For the use of registered medical practitioner

GENERIC NAME

Montelukast Sodium and Fexofenadine Hydrochloride Tablets.

BRAND NAME

Montair FX® Tablets

BLACK BOX WARNING

SERIOUS NEUROPSYCHIATRIC EVENTS

Serious neuropsychiatric (NP) events have been reported with the use of montelukast. The types of events reported were highly variable, and included, but were not limited to, agitation, aggression, depression, sleep disturbances, suicidal thoughts and behaviour (including suicide). The mechanisms underlying NP events associated with montelukast use are currently not well understood.

Because of the risk of NP events, the benefits of montelukast may not outweigh the risks in some patients, particularly when the symptoms of disease may be mild and adequately treated with alternative therapies. Reserve the use of montelukast for patients with allergic rhinitis who have an inadequate response or intolerance to an alternative. In patients with asthma or exercise-induced bronchoconstriction, consider the benefits and risks before prescribing montelukast.

Discuss the benefits and risks of montelukast with patients and caregivers when prescribing montelukast. Advise patients and/or caregivers to be alert for changes in behaviour or new NP symptoms when taking montelukast. If changes in behaviour are observed, or if new NP symptoms or suicidal thoughts and/or behaviour occur, advise patients to discontinue MONTAIR FX Tablet and contact a healthcare provider immediately.

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Montelukast Sodium IP equivalent

to Montelukast……...10 mg

Fexofenadine Hydrochloride IP……120 mg

Excipients…….q.s

Colours: Ferric Oxide USP NF (Yellow) & Titanium Dioxide IP

DOSAGE FORM(S) AND STRENGTH(S)

Oral Tablet (Montelukast Sodium 10 mg & Fexofenadine Hydrochloride 120 mg)

CLINICAL PARTICULAR

Therapeutic Indication

MONTAIR FX tablet is indicated for the relief of symptoms of allergic rhinitis (Seasonal and Perennial) whenever a combination is indicated.

Posology & Method of Administration

Posology: MONTAIR FX tablet is indicated once daily for the age group of 15 years and above.

Method of Administration: To be taken orally

Contraindication

In patients with a known hypersensitivity to montelukast, fexofenadine or to any of the excipients.

Special Warnings & Precaution for Use

Patients should be advised never to use oral montelukast to treat acute asthma attacks and to keep their usual appropriate rescue medication for this purpose readily available. If an acute attack occurs, a short-acting inhaled beta-agonist should be used. Patients should seek their doctor's advice as soon as possible if they need more inhalations of short-acting beta-agonists than usual.

Montelukast should not be substituted abruptly for inhaled or oral corticosteroids.

There are no data demonstrating that oral corticosteroids can be reduced when montelukast is given concomitantly.

In rare cases, patients on therapy with anti-asthma agents including 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 cases have been sometimes associated with the reduction or withdrawal of oral corticosteroid therapy. Although a causal relationship with leukotriene receptor antagonism has not been established, physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. Patients who develop these symptoms should be reassessed and their treatment regimens evaluated.

Treatment with montelukast does not alter the need for patients with aspirin-sensitive asthma to avoid taking aspirin and other non-steroidal anti-inflammatory drugs.

Neuropsychiatric events have been reported in adults, adolescents, and children taking montelukast. Patients and physicians should be alerted for neuropsychiatric events. Patients and/or caregivers should be instructed to notify their physician if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with Montelukast if such events occur.

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Drugs Interactions

Fexofenadine

The coadministration of fexofenadine hydrochloride with erythromycin or ketoconazole resulted in no significant increases in QTc. No differences in adverse effects were reported whether these agents were administered alone or in combination.

Administration of an antacid containing aluminium and magnesium hydroxide gels 15 minutes prior to fexofenadine hydrochloride, caused a reduction in the bioavailability. It is advisable to leave 2-hours between the administration of fexofenadine hydrochloride and aluminium- and magnesium hydroxide-containing antacids.

No interaction between fexofenadine and omeprazole was observed.

Drug Interaction with Erythromycin and Ketoconazole

Fexofenadine hydrochloride has been shown to exhibit minimal (ca. 5%) metabolism. However, co–administration of fexofenadine hydrochloride with ketoconazole and erythromycin led to increased plasma levels of fexofenadine hydrochloride. Fexofenadine hydrochloride had no effect on the pharmacokinetics of erythromycin and ketoconazole. In two separate studies, fexofenadine hydrochloride 120 mg twice daily (two times the recommended twice daily dose) was co-administered with erythromycin 500 mg every 8 hours or ketoconazole 400 mg 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 patients were administered fexofenadine hydrochloride alone or in combination with erythromycin or ketoconazole.

Drug Interactions with Antacids

Administration of 120 mg of fexofenadine hydrochloride (2 x 60 mg capsule) within 15 minutes of an aluminum and magnesium containing antacid (Maalox®) decreased fexofenadine AUC by 41% and C_{max} by 43%. Fexofenadine should not be taken closely in time with aluminum and magnesium containing antacids.

Montelukast

Montelukast may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma. No dose adjustment is needed when montelukast is coadministered with theophylline, prednisone, prednisolone, oral contraceptives (ethinyl estradiol/ norethindrone 35/1), terfenadine, digoxin, and warfarin.

The area under the plasma concentration curve (AUC) for montelukast was decreased approximately 40% in subjects with co-administration of phenobarbital. Since montelukast is metabolised by CYP 3A4, 2C8, and 2C9, caution should be exercised, particularly in children, when montelukast is co-administered with inducers of CYP 3A4, 2C8, and 2C9, such as phenytoin, phenobarbital and rifampicin.

In vitro studies have shown that Montelukast is a potent inhibitor of CYP 2C8. However, data from a clinical drug-drug interaction study involving montelukast and rosiglitazone (a probe substrate representative of medicinal products primarily metabolized by CYP 2C8) demonstrated that montelukast does not inhibit CYP 2C8 in vivo. Therefore, montelukast is not anticipated to markedly alter the metabolism of medicinal products metabolised by this enzyme (e.g., paclitaxel, rosiglitazone, and repaglinide.)

In vitro studies have shown that Montelukast is a substrate of CYP 2C8, and to a less significant extent, of 2C9, and 3A4. In a clinical drug-drug interaction study involving montelukast and gemfibrozil (an inhibitor of both CYP 2C8 and 2C9) gemfibrozil increased the systemic exposure of montelukast by 4.4-fold. No routine dosage adjustment of montelukast is required upon co-administration with gemfibrozil or other potent inhibitors of CYP 2C8, but the physician should be aware of the potential for an increase in adverse reactions.

Based on *in vitro* data, clinically important drug interactions with less potent inhibitors of CYP 2C8 (e.g. trimethoprim) are not anticipated. Co-administration of montelukast with itraconazole, a strong inhibitor of CYP 3A4, resulted in no significant increase in the systemic exposure of montelukast.

Use in Special Population

Fexofenadine:

Patients with Renal Impairment

In subjects with mild to moderate (creatinine clearance 41-80 mL/min) and severe (creatinine clearance 11-40 mL/min) renal impairment, peak plasma concentrations of fexofenadine were 87% and 111% greater, respectively, and mean elimination half-lives were 59% and 72% longer, respectively, than observed in healthy subjects. Peak plasma concentrations in subjects on dialysis (creatinine clearance ≤10 mL/min) were 82% greater and half-life was 31% longer than observed in healthy subjects. Based on increases in bioavailability and half-life, a dose of 60 mg once daily is recommended as the starting dose in adult patients with decreased renal function. For pediatric patients with decreased renal function, the recommended starting dose of fexofenadine is 30 mg

once daily for patients 2 to 11 years of age and 15 mg once daily for patients 6 months to less than 2 years of age.

Patients with Hepatic Impairment

The pharmacokinetics of fexofenadine hydrochloride in subjects with hepatic impairment did not differ substantially from that observed in healthy subjects.

Pregnant Women

No data available.

Lactating Women

No data available.

Geriatric patients:

In older subjects (≥65 years old), peak plasma levels of fexofenadine were 99% greater than those observed in younger subjects (≥65 years old). Mean fexofenadine elimination halflives were similar to those observed in younger subjects.

Pediatric patients:

A population pharmacokinetic analysis was performed with data from 77 pediatric subjects (6 months to 12 years of age) with allergic rhinitis and 136 adult subjects. The individual apparent oral clearance estimates of fexofenadine were on average 44% and 36% lower in pediatric subjects 6 to 12 years (n=14) and 2 to 5 years of age (n=21), respectively, compared to adult subjects.

Effect of Gender:

Across several trials, no clinically significant gender-related differences were observed in the pharmacokinetics of fexofenadine hydrochloride.

Montelukast:

Patients with Hepatic Impairment:

Patients with mild-to-moderate hepatic insufficiency and clinical evidence of cirrhosis had evidence of decreased metabolism of montelukast resulting in 41% (90% CI=7%, 85%) higher mean montelukast AUC following a single 10-mg dose. The elimination of montelukast was slightly prolonged compared with that in healthy subjects (mean half-life, 7.4 hours). No dosage adjustment is required in patients with mild-to-moderate hepatic insufficiency. The pharmacokinetics of montelukast in patients with more severe hepatic impairment or with hepatitis have not been evaluated.

Patients with Renal Impairment:

Since montelukast and its metabolites are not excreted in the urine, the pharmacokinetics of montelukast were not evaluated in patients with renal insufficiency. No dosage adjustment is recommended in these patients.

Gender: The pharmacokinetics of montelukast are similar in males and females.

Race: Pharmacokinetic differences due to race have not been studied.

Adolescents and Pediatric Patients:

Pharmacokinetic studies evaluated the systemic exposure of the 4- mg oral granule formulation in pediatric patients 6 to 23 months of age, the 4-mg chewable tablets in pediatric patients 2 to 5 years of age, the 5-mg chewable tablets in pediatric patients 6 to 14 years of age, and the 10-mg film-coated tablets in young adults and adolescents ≥15 years of age.

The plasma concentration profile of montelukast following administration of the 10-mg film-coated tablet is similar in adolescents ≥15 years of age and young adults. The 10-mg film-coated tablet is recommended for use in patients ≥15 years of age.

The mean systemic exposure of the 4-mg chewable tablet in pediatric patients 2 to 5 years of age and the 5-mg chewable tablets in pediatric patients 6 to 14 years of age is similar to the mean systemic exposure of the 10-mg film-coated tablet in adults. The 5-mg chewable tablet should be used in pediatric patients 6 to 14 years of age and the 4-mg chewable tablet should be used in pediatric patients 2 to 5 years of age.

In children 6 to 11 months of age, the systemic exposure to montelukast and the variability of plasma montelukast concentrations were higher than those observed in adults. Based on population analyses, the mean AUC (4296 ng•hr/mL [range 1200 to 7153]) was 60% higher and the mean Cmax (667 ng/mL [range 201 to 1058]) was 89% higher than those observed in adults (mean AUC 2689 ng•hr/mL [range 1521 to 4595]) and mean Cmax (353 ng/mL [range 180 to 548]). The systemic exposure in children 12 to 23 months of age was less variable, but was still higher than that observed in adults. The mean AUC (3574 ng•hr/mL [range 2229 to 5408]) was 33% higher and the mean Cmax (562 ng/mL [range 296 to 814]) was 60% higher than those observed in adults. Safety and tolerability of montelukast in a single-dose pharmacokinetic study in 26 children 6 to 23 months of age were similar to that of patients two years and above. The 4-mg oral granule formulation should be used for pediatric patients 12 to 23 months of age for the treatment of asthma, or for pediatric patients 6 to 23 months of age for the treatment of perennial allergic rhinitis. Since the 4-mg oral granule formulation is bioequivalent to the 4-mg chewable tablet, it can also be used as an alternative formulation to the 4-mg chewable tablet in pediatric patients 2 to 5 years of age.

Effects on Ability to Drive & Use Machines

Fexofenadine + Montelukast has no or negligible influence on the ability to drive and use machines. However, individuals have reported drowsiness or dizziness.

Undesirable Effects

Fexofenadine

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 frequent adverse events reported with fexofenadine include:

>3%: headache,

1-3%: drowsiness, dizziness and nausea.

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 paroniria. 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 pediatric 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 pediatric patients 6 months to 5 years of age, there were no unexpected adverse events in patients treated with fexofenadine hydrochloride.

Montelukast

The following adverse reactions have been reported in post-marketing use:

System Organ Class	Adverse Reaction	Frequency Category
Infections and infestations	upper respiratory infection	Very Common
Blood and lymphatic system disorders	increased bleeding tendency	Rare
	Thrombocytopenia	Very Rare
Immune system disorder	hypersensitivity reactions including anaphylaxis	Uncommon
	hepatic eosinophilic infiltration	Very Rare

Psychiatric disorders	dream abnormalities including nightmares, insomnia, somnambulism, anxiety, agitation including aggressive behaviour or hostility, depression, psychomotor hyperactivity (including irritability, restlessness, tremor)	Uncommon
	disturbance in attention, memory impairment, tic	Rare
	hallucinations, disorientation, suicidal thinking and behaviour (suicidality) Obsessive-compulsive symptoms, dysphemia	Very Rare
	Obsessive-compulsive symptoms, dysphemia	Not Known
Nervous system disorder	dizziness, drowsiness paresthesia/hypoesthesia, seizure	Uncommon
Cardiac disorders	palpitations	Rare
Respiratory, thoracic and mediastinal disorders	epistaxis	Uncommon
	Churg-Strauss Syndrome (CSS), pulmonary eosinophilia	Very Rare
Gastrointestinal disorders	Diarrhoea , nausea , vomiting	Common
	dry mouth, dyspepsia	Uncommon
Hepatobiliary disorders	elevated levels of serum transaminases (ALT, AST)	Common
	Hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury).	Very Rare
Skin and subcutaneous tissue disorders	Rash	Common
	bruising, urticaria, pruritus	Uncommon
	angioedema	Rare

	erythema nodosum, erythema multiforme	Very Rare
Musculoskeletal and connective tissue disorders	arthralgia, myalgia including muscle cramps	Uncommon
Renal and urinary disorders	Enuresis in children	Uncommon
General disorders and administration site conditions	Pyrexia	Common
	asthenia/fatigue, malaise, oedema,	Uncommon

Frequency category: Defined for each adverse reaction by the incidence reported in the clinical trials data base: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000).

This adverse experience, reported as very common in the patients who received montelukast, was also reported as very common in the patients who received placebo in clinical trials.

Frequency category: Rare.

This adverse experience, reported as common in the patients who received montelukast, was also reported as common in the patients who received placebo in clinical trials.

Reporting Of Suspected Adverse Reactions

In case your patient experiences any side-effect/s, write to drugsafety@cipla.com. You can also report side-effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024 or you can report to Cipla Ltd on 18002677779. By reporting side-effects, you can help provide more information on the safety of this product.

Overdose

Fexofenadine

Human Experience:

Most reports of fexofenadine hydrochloride overdose contain limited information. However, dizziness, drowsiness, and dry mouth have been reported. Single doses up to 800 mg and doses up to 690 mg BID for 1 month or 240 mg QD for 1 year were studied in healthy subjects without the development of clinically significant adverse events as compared to placebo. The maximum tolerated dose of fexofenadine was not established.

Management:

Consider standard measures to remove any unabsorbed drug. Symptomatic and supportive treatment is recommended. Hemodialysis did not effectively remove fexofenadine from blood.

Montelukast

In chronic asthma studies, montelukast has been administered at doses up to 200 mg/day to patients for 22 weeks and in short term studies, up to 900 mg/day to patients for approximately one week without clinically important adverse experiences.

There have been reports of acute overdose in post-marketing experience and clinical studies with montelukast. These include reports in adults and children with a dose as high as 1000 mg (approximately 61 mg/kg in a 42 month old child). The clinical and laboratory findings observed were consistent with the safety profile in adults and paediatric patients. There were no adverse experiences in the majority of overdose reports.

Symptoms of overdose

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.

Management of overdose

No specific information is available on the treatment of overdose with montelukast. It is not known whether montelukast is dialysable by peritoneal- or haemo-dialysis.

PHARMACOLOGICAL PROPERTIES

Mechanism of Action

Fexofenadine

Fexofenadine hydrochloride, the major active metabolite of terfenadine, is an antihistamine with selective H1-receptor antagonist activity. Both enantiomers of fexofenadine hydrochloride displayed approximately equipotent antihistaminic effects. Fexofenadine hydrochloride inhibited antigen-induced bronchospasm in sensitized guinea pigs and histamine release from peritoneal mast cells in rats. The clinical significance of these findings is unknown. In laboratory animals, no anticholinergic or alpha1-adrenergic 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.

Montelukast:

The cysteinyl leukotrienes (LTC4, LTD4, LTE4) are products of arachidonic acid metabolism and are released from various cells, including mast cells and eosinophils. These eicosanoids bind to cysteinyl leukotriene (CysLT) receptors. The CysLT type-1

(CysLT1) receptor is found in the human airway (including airway smooth muscle cells and airway macrophages) and on other pro-inflammatory cells (including eosinophils and certain myeloid stem cells). CysLTs have been correlated with the pathophysiology of asthma and allergic rhinitis. In asthma, leukotriene-mediated effects include airway edema, smooth muscle contraction, and altered cellular activity associated with the inflammatory process. In allergic rhinitis, CysLTs are released from the nasal mucosa after allergen exposure during both early- and late-phase reactions and are associated with symptoms of allergic rhinitis.

Montelukast is an orally active compound that binds with high affinity and selectivity to the CysLT1 receptor (in preference to other pharmacologically important airway receptors, such as the prostanoid, cholinergic, or β-adrenergic receptor). Montelukast inhibits physiologic actions of LTD4 at the CysLT1 receptor without any agonist activity.

Pharmacodynamic properties

Fexofenadine

Human histamine skin wheal and flare studies in adults following single and twice daily doses of 20 and 40 mg fexofenadine hydrochloride demonstrated that the drug exhibits an antihistamine effect by 1 hour, achieves maximum effect at 2 to 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. The clinical significance of these observations is unknown.

Histamine skin wheal and flare studies in 7- to 12-year-old subjects showed that following a single dose of 30 or 60 mg, antihistamine effect was observed at 1 hour and reached a maximum by 3 hours. Greater than 49% inhibition of wheal area, and 74% inhibition of flare area were maintained for 8 hours following the 30 and 60 mg dose.

No statistically significant increase in mean QTc interval compared to placebo was observed in 714 adult subjects with seasonal allergic rhinitis given fexofenadine hydrochloride capsules in doses of 60 to 240 mg twice daily for 2 weeks. Pediatric subjects from 2 placebo-controlled trials (n=855) treated with up to 60 mg fexofenadine hydrochloride twice daily demonstrated no significant treatment- or dose-related increases in QTc. In addition, no statistically significant increase in mean QTc interval compared to placebo was observed in 40 healthy adult subjects given fexofenadine hydrochloride as an oral solution at doses up to 400 mg twice daily for 6 days, or in 230 healthy adult subjects given fexofenadine hydrochloride 240 mg once daily for 1 year. In subjects with chronic idiopathic urticaria, there were no clinically relevant differences for any ECG intervals, including QTc, between those treated with fexofenadine hydrochloride 180 mg once daily (n = 163) and those treated with placebo (n = 91) for 4 weeks.

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. In a

placebo-controlled, crossover study (n=12), Montelukast inhibited early- and late-phase bronchoconstriction due to antigen challenge by 75% and 57%, respectively.

The effect of Montelukast on eosinophils in the peripheral blood was examined in clinical trials. In patients with asthma aged 2 years and older who received Montelukast, a decrease in mean peripheral blood eosinophil counts ranging from 9% to 15% was noted, compared with placebo, over the double-blind treatment periods. In patients with seasonal allergic rhinitis aged 15 years and older who received Montelukast, a mean increase of 0.2% in peripheral blood eosinophil counts was noted, compared with a mean increase of 12.5% in placebo-treated patients, over the double-blind treatment periods; this reflects a mean difference of 12.3% in favor of Montelukast. The relationship between these observations and the clinical benefits of montelukast noted in the clinical trials is not known.

Pharmacokinetics Properties

Fexofenadine

The pharmacokinetics of fexofenadine hydrochloride in subjects with seasonal allergic rhinitis and subjects with chronic urticaria were similar to those in healthy subjects.

Absorption:

Fexofenadine hydrochloride was rapidly absorbed following oral administration of a single 60 mg capsule to healthy adult subjects, the mean maximum plasma concentration (Cmax) was 131 ng/mL. Following single dose oral administrations of either the 60 and 180 mg tablet to healthy adult male subjects, mean Cmax were 142 and 494 ng/mL, respectively. The tablet formulations are bioequivalent to the capsule when administered at equal doses. Fexofenadine hydrochloride pharmacokinetics are linear for oral doses up to a total daily dose of 240 mg (120 mg twice daily). The administration of the 60 mg capsule contents mixed with applesauce did not have a significant effect on the pharmacokinetics of fexofenadine in adults. Co-administration of 180 mg fexofenadine hydrochloride tablet with a high fat meal decreased the mean area under the curve (AUC) and (Cmax) of fexofenadine by 21 and 20% respectively.

Distribution:

Fexofenadine hydrochloride is 60% to 70% bound to plasma proteins, primarily albumin and α1- acid glycoprotein.

Elimination:

The mean elimination half-life of fexofenadine was 14.4 hours following administration of 60 mg, twice daily, in normal volunteers. Human mass balance studies documented a recovery of approximately 80% and 11% of the [^{14}C] fexofenadine hydrochloride dose in the feces and urine, respectively. Because the absolute bioavailability of fexofenadine hydrochloride has not been established, it is unknown if the fecal component represents unabsorbed drug or the result of biliary excretion.

Metabolism:

Approximately 5% of the total oral dose was metabolized.

Montelukast

Montelukast is rapidly absorbed following oral administration. After administration of the 10-mg filmcoated tablet to fasted adults, the mean peak montelukast plasma concentration (C_{max}) is achieved in 3 to 4 hours (T_{max}). The mean oral bioavailability is 64%. The oral bioavailability and C_{max} are not influenced by a standard meal in the morning.

For the 5-mg chewable tablet, the mean C_{max} is achieved in 2 to 2.5 hours after administration to adults in the fasted state. The mean oral bioavailability is 73% in the fasted state versus 63% when administered with a standard meal in the morning.

For the 4-mg chewable tablet, the mean C_{max} is achieved 2 hours after administration in pediatric patients 2 to 5 years of age in the fasted state.

The 4-mg oral granule formulation is bioequivalent to the 4-mg chewable tablet when administered to adults in the fasted state. The co-administration of the oral granule formulation with applesauce did not have a clinically significant effect on the pharmacokinetics of montelukast. A high fat meal in the morning did not affect the AUC of montelukast oral granules; however, the meal decreased C_{max} by 35% and prolonged T_{max} from 2.3 ± 1.0 hours to 6.4 ± 2.9 hours.

The safety and efficacy of Montelukast in patients with asthma were demonstrated in clinical trials in which the 10-mg film-coated tablet and 5-mg chewable tablet formulations were administered in the evening without regard to the time of food ingestion. The safety of Montelukast in patients with asthma was also demonstrated in clinical trials in which the 4-mg chewable tablet and 4-mg oral granule formulations were administered in the evening without regard to the time of food ingestion. The safety and efficacy of Montelukast in patients with seasonal allergic rhinitis were demonstrated in clinical trials in which the 10- mg film-coated tablet was administered in the morning or evening without regard to the time of food ingestion.

Distribution

Montelukast is more than 99% bound to plasma proteins. The steady state volume of distribution of montelukast averages 8 to 11 liters. Orally administered montelukast distributes into the brain in rats.

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.

In vitro studies using human liver microsomes indicate that CYP3A4, 2C8, and 2C9 are involved in the metabolism of montelukast. At clinically relevant concentrations, 2C8 appears to play a major role in the metabolism of montelukast.

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 urine. 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%).

NON-CLINICAL PROPERTIES

Animal Toxicology or Pharmacology

Fexofenadine

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential and reproductive toxicity of fexofenadine hydrochloride were assessed using terfenadine studies with adequate fexofenadine hydrochloride exposure (based on plasma area-under-the-concentration vs. time [AUC] values). No evidence of carcinogenicity was observed in an 18-month study in mice and in a 24-month study in rats at oral doses up to 150 mg/kg of terfenadine (which led to fexofenadine exposures that were respectively approximately 3 and 5 times the exposure from the maximum recommended daily oral dose of fexofenadine hydrochloride in adults and children).

Montelukast

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of tumorigenicity was seen in carcinogenicity studies of either 2 years in Sprague-Dawley rats or 92 weeks in mice at oral gavage doses up to 200 mg/kg/day or 100 mg/kg/day, respectively. The estimated exposure in rats was approximately 120 and 75 times the AUC for adults and children, respectively, at the maximum recommended daily oral dose. The estimated exposure in mice was approximately 45 and 25 times the AUC for adults and children, respectively, at the maximum recommended daily oral dose.

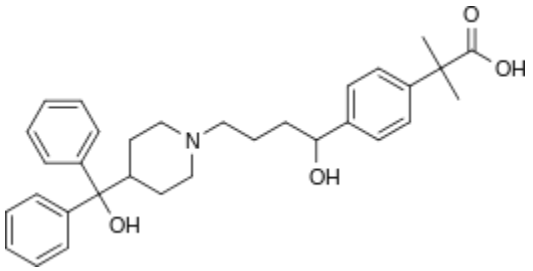
Montelukast demonstrated no evidence of mutagenic or clastogenic activity in the following assays: the microbial mutagenesis assay, the V-79 mammalian cell mutagenesis assay, the alkaline elution assay in rat hepatocytes, the chromosomal

aberration assay in Chinese hamster ovary cells, and in the in vivo mouse bone marrow chromosomal aberration assay.

In fertility studies in female rats, montelukast produced reductions in fertility and fecundity indices at an oral dose of 200 mg/kg (estimated exposure was approximately 70 times the AUC for adults at the maximum recommended daily oral dose). No effects on female fertility or fecundity were observed at an oral dose of 100 mg/kg (estimated exposure was approximately 20 times the AUC for adults at the maximum recommended daily oral dose). Montelukast had no effects on fertility in male rats at oral doses up to 800 mg/kg (estimated exposure was approximately 160 times the AUC for adults at the maximum recommended daily oral dose).

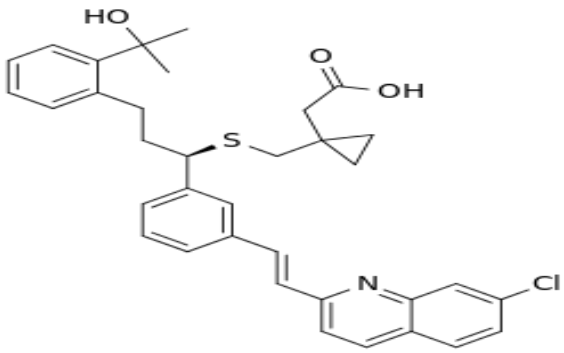
DESCRIPTION

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



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

Montelukast sodium is described chemically as [R-(E)]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]cyclopropaneacetic acid, monosodium salt. The empirical formula is $C_{35}H_{35}ClNNaO3S$, and its molecular weight is 608.18. The structural formula is:



PHARMACEUTICAL PARTICULARS

Incompatibilities

Not Applicable

Shelf life

As on the Pack.

Packaging Information

MONTAIR FX tablets in a strip pack of 15 tablets.

Storage & Handling Instruction

Store in a dry & dark place, at a

temperature not exceeding 30℃.

Keep out of reach of children

PATIENT COUNSELLING INFORMATION

- **What is the MONTAIR FX tablet and What is it used for?**
  MONTAIR FX tablet is a combination of Montelukast sodium 10 mg and Fexofenadine Hydrochloride 120 mg, indicated for the relief of symptoms of allergic rhinitis (Seasonal and Perennial) whenever a combination is indicated.

- **What do you need to know before taking MONTAIR FX tablet?**
  DO NOT TAKE MONTAIR FX tablet if:
  - You have a history of allergy to any of its ingredients.
  - Rare hereditary problems of galactose intolerance.
  - Lapp lactose deficiency or glucose-galactose malabsorption.

  Warning and Precautions:
  You should never use oral montelukast to treat acute asthma attacks and to keep their usual appropriate rescue medication for this purpose readily available. In case of an acute attack of asthma, **consult your doctor** for rescue medication.
  MONTAIR FX tablet should not be substituted abruptly for inhaled or oral corticosteroids.

  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. In case you develop such symptoms, please **consult your doctor** for reassessment and re-evaluation of your treatment.

Neuropsychiatric events have been reported in adults, adolescents, and children taking montelukast. If these neuropsychiatric changes occur, you should **alert your physician** to evaluate the risk and benefit ratio for using montelukast.

Tell your doctor if you are taking any of the following medicines as montelukast and fexofenadine may have effects on those medicines:

Erythromycin or Ketoconazole

Antacids containing aluminum and magnesium.

Phenobarbitals

Phenytoin

Rifampicin

Gemfibrozil

Effects on ability to drive & use machines:

Fexofenadine + Montelukast has no or negligible influence on the ability to drive and use machines. However, individuals have reported drowsiness or dizziness.

- **What are the possible side effects of MONTAIR FX tablet?**
  Like all medicines, this medicine can cause side effects, although not everybody gets them.

  The most frequent adverse events reported with fexofenadine include:

  >3%: headache,

  1-3%: drowsiness, dizziness and nausea.

  Few uncommon adverse events reported with fexofenadine include:

  Fatigue

  Insomnia

  Nervousness

  Sleep disorder or paroniria

  Few rarely reported adverse events with fexofenadine include:

  Rash

  Urticaria

Pruritis and hypersensitivity reactions with manifestations such as angioedema, chest tightness, dyspnea, flushing and systemic anaphylaxis.

With Montelukast the following adverse events have been reported:

System Organ Class	Adverse Reaction	Frequency Category
Infections and infestations	upper respiratory infection	Very Common
Blood and lymphatic system disorders	increased bleeding tendency	Rare
	Thrombocytopenia	Very Rare
Immune system disorder	hypersensitivity reactions including anaphylaxis	Uncommon
	hepatic eosinophilic infiltration	Very Rare
Psychiatric disorders	dream abnormalities including nightmares, insomnia, somnambulism, anxiety, agitation including aggressive behaviour or hostility, depression, psychomotor hyperactivity (including irritability, restlessness, tremor)	Uncommon
	disturbance in attention, memory impairment, tic	Rare
	hallucinations, disorientation, suicidal thinking and behaviour (suicidality) Obsessive-compulsive symptoms, dysphemia	Very Rare
	Obsessive-compulsive symptoms, dysphemia	Not Known
Nervous system disorder	dizziness, drowsiness paresthesia/hypoesthesia, seizure	Uncommon
Cardiac disorders	palpitations	Rare
	epistaxis	Uncommon

Respiratory, thoracic and mediastinal disorders	Churg-Strauss Syndrome (CSS), pulmonary eosinophilia	Very Rare
Gastrointestinal disorders	Diarrhoea , nausea , vomiting	Common
	dry mouth, dyspepsia	Uncommon
Hepatobiliary disorders	elevated levels of serum transaminases (ALT, AST)	Common
	Hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury).	Very Rare
Skin and subcutaneous tissue disorders	Rash	Common
	bruising, urticaria, pruritus	Uncommon
	angioedema	Rare
	erythema nodosum, erythema multiforme	Very Rare
Musculoskeletal and connective tissue disorders	arthralgia, myalgia including muscle cramps	Uncommon
Renal and urinary disorders	Enuresis in children	Uncommon
General disorders and administration site conditions	Pyrexia	Common
	asthenia/fatigue, malaise, oedema,	Uncommon

Frequency category: Defined for each adverse reaction by the incidence reported in the clinical trials data base: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000).

This adverse experience, reported as very common in the patients who received montelukast, was also reported as very common in the patients who received placebo in clinical trials.

Frequency category: Rare.

This adverse experience, reported as common in the patients who received montelukast, was also reported as common in the patients who received placebo in clinical trials.

Reporting Of Suspected Adverse Reactions

In case your patient experiences any side-effect/s, write to drugsafety@cipla.com. You can also report side-effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024 or you can report to Cipla Ltd on 18002677779. By reporting side-effects, you can help provide more information on the safety of this product.

- **How should I store MONTAIR FX tablet?**
  Store dry & dark place, at a temperature not exceeding 30℃.
  Keep out of reach of children.
  Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.
  The medicinal product does not require any special storage conditions.
  Do not throw away any medicines via wastewater or household waste. Ask your doctor how to throw away medicines you no longer use. These measures will help protect the environment.

DETAILS OF MANUFACTURER

Manufactured by: Pure & Cure Healthcare Pvt. Ltd

(A subsidiary of Akums Drugs & Pharmaceuticals Ltd.)

Plot No. 26A, 27-30, Sector-8A, I.I.E., SIDCUL,

Ranipur, Haridwar-249 403, Uttarakhand, INDIA.

Marketed by: CIPLA LTD

Regd. Office: Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai – 400 013, INDIA.

DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

31/UA/2013 dated 16/09/2020

DATE OF REVISION

24/09/2024