chloroform and hexane.

Telfast 30 mg, 60 mg, 120 mg and 180 mg tablets contain 30 mg, 60 mg, 120 mg and 180 mg of fexofenadine HCl, respectively. Telfast tablets also contain the following excipients: croscarmellose sodium, pregelatinised maize starch, microcrystalline cellulose, magnesium stearate, hypromellose, povidone, titanium dioxide, colloidal anhydrous silica, macrogol 400, Pigment Blend Pink PB1254 (ARTG PI No.3225) and Pigment Blend Yellow PB1255 (ARTG PI No.3226).

Telfast Children's Elixir contains 6 mg/mL of fexofenadine HCl. Telfast Children's Elixir also contains the following excipients: polypropylene glycol, edetate disodium, propyl hydroxybenzoate, butyl hydroxybenzoate, xanthan gum, poloxamer 407, titanium dioxide, sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, artificial raspberry cream flavour (ARTG PI No. 12546), sucrose, xylitol and purified water.

PHARMACOLOGY
The antihistaminic effects of fexofenadine have been demonstrated in animal systems in vitro and in vivo. Oral administration of fexofenadine to guinea pigs, indicated that fexofenadine antagonised histamine-induced skin wheals in a dose-dependent manner. Fexofenadine and terfenadine antagonised the contractile effects of histamine in the guinea pig ileum in vitro. In this model fexofenadine was found to be a more selective histamine antagonist than terfenadine.
Fexofenadine inhibited antigen-induced bronchospasm in sensitised guinea pigs and, at high doses (>100-fold higher than those required for antihistaminic activity), inhibited histamine release from peritoneal mast cells of the rat. In laboratory animals, no anticholinergic or alpha-1-adrenergic receptor blocking effects were observed. Radiolabelled tissue distribution studies in rat indicated that fexofenadine does not cross the blood-brain barrier.

Fexofenadine is not associated with significant ECG abnormalities. Studies have shown that fexofenadine does not affect the action potential or ion channel currents (I_K, I_Ca, I_Na) in either guinea pig or neonatal rat myocytes. Fexofenadine was 583 times less potent than terfenadine in blocking a delayed rectifier potassium channel cloned from human heart. Additionally, doses of fexofenadine ten times greater than the dose of terfenadine that produces prolongation of QTC intervals do not prolong QTC intervals in anaesthetised rabbits and conscious dogs.

Pharmacokinetics

Fexofenadine HCl is rapidly absorbed into the body following oral administration, with t_{max} occurring approximately 1 - 3 hours post-dose. Following administration of a single 60 mg oral dose to healthy volunteers, fexofenadine HCl was rapidly absorbed, with a mean C_{max} of 209 ng/mL. Following the administration of single oral doses of 120 mg and 180 mg fexofenadine HCl, the mean C_{max} values were approximately 427 ng/mL and 494 ng/mL, respectively.

The absolute bioavailability following fexofenadine HCl administration was estimated to be 33%. Co-administration with food has no clinically significant effect on the absorption of fexofenadine HCl.

The single and multiple dose pharmacokinetics of fexofenadine are linear for oral doses up to 120 mg bd. A dose of 240 mg bd produced a slightly greater than proportional increase (8.8%) in steady state area under the curve, indicating that fexofenadine pharmacokinetics are practically linear at daily doses between 40 mg and 240 mg. Fexofenadine is 60% to 70% bound to plasma proteins.

Fexofenadine undergoes negligible metabolism. Following a single radiolabelled 60 mg oral dose, approximately 80% and 11% of the total [14C]-fexofenadine dose was excreted in faeces and urine respectively.

The plasma concentration vs. time profiles of fexofenadine follow a bi-exponential decline with a mean terminal elimination half-life ranging from 14 to 15 hours following multiple dosing.

The pharmacokinetics of fexofenadine in seasonal allergic rhinitis patients are similar to those in healthy subjects.

Studies indicated that females may be exposed to higher plasma levels than males, however, there was no indication of any difference in efficacy or in the frequency of adverse events reported. Elderly patients, patients with hepatic impairment and patients with cardiac disease exposed to fexofenadine by administration of terfenadine showed no statistically significant differences in pharmacokinetic parameters for fexofenadine compared to healthy individuals. Although peak plasma level and half-life were increased 68% and 15% respectively in elderly patients and 54% and 19% respectively in patients with renal disease, regardless of disease severity, these levels are within the range of plasma levels shown to be tolerated in short term dose ranging trials.

The pharmacokinetics of fexofenadine in children and adults are similar, including t_{max}, clearance (corrected for body surface area), t_{1/2} and volume of distribution, because fexofenadine undergoes negligible metabolism, with 80% of the dose being eliminated unchanged in the faeces. In contrast, other H1-receptor antagonists, which are extensively metabolised in the hepatic cytochrome P450 system, usually have shorter half-life values in children than adults.

In children, studies indicate that 30 or 60 mg fexofenadine suppresses the histamine
induced wheal and flare within 1 to 2 hours, with both doses producing similar mean maximal suppression.

A dose of 5 mL of Telfast Children’s Elixir containing 30 mg of fexofenadine HCl is bioequivalent to a 30 mg dose of Telfast tablets. Following oral administration of a 30 mg dose of Telfast Children’s Elixir to healthy adult subjects, the mean C\text{max} was 118.0 ng/mL and occurred at approximately 1.0 hour.

**CLINICAL TRIALS**

An escalating acute dose study demonstrated antihistaminic activity via skin wheal and flare inhibition at doses ranging from 40 mg to 800 mg, with maximum inhibition reaching a plateau at a dose of 130 mg. An escalating repeat dose study demonstrated increasing skin flare inhibition at twice daily doses ranging from 20 mg to 690 mg. During both acute dose and repeat dose studies, an antihistaminic effect was observed within one hour, achieving maximum effect within 2 - 4 hours and lasting a minimum of 12 hours. There was no evidence of tolerance to these effects after 28 days of dosing.

In dose ranging studies, fexofenadine HCl was shown to relieve the symptoms of seasonal allergic rhinitis, significantly reducing total symptom scores (including scores for sneezing, rhinorrhea, itchy nose, palate and/or throat, and itchy, watery, red eyes) over a dosage range of 40 mg to 240 mg twice daily. In a double-blind, placebo-controlled trial of 208 patients with chronic idiopathic urticaria, fexofenadine HCl 180 mg and 240 mg once daily for 6 weeks were found to significantly reduce total symptom scores (number of wheals (hives) and pruritus).

In a double-blind, placebo-controlled clinical efficacy study involving 821 patients with seasonal allergic rhinitis, fexofenadine HCl 120 mg and 180 mg once daily were found to be significantly superior to placebo in relieving symptoms of seasonal allergic rhinitis, including sneezing, rhinorrhea, itchy nose, palate and/or throat, itchy, red or watery eyes and nasal congestion, after 24 hours. There was no statistically significant difference in efficacy between the two doses of fexofenadine, however the 180mg dose did show a trend toward greater reduction in the mean total symptom score.

In a double blind placebo controlled study, 861 patients aged 12 – 65 years were randomised to receive either 120 mg fexofenadine or 180 mg fexofenadine or placebo, once daily for a 2 week period. The primary efficacy measure was change from baseline of average total symptom score. Both doses provided significant (p≤ 0.05) improvement in symptoms of seasonal allergic rhinitis, compared to placebo. While there was no statistically significant difference in efficacy between the two doses, the 180 mg dose showed a trend toward greater reduction in the average total symptom score.

In a double blind placebo controlled study investigating quality-of-life, 845 patients aged 12 - 65 years were randomised to receive 120 mg fexofenadine or 180 mg fexofenadine or placebo once daily for a 2 week period. The primary efficacy measures were change from baseline in a quality-of-life score and in a work / activity impairment score. Patients receiving either 120 mg or 180 mg dose reported a significant (p≤ 0.006) improvement in overall quality-of-life score and a significant (p≤0.004) reduction in work / activity impairment score, compared to placebo. No statistical comparison was made between the effects of the two doses of fexofenadine.

The incidence of drowsiness in controlled clinical seasonal allergic rhinitis trials was similar when comparing patients treated with fexofenadine and placebo. There was no dose-related increase in drowsiness.

The effects of fexofenadine on the QTc interval have been investigated in a variety of studies at doses up to 800 mg/day. There were no statistically significant differences in QTc interval between fexofenadine and placebo treated patients. Similarly, there were no statistically significant differences from placebo or dose-related changes in other ECG parameters as a result of fexofenadine treatment.
Also, no statistically significant change in QTc intervals was observed in long term studies in healthy subjects given fexofenadine HCl 60 mg twice daily for 6 months and 240 mg once daily for 12 months, when compared to placebo.

Interaction studies in healthy volunteers between fexofenadine and erythromycin or ketoconazole demonstrated that although the plasma AUC for fexofenadine increased approximately 2 - 3 fold, there were no significant effects on mean or maximal QTc, nor were there any effects on the incidence of adverse events. Although these plasma levels were above those seen with the recommended dose, they were within the range of plasma levels achieved in controlled dose ranging clinical trials. Fexofenadine had no effect on the pharmacokinetics of erythromycin or ketoconazole (see Interactions with other Medicines for further information).

Across the clinical trials, patients between the ages of 12 to 16 years have received doses ranging from 20 mg to 240 mg twice daily. Adverse events were similar in this group compared to patients above the age of 16 years.

INDICATIONS
Relief of symptoms associated with seasonal allergic rhinitis and allergic rhinitis in adults and children from 2 years of age.
Relief of symptoms of urticaria in adults and children from 6 months of age.

CONTRAINDICATIONS
Telfast is contraindicated in patients with a known hypersensitivity to fexofenadine, terfenadine or any of its excipients.

PRECAUTIONS

Effects on Fertility
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 respectively; these doses produced plasma AUC values of fexofenadine that were equal to or greater than three times the human therapeutic value respectively (based on a 60 mg twice daily fexofenadine HCl dose).

Use in Pregnancy
Category B2. Reproductive toxicity of fexofenadine in animals was assessed through terfenadine exposure. No evidence of teratogenicity was observed in animal reproduction studies (rat and rabbit) when terfenadine was given at oral doses of up to 300 mg/kg/day throughout organogenesis, which corresponds to levels of systemic fexofenadine exposure 4- and 32-fold higher, respectively, than those anticipated in clinical use. Decreased pup weight and survival occurred in rats when terfenadine was given at oral doses of 150 mg/kg/day and above throughout pregnancy and lactation.

There are no studies in pregnant women exposed to fexofenadine alone or through the administration of terfenadine.

Use in Lactation
Telfast is not recommended for nursing women unless, in the physician’s judgment, the potential benefit to the patient outweighs the potential risk to the infant. There are no data on the content of human milk after administering fexofenadine. However, when terfenadine was administered to nursing mothers, fexofenadine was found to cross into human breast milk.

Exposure of rats to fexofenadine and terfenadine through the administration of terfenadine at dietary doses of 150 and 300 mg/kg/day throughout pregnancy and lactation
(corresponding to systemic exposure at levels (AUC) approximately 3- and 6-fold higher than those anticipated in clinical use) caused decreased pup weight gain and survival. The relative risks of these effects from terfenadine or fexofenadine are unknown. Effects on pups exposed to fexofenadine only during lactation are unknown.

**Paediatric Use**
Safety and effectiveness of Telfast has not been established in children under 2 years of age for allergic rhinitis and under 6 months of age for chronic idiopathic urticaria.
Telfast 30 mg tablets is intended for paediatric patients 6 to 11 years of age and Telfast Children’s Elixir for children from 6 months.

**Carcinogenicity**
The carcinogenic potential and reproductive toxicity of fexofenadine HCl were assessed using terfenadine studies. No evidence of carcinogenicity was observed when mice and rats were given daily oral doses of 50 and 150 mg/kg of terfenadine for 18 and 24 months, respectively; these doses resulted in plasma AUC values of fexofenadine that were two to four times the human therapeutic value (based on a 60 mg twice daily fexofenadine HCl dose).
Fexofenadine showed no genotoxic activity in a series of assays for gene mutations and chromosomal damage.

**Interactions with other Medicines**
As fexofenadine undergoes negligible hepatic biotransformation, it is unlikely to interact with other drugs through hepatic metabolism.
The pharmacokinetics of fexofenadine HCl and pseudoephedrine are not altered when both drugs are co-administered.
Coadministration of fexofenadine with erythromycin or ketoconazole has been found to result in a 2 - 3 times increase in the level of fexofenadine in plasma. The changes were not accompanied by any effects on the QT interval and were not associated with any increase in adverse events compared to the drugs given singly. Fexofenadine had no effect on the pharmacokinetics of erythromycin or ketoconazole.
Animal studies have shown that the increase in plasma levels of fexofenadine observed after coadministration of erythromycin or ketoconazole appears to be due to an increase in gastrointestinal absorption and either a decrease in biliary excretion or gastrointestinal secretion respectively.
No interaction between fexofenadine and omeprazole has been observed. However, the administration of an antacid containing aluminium and magnesium hydroxide gel 15 minutes prior to fexofenadine HCl causes a reduction in bioavailability, most likely due to binding in the gastrointestinal tract. It is advisable to leave 2 hours between administration of fexofenadine HCl and aluminium and magnesium hydroxide containing antacids.

**ADVERSE EFFECTS**
Telfast is generally well tolerated. 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 common adverse events reported in controlled clinical trials were headache, fatigue, dizziness or drowsiness and nausea. No apparent dose trends were revealed in adverse events.
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 postmarketing surveillance include: fatigue, insomnia, nervousness, and sleep disorders or paranoia. 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 paediatric seasonal allergic rhinitis patients (6-11 years 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 paediatric patients 6 months to 5 years of age, there were no unexpected adverse events in patients treated with fexofenadine hydrochloride.

DOSAGE AND ADMINISTRATION

Paediatrics

Allergic Rhinitis and Seasonal Allergic Rhinitis:
Children aged 2 to 11 years: 30 mg twice daily, when required.

Urticaria:
Children aged 6 to 23 months: 15 mg twice daily, when required.
Children aged 2 to 11 years: 30 mg twice daily, when required.

Adults and Children aged 12 years or older

Allergic Rhinitis:
60 mg twice daily, when required.

Seasonal Allergic Rhinitis:
120 mg or 180 mg once daily, when required.

Urticaria:
180 mg once daily, when required.

Dosage adjustment is not required in the elderly or in patients with hepatic or renal impairment.

OVERDOSAGE

There is no clinical experience with a fexofenadine overdose. The maximum single dose tested in clinical trials is 800 mg in six healthy subjects. In a multiple-dose study, doses of 690 mg every 12 hours for 28.5 days were given to three healthy subjects and, in another study with forty subjects, a dose of 400 mg every 12 hours was given for 6.5 days. No clinically significant adverse events were reported in these studies.

In the case of an overdose, standard measures to remove any unabsorbed drug should be employed. Symptomatic and supportive treatment is recommended. Haemodialysis is not an effective means of removing fexofenadine from plasma.

Contact the Poisons Information Centre for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

Telfast 30mg Tablets

Peach, round, standard convex film-coated tablets engraved with 03 on one side and e on the other. Each tablet contains fexofenadine HCl 30 mg equivalent to 28 mg fexofenadine. Available in blister packs of 20 tablets. Store below 25°C.
Telfast 60mg Tablets
Peach, oval, double convex, film-coated tablets. Each tablet contains fexofenadine HCl 60 mg equivalent to 56 mg fexofenadine. Available in blister packs of 20 tablets. Store below 25°C.

Telfast 120 mg Tablets
Peach, modified capsule shaped, debossed, film-coated tablets. Each tablet contains fexofenadine HCl 120 mg equivalent to 112 mg fexofenadine. Available in blister packs of 10 and 30 tablets. Store below 25°C.

Telfast 180 mg Tablets
Peach, capsule shaped, deossed, film-coated tablets. Each tablet contains fexofenadine HCl 180 mg equivalent to 168 mg fexofenadine. Available in blister packs of 10 and 30 tablets. Store below 25°C.

Telfast Children's Elixir
White uniform aqueous suspension, with a raspberry cream flavour. Each mL of elixir contains fexofenadine HCl 6 mg (30 mg/5mL) equivalent to 5.6 mg fexofenadine. Available in bottle presentation of 150 mL. Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR
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POISON SCHEDULE OF THE MEDICINE
Pharmacy Medicine (Schedule 2)

DATE OF APPROVAL
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