

Fexofast

Fexofenadine Tablets

Presentation

Fexofast 120 Peach coloured, circular, biconvex film coated tablets, embossed with 'F' on one side and plain on the other side. Each tablet contains 120 mg of fexofenadine hydrochloride.

Fexofast 180 Peach coloured, capsule shaped, biconvex film coated tablets, embossed with 'F' on one side and plain on the other side. Each tablet contains 180 mg of fexofenadine hydrochloride.

Uses

Actions

Fexofenadine is the carboxylic acid metabolite of terfenadine and largely responsible for the antihistaminic effects of terfenadine. Fexofenadine is an orally active non-sedating H₁-receptor antagonist and is effective for the relief of symptoms associated with allergic rhinitis (sneezing, rhinorrhea, pruritus and lacrimation) and urticaria.

The antihistaminic effects of fexofenadine have been demonstrated in animal systems both *in vitro* and *in vivo*. Oral administration of fexofenadine to guinea pigs indicated that fexofenadine antagonised histamine induced skin weals 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 times higher than those required for antihistaminic activity) inhibited histamine release from peritoneal mast cells of the rat. In laboratory animals, no anticholinergic or α_1 -adrenergic receptor blocking effects were observed. Radiolabelled tissue distribution studies in rats 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 of potassium, calcium or sodium ions 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, which produces prolongation of QTc interval, do not prolong QTc interval in anaesthetised rabbits and conscious dogs.

Pharmacodynamics

An escalating acute dose study demonstrated antihistaminic activity via skin weal and flare inhibition at doses ranging from 40 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 to 690 mg. During both acute dose and repeat dose studies, an antihistaminic effect was observed within an hour, achieving maximum effect within 2 to 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 hydrochloride was shown to relieve the symptoms of seasonal allergic rhinitis, significantly reducing total symptom scores (including scores for sneezing, rhinorrhoea, itchy nose, palate and/or throat, and itchy, watery, red eyes) over a dosage range of 40 to 240 mg twice daily. In a double blind, placebo controlled trial of 208 patients with chronic idiopathic urticaria, fexofenadine hydrochloride 180 and 240 mg once daily for six weeks were found to significantly reduce total symptom scores (number of weals (hives) and pruritus).

In a double blind, placebo controlled clinical efficacy study involving 821 patients with seasonal allergic rhinitis, fexofenadine hydrochloride 120 and 180 mg once daily were found to be significantly superior to placebo in relieving symptoms of seasonal allergic rhinitis including sneezing, rhinorrhoea, 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 180 mg 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 to 65 years were randomised to receive either fexofenadine 120 mg or 180 mg or placebo once daily for a 2-week period. The primary efficacy measure was a change from baseline of average total symptom score. Both doses provided significant ($p \leq 0.05$) 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 towards a greater reduction in the average total symptom score.

In a double blind placebo controlled study investigating the quality of life, 845 patients aged 12 to 65 years were randomised to receive fexofenadine 120 mg or 180 mg or placebo once daily for a 2-week period. The primary efficacy measures were changes from baseline in a quality of life score and in a work/activity impairment score. Compared to placebo, patients receiving either 120 mg or 180 mg dose reported a significant ($p \leq 0.006$) improvement in overall quality of life score and a significant ($p \leq 0.004$) reduction in work/activity impairment score. 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, when compared to placebo, no statistically significant change in QTc interval was observed in long-term studies in healthy subjects given fexofenadine hydrochloride 60 mg twice daily for 6 months or 240 mg once daily for 12 months.

Interaction studies in healthy volunteers between fexofenadine and erythromycin or ketoconazole demonstrated that the plasma area under the curve (AUC) for fexofenadine increased approximately twofold to threefold. However, there were no significant effects on the 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**).

Across the clinical trials, for patients between the ages of 12 and 16 years received doses ranging from 20 to 240 mg twice daily, the adverse events reported were similar to those reported by patients above the age of 16 years.

Pharmacokinetics

Absorption

Fexofenadine hydrochloride is rapidly absorbed into the body following oral administration, with T_{max} occurring approximately one to three hours post-dose. Co-administration with food has no clinically significant effect on the absorption of fexofenadine hydrochloride.

Following administration of a single 60 mg oral dose to healthy volunteers, fexofenadine hydrochloride was rapidly absorbed with a mean C_{max} of 209 ng/mL. Following the administration of single oral doses of fexofenadine hydrochloride 120 and 180 mg, the mean C_{max} values were approximately 427 ng/mL and 494 ng/mL, respectively. The absolute bioavailability following fexofenadine hydrochloride administration was estimated to be 33%.

Distribution

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

Metabolism

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

Elimination

The plasma concentration versus 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.

Pharmacokinetics in special populations

The pharmacokinetics of fexofenadine in patients with seasonal allergic rhinitis is 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 or cardiac diseases exposed to fexofenadine by the 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 in adults.

Indications

Fexofast 120 is indicated for the relief of symptoms associated with seasonal and perennial allergic rhinitis in adults and children aged 12 years or older.

Fexofast 180 is indicated for the relief of symptoms associated with seasonal allergic rhinitis and urticaria in adults and children aged 12 years or older.

Dosage and Administration

Perennial allergic rhinitis

The recommended dose is one Fexofast 120 mg tablet once daily for adults and children aged 12 years and over, when required.

Seasonal allergic rhinitis

The recommended dose is either one Fexofast 120 mg tablet or one Fexofast 180 mg tablet once daily for adults and children aged 12 years and over, when required.

Urticaria

The recommended dose is one Fexofast 180 mg tablet once daily for adults and children aged 12 years and over, when required.

Special risk groups

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

Contraindications

Fexofast is contraindicated in patients with known hypersensitivity to fexofenadine, terfenadine or any component of the product (see **Further Information**).

Warnings and Precautions

Special risk groups

No dosage adjustment is required in the elderly patients or patients with renal or hepatic impairment as there were no statistically significant differences in the pharmacokinetic parameters for fexofenadine compared to healthy individuals (see Pharmacokinetics). However, fexofenadine should still be administered with care in these special groups.

Lactose intolerance

Fexofast contains lactose. Patients with lactose intolerance, rare hereditary problems of galactose intolerance should not take this medicine.

Carcinogenicity, mutagenesis, impairment of fertility

The carcinogenic potential and reproductive toxicity of fexofenadine were assessed using terfenadine studies. No evidence of carcinogenicity was observed when mice and rats were given daily oral doses of terfenadine 50 and 150 mg/kg 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 dose of fexofenadine hydrochloride 60 mg twice daily).

Fexofenadine showed no genotoxic activity in a series of assays for gene mutations and chromosomal damage.

In rat fertility studies, dose related reductions in implants and increases in post-implantation losses were observed at oral doses equal to or greater than

terfenadine 150 mg/kg. These doses produced plasma AUC values of fexofenadine that were equal to or greater than three times the human therapeutic value (based on a dose of fexofenadine hydrochloride 60 mg twice daily).

Use in pregnancy (Category B2)

There are no studies in pregnant women exposed to fexofenadine alone or through the administration of terfenadine. As with other medications, fexofenadine should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Reproductive toxicity of fexofenadine in animals was assessed through terfenadine exposure. Data from supporting pharmacokinetic studies, showing the extent of fexofenadine exposure, demonstrated that these studies are relevant to the assessment of fexofenadine hydrochloride. No evidence of teratogenicity was observed in animal reproduction studies (rats and rabbits) when terfenadine was given at oral doses of up to 300 mg/kg/day throughout organogenesis, which corresponds to levels of systemic fexofenadine exposure fourfold 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.

No effects on male or female fertility, or perinatal or postnatal development, were observed in terfenadine animal studies at non-maternally toxic doses.

Use in lactation

Fexofenadine is not recommended for breastfeeding women unless, in the doctor's judgment, the potential benefit to the patient outweighs the potential risk to the infant. There is no data on the content of human milk after administering fexofenadine. However, when terfenadine was administered to breastfeeding 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 AUC levels approximately threefold and sixfold 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.

Use in children

There is currently not enough information available to recommend the use of fexofenadine 120 mg or 180 mg in children under the age of 12 years.

Effects on ability to drive and use machinery

It has been shown that fexofenadine has no significant effects on central nervous system function. Thus, it is unlikely to produce an effect on the ability

to drive or operate machinery. However, some people may be more sensitive and have unusual reactions to medicines, and care should be taken before driving or performing tasks that require alertness.

Adverse Effects

Fexofenadine is generally well tolerated. In placebo controlled clinical trials, the most commonly reported adverse events were headache (> 3%), drowsiness, nausea, and dizziness (1 to 3%). The incidence of these events observed with fexofenadine was similar to that observed with placebo.

Events that have been reported with incidences less than 1% and similar to placebo during controlled clinical trials, and those have been reported rarely during post-marketing surveillance, are fatigue, insomnia, nervousness and sleep disorders or paroniria.

In rare cases, rash, urticaria, pruritis and hypersensitivity reactions such as angio-oedema, dyspnoea, chest tightness, flushing and systemic anaphylaxis have been reported.

No notable dose effects on QTc were found.

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

Interactions

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

Erythromycin and ketoconazole

Fexofenadine had no effect on the pharmacokinetics of erythromycin or ketoconazole. However, co-administration of fexofenadine with erythromycin or ketoconazole has been found to result in a two to three times increase in the level of fexofenadine in plasma. These changes were not accompanied by any effects on the QT interval or associated with any increase in adverse events compared to the drugs given singly. The concentration of fexofenadine experienced by individuals during the interaction studies are well within the range experienced in acute and chronic dose tolerance studies.

In animal studies, the increase in plasma levels of fexofenadine observed after co-administration 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.

Omeprazole and antacids

No interaction between fexofenadine and omeprazole was observed. However, administration of an antacid containing aluminium and magnesium

hydroxide gels 15 minutes prior to fexofenadine caused a reduction in bioavailability, most likely due to binding in the gastrointestinal tract. It is advisable to leave two hours between the administration of fexofenadine and aluminium and magnesium hydroxide containing antacids.

Pseudoephedrine

The pharmacokinetics of fexofenadine and pseudoephedrine are not altered when both drugs are co-administered.

Overdosage

Symptoms

There is no clinical experience with a fexofenadine overdose. It may be expected that the signs and symptoms mentioned under **Adverse Effects** would be more pronounced in overdose.

The maximum single dose tested in clinical trials was 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. In another study with 40 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.

Clinical signs of toxicity and effects on body weight or food consumption were not observed in acute toxicity studies in several animal species administered with fexofenadine by oral lavage at doses of 2,000 mg/kg.

Treatment

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.

Pharmaceutical Precautions

Shelf-life of 24 months

Store in a cool, dry place where temperature stays below 25°C

Medicine Classification

Pharmacy Only Medicine

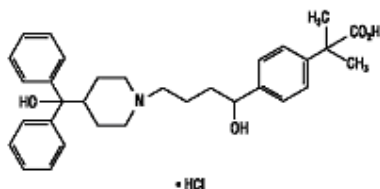
Package Quantities

Blister packs of 10 and 30 tablets

Further Information

Fexofast contains hydrochloride salt of fexofenadine. The chemical name is benzene acetic acid, 4-[1-hydroxy-4[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]- α,α -dimethyl-, hydrochloride.

Its structural formula is



$C_{32}H_{39}NO_4 \cdot HCl$ Molecular weight: 538.13 CAS No.: 153439-40-8

Fexofenadine is the carboxylic acid metabolite of terfenadine and administered as the hydrochloride salt in Fexofast. Fexofenadine occurs as a fine white to off-white powder and 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. Fexofenadine hydrochloride is an equimolar mixture of two enantiomers.

Fexofast tablets come in two strengths and contain either 120 mg or 180 mg of fexofenadine hydrochloride. The tablets also contain microcrystalline cellulose, lactose, povidone, croscarmellose sodium, maize starch, sodium lauryl sulfate, purified talc, magnesium stearate and Opadry II Brown 85G86605. The tablets are gluten free.

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