MTFx Tablet

Montelukast & Fexofenadine

COMPOSITION

MTnL Tablets

Each film-coated tablet contains:

Montelukast sodium equivalent to montelukast	10 mg
Fexofenadine hydrochloride	120 mg
Excipients	q.s.

DESCRIPTION

Montelukast sodium is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene (CysLT1), receptor.

Fexofenadine hydrochloride, the pharmacologically active metabolite of terfenadine, is a potent and selective antagonist of peripheral H1-receptors.

Recent studies have demonstrated that Allergic Rhinitis [AR] when treated concomitantly with an antileukotriene (montelukast) and an antihistamine (fexofenadine), shows significantly better symptom relief compared with the modest improvement of rhinitis symptoms with each of the treatments alone.

PHARMACOLOGY

As **MTFx** is a combination of Montelukast and Fexofenadine; the pharmacological properties of both the molecules are given separately:

Pharmacodynamics

MONTELUKAST

Montelukast causes inhibition of airway cysteinyl leukotriene receptors as demonstrated by the ability to inhibit bronchoconstriction due to inhaled LTD4 in asthmatics. Doses as low as 5 mg cause substantial blockage of LTD4 -induced bronchoconstriction.

FEXOFENADINE

Fexofenadine hydrochloride is a non-sedating H1 antihistamine. Fexofenadine is a pharmacologically active metabolite of terfenadine.

In seasonal allergic rhinitis patients who were given fexofenadine hydrochloride up to 240 mg twice daily for 2 weeks, no significant differences in the QTc intervals were observed when compared to placebo. Also, no significant change in the QTc intervals was observed in healthy subjects given fexofenadine hydrochloride up to 60 mg twice daily for 6 months, 400 mg twice daily for 6.5 days, and 240 mg once daily for 1 year, when compared to placebo.

Pharmacokinetics

MONTELUKAST

Absorption

After administration of a 10-mg tablet to fasted adults, the mean peak montelukast plasma concentration (Cmax) is achieved in 3 to 4 hours (Tmax). The mean oral bioavailability is 64%. The oral bioavailability and Cmax are not influenced by a standard meal in the morning.

Distribution

Montelukast is more than 99% bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8 to 11 liters.

Metabolism

Montelukast is extensively metabolized. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and pediatric patients.

Elimination

The plasma clearance of montelukast averages 45 mL/min in healthy adults. Following an oral dose of radiolabeled montelukast, 86% of the radioactivity was recovered in 5-day fecal collections and <0.2% was recovered in urines. Coupled with estimates of montelukast oral bioavailability, this indicates that montelukast and its metabolites are excreted almost exclusively via the bile.

In several studies, the mean plasma half- life of montelukast ranged from 2.7 to 5.5 hours in healthy young adults. The pharmacokinetics of montelukast are nearly linear for oral doses up to 50 mg. During once daily dosing with 10-mg montelukast, there is little accumulation of the parent drug in plasma (~14%).

FEXOFENADINE

The single- and multiple-dose pharmacokinetics of fexofenadine are linear for oral doses up to 120 mg b.i.d. A dose of 240 mg b.i.d. produced a slightly greater than proportional increase (8.8%) in the steady-state area under the curve (AUC), indicating that fexofenadine pharmacokinetics are practically linear at doses between 40 mg and 240 mg taken daily.

Absorption

Fexofenadine hydrochloride is rapidly absorbed into the body following oral administration, with the Tmax occurring at approximately 1–3 hours post-dose. The mean Cmax value was approximately 427 ng/ml following the administration of a 120 mg dose once daily.

Distribution

Fexofenadine is 60–70% plasma protein-bound.

Biotransformation

Fexofenadine undergoes negligible metabolism (hepatic or non-hepatic) as it was the only major compound identified in the urine and faeces of animals and humans. The plasma concentration profiles of fexofenadine follow a bi-exponential decline, with a terminal elimination half-life ranging from 11 to 15 hours after multiple dosing.

Elimination

The major route of elimination is believed to be via biliary excretion, while up to 10% of the ingested dose is excreted unchanged through the urine.

INDICATIONS

MTFx Tablets are indicated for:

- Allergic rhinitis
- Asthma
- Upper Respiratory Tract Infections

DOSAGE & ADMINISTRATION

Adults [>15years]: 1 MTFx Tablet once daily

CONTRAINDICATIONS

MTnL is contraindicated in patients with known hypersensitivity to montelukast sodium, Fexofenadine or to any other component of this product.

WARNINGS & PRECAUTIONS

MONTELUKAST

Eosinophilic Conditions

In rare cases, patients on therapy with Montelukast may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition, which is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy.

FEXOFENADINE

As with most new medicinal products there is only limited data in the elderly and renally or hepatically impaired patients. Fexofenadine hydrochloride should be administered with care in these special groups.

Patients with a history of or ongoing cardiovascular disease should be warned that antihistamines as a drug class have been associated with the adverse events of tachycardia and palpitations.

Based on the pharmacodynamic profile and reported adverse events, it is unlikely that fexofenadine hydrochloride tablets will produce an effect on the ability to drive or use machines. In objective tests, fexofenadine has been shown to have no significant effects on the central nervous system function. This means that patients may drive or perform tasks that require concentration. However, in order to identify sensitive people who have an unusual reaction to drugs, it is advisable to check the individual response before driving or performing complicated tasks.

DRUG INTERACTIONS

MONTELUKAST

In drug-interaction studies, the recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following drugs: theophylline, prednisone, prednisolone, oral contraceptives (norethindrone 1 mg/ethinyl estradiol 35 mcg), terfenadine, digoxin, and warfarin.

Although additional specific interaction studies were not performed, montelukast was used concomitantly with a wide range of commonly prescribed drugs in clinical studies without evidence of clinical adverse interactions. These medications included thyroid hormones, sedative hypnotics, non-steroidal anti-inflammatory agents, benzodiazepines, and decongestants.

Phenobarbital, which induces hepatic metabolism, decreased the AUC of montelukast approximately 40% following a single 10-mg dose of montelukast. No dosage adjustment for montelukast is recommended. It is reasonable to employ appropriate clinical monitoring when potent cytochrome P450 enzyme inducers, such as phenobarbital or rifampin, are co-administered with montelukast.

FEXOFENADINE

Fexofenadine does not undergo hepatic biotransformation and, therefore, will not interact with other drugs through hepatic mechanisms. Co-administration of fexofenadine hydrochloride with erythromycin or ketoconazole has been found to result in an increase by two to three times in the level of fexofenadine in plasma. The changes were not accompanied by any effects on the QTc interval and were not associated with any increase in adverse events compared to the drugs given singly.

Animal studies have shown that the increase in plasma levels of fexofenadine, observed after the co-administration of erythromycin or ketoconazole, appears to be due to an increase in gastrointestinal absorption and a decrease in either the biliary excretion or gastrointestinal secretion, respectively.

No interaction between fexofenadine and omeprazole was observed. However, the administration of an antacid containing aluminium and magnesium hydroxide gels, 15 minutes prior to fexofenadine hydrochloride, caused a reduction in the bioavailability, most likely due to binding in the gastrointestinal tract. It is advisable to leave a 2-hour gap between the administration of fexofenadine hydrochloride and aluminium- and magnesium hydroxide-containing antacids.

Fruit juices such as grapefruit, orange and apple may reduce the bioavailability and exposure of fexofenadine. Based on the population pharmacokinetics analysis of the combined data from grapefruit and orange juices studies with the data from a bioequivalence study, the bioavailability of fexofenadine was reduced by 36%. Therefore, to maximize the effects of fexofenadine, it is recommended that fexofenadine should be taken with water.

Renal Impairment

As with most new drugs, there is only limited data in renally impaired patients. Fexofenadine hydrochloride should be administered with care in these special groups.

Hepatic Impairment

As with most new drugs, there is only limited data in hepatically impaired patients. Fexofenadine hydrochloride should be administered with care in these special

groups.

Pregnancy

There are no adequate and well-controlled studies of either montelukast or fexofenadine in pregnant women. Limited animal studies do not indicate the direct or indirect harmful outcomes with respect to the effects on pregnancy, embryonal/foetal development, parturition, or postnatal development. Because animal reproduction studies are not always predictive of human response, MONTAIR FX Tablets should be used during pregnancy only if it is considered to be clearly essential.

Lactation

It is not known if montelukast is excreted in human milk. There are no data on the content of human milk after administering fexofenadine hydrochloride. However, when terfenadine was administered to nursing mothers, fexofenadine was found to cross into human breast milk. Therefore, MONTAIR FX Tablets are not recommended for nursing mothers.

Pediatric Use:

Montelukast

The safety of Montelukast 4- mg chewable tablets in pediatric patients aged 2 to 14 years with allergic rhinitis is supported by data from studies conducted in pediatric patients aged 2 to 14 years with asthma. A safety study in pediatric patients 2 to 14 years of age with seasonal allergic rhinitis demonstrated a similar safety profile. The safety and effectiveness in pediatric patients below the age of 12 months with asthma and 6 months with allergic rhinitis have not been established.

Fexofenadine

The safety and effectiveness of montelukast and fexofenadine in paediatric patients below the age of 6 months have not been established.

Geriatric Use

Montelukast:

No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Fexofenadine:

There is no data on the geriatric use of this combination. However, the following data is available on the individual components

UNDESIRABLE EFFECTS

Montelukast

Common side effects include dyspepsia, abdominal pain, rash, dizziness, headache, fatigue, fever, trauma, cough, nasal congestion.

Fexofenadine

In controlled clinical trials, the most commonly reported adverse events were headache (7.3%), drowsiness (2.3%), nausea (1.5%) and dizziness (1.5%). The incidence of these events observed with fexofenadine was similar to that observed with placebo. Back pain and dysmenorrhoea were also observed in clinical trials with fexofenadine.

Events that have been reported with incidences of less than 1% and similar to placebo in controlled trials, and have also been reported rarely during postmarketing surveillance include the following: Fatigue, insomnia, nervousness and sleep disorders or paroniria such as nightmares/ excessive dreaming (paroniria), as well as tachycardia, palpitations and diarrhoea. In rare cases, rash, urticaria, pruritus, and hypersensitivity reactions with manifestations such as angio-oedema, chest tightness, dyspnoea, flushing and systemic anaphylaxis have also been reported. Other reported effects included skin disorders such as rash, urticaria and pruritis.

OVERDOSAGE

There is no data to prove the overdosage of this combination. However, overdosage has been reported with individual molecules.

MONTELUKAST

There have been reports of acute over-dosage in post-marketing experience and clinical studies with montelukast. These include reports in adults and children with a dose as high as 1000 mg. The clinical and laboratory findings observed were

consistent with the safety profile in adults and pediatric patients. There were no adverse experiences in the majority of over-dosage reports. The most frequently occurring adverse experiences were consistent with the safety profile of montelukast and included abdominal pain, somnolence, thirst, headache, vomiting and psychomotor hyperactivity.
It is not known whether montelukast is removed by peritoneal dialysis or hemodialysis.

FEXOFENADINE
Dizziness, drowsiness, fatigue and dry mouth have been reported with overdosage of fexofenadine hydrochloride. Single doses up to 800 mg and doses up to 690 mg twice daily for 1 month, or 240 mg once daily for 1 year have been administered to healthy subjects without the development of clinically significant adverse events, as compared with placebo. The maximum tolerated dose of fexofenadine hydrochloride has not been established. Standard measures should be considered to remove any unabsorbed medicinal product. Symptomatic and supportive treatment is recommended. Haemodialysis does not effectively remove fexofenadine hydrochloride from blood.

Incompatibility

PRESENTATION
MTFx Tablet is available in a strip of 10 tablets

STORAGE
Store in a cool dry place.
Protect from moisture and light.