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For the use of a Registered Medical Practitioner or a Hospitalor a Laboratory

ASTHATOR

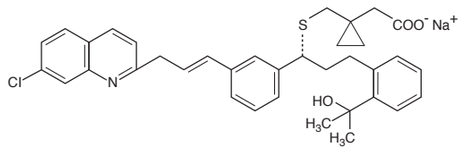
(Montelukast Sodium Tablets 5mg/10mg)

DESCRIPTION

Montelukast sodium, the active ingredient in ASTHATOR 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- cyclopropaneacetic acid, monosodium salt.quinolinyl) ethenyl) phenyl)-3-(2-(1-hydroxy -1-methylethyl) phenyl) propyl) thio) methyl).

The empirical formula is $C_{35}H_{35}ClNNaO_3S$, and its molecular weight is 608.18.



Montelukast sodium is a hygroscopic, optically active, white to off-white powder. Montelukast sodium is freely soluble in ethanol, methanol, and water and practically insoluble in acetonitrile.

CLINICAL PHARMACOLOGY

Pharmacodynamics

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 receptors (CysLT) found in the human airway. Cysteinyl leukotrienes and leukotriene receptor occupation have been correlated with the pathophysiology of asthma, including airway edema, smooth muscle contraction, and altered cellular activity associated with the inflammatory process, which contribute to the signs and symptoms of asthma.

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 (beta)-adrenergic receptor). Montelukast inhibits physiologic actions of LTD4 at the CysLT1 receptor without any agonist activity.

Pharmacokinetics

Absorption

Montelukast is rapidly absorbed following oral administration.

After administration of the 10mg 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 5mg 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.

After administration of the 4 mg tablet to paediatric patients 2 to 5 years of age in the fasted state, C_{max} is achieved 2 hours after administration. The mean $C_{max}$is 66% higher while mean C_{min} is lower than in adults receiving a 10 mg tablet.

The safety and efficacy of Asthator were demonstrated in clinical trials in which both formulations were administered in the evening without regard to the timing 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. Studies in rats with radiolabeled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabeled material at 24 hours postdose were minimal in all other tissues.

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 cytochromes P450 3A4 and 2C9 are involved in the metabolism of montelukast. Clinical studies investigating the effect of known inhibitors of cytochromes P450 3A4 (e.g., ketoconazole, erythromycin) or 2C9 (e.g., fluconazole) on montelukast pharmacokinetics have not been conducted. Based on further *In vitro* results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6.

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 is nearly linear for oral doses up to 50 mg. During once-daily dosing with 10mg montelukast, there is little accumulation of the parent drug in plasma (~14%).

Special Populations

Gender:

The pharmacokinetics of montelukast is similar in males and females.

Elderly:

The pharmacokinetic profile and the oral bioavailability of a single 10mg oral dose of montelukast are similar in elderly and younger adults. The plasma half-life of montelukast is slightly longer in the elderly. No dosage adjustment in the elderly is required.

Race:

Pharmacokinetic differences due to race have not been studied.

Hepatic Insufficiency:

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 area under the plasma concentration curve (AUC) following a single 10mg 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 Asthator in patients with more severe hepatic impairment or with hepatitis has not been evaluated.

Renal Insufficiency:

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

Adolescents and Pediatric Patients:

The plasma concentration profile of montelukast following administration of the 10mg tablet is similar in adolescents (>/=) 15 years of age and young adults. The 10mg tablet is recommended for use in patients (>/=) 15 years of age.

INDICATIONS

Asthator is indicated in the treatment of asthma as add-on therapy in those patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom 'as-needed' short-acting β-agonists provide inadequate clinical control of asthma.

Asthator may also be an alternative treatment option to low-dose inhaled corticosteroids for patients with mild persistent asthma who do not have a recent history of serious asthma attacks that required oral corticosteroid use, and who have demonstrated that they are not capable of using inhaled corticosteroids

Asthator is also indicated in the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

SPECIAL WARNINGS AND PRECAUTIONS 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 β-agonist should be used. Patients should seek their doctor's advice as soon as possible if they need more inhalations of short-acting β-agonists than usual.

Montelukast should not be abruptly substituted 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 usually, but not always, have been associated with the reduction or withdrawal of oral corticosteroid therapy. The possibility that leukotriene receptor antagonists may be associated with emergence of Churg-Strauss syndrome can neither be excluded nor 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.

Asthator contains aspartame, a source of phenylalanine; hence it should be prescribed cautiously to the patients with phenylketonuria.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No evidence of tumorigenicity was seen in a 2-year carcinogenicity study in Sprague Dawley rats, at oral (gavage) doses up to 200 mg/kg/day (approximately 160 times the maximum recommended daily oral dose in adults and 190 times the maximum recommended daily oral dose in children, on a mg/m^2 basis) or in a 92-week carcinogenicity study in mice at oral doses up to 100 mg/kg/day (approximately 40 times the maximum recommended daily oral dose in adults and 50 times the maximum recommended daily oral dose in children, on a mg/m^2 basis).

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 (approximately 160 times the maximum recommended daily oral dose in adults, on a mg/m^2 basis).

No effects on female fertility or fecundity were observed at an oral dose of 100 mg/kg (approximately 80 times the maximum recommended daily oral dose in adults, on a mg/m^2 basis).

Montelukast had no effects on fertility in male rats at oral doses up to 800 mg/kg (approximately 650 times the maximum recommended daily oral dose in adults, on a mg/m^2 basis).

PREGNANCY AND TERATOGENIC EFFECTS

PREGNANCY CATEGORY B:

No teratogenicity was observed in rats at oral doses up to 400 mg/kg/day (approximately 320 times the maximum recommended daily oral dose in adults, on a mg/m^2 basis) and in rabbits at oral doses up to 300 mg/kg/day (approximately 490 times the maximum recommended daily oral dose in adults, on a mg/m^2 basis). Montelukast crosses the placenta following oral dosing in rats and rabbits. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ASTHATOR should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Studies in rats have shown that montelukast is excreted in milk. It is not known if montelukast is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ASTHATOR is given to a nursing mother.

PEDIATRIC USE

The safety and effectiveness in pediatric patients below the age of 6 years have not been established. Long-term trials evaluating the effect of chronic administration of ASTHATOR on linear growth in pediatric patients have not been conducted.

GERIATRIC USE

Of the total number of subjects in clinical studies of montelukast, 3.5% were 65 years of age and over and 0.4% was 75 years of age and over. 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.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:

Montelukast may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma. In drug-interactions 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 (ethinyl oestradiol/ 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, caution should be exercised, particularly in children, when montelukast is co-administered with inducers of CYP 3A4, 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 drugs primarily metabolised by CYP 2C8) demonstrated that montelukast does not inhibit CYP 2C8 in vivo. Therefore, montelukast is not anticipated to markedly alter the metabolism of drugs metabolised by this enzyme (eg., paclitaxel, rosiglitazone, and repaglinide).

ADVERSE REACTIONS

The following drug-related adverse reactions in clinical studies were reported commonly (>1/100, <1/10) in patients treated with montelukast and at a greater incidence than in patients treated with placebo:

Body System Class	Adult Patients 15 years and older (two 12-week studies; n=795)	Paediatric Patients 6 to 14 years old (one 8-week study; n=201) (two 56-week studies; n=615)	Paediatric Patients 2 to 5 years old (one 12-week study; n=461) (one 48-week study; n=278)
Body as a whole	abdominal pain		abdominal pain
Digestive system disorders			thirst
Nervous system/psychiatric	headache	headache	

With prolonged treatment in clinical trials with a limited number of patients for up to 2 years for adults, and up to 12 months for paediatric patients 6 to 14 years of age, the safety profile did not change.

Cumulatively, 502 paediatric patients 2 to 5 years of age were treated with montelukast for at least 3 months, 338 for 6 months or longer, and 534 patients for 12 months or longer. With prolonged treatment, the safety profile did not change in these patients either.

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

Body as whole: asthenia/fatigue, malaise, oedema, hypersensitivity reactions including anaphylaxis, angioedema, urticaria, pruritus, rash and one isolated report of hepatic eosinophilic infiltration

Nervous system/psychiatric: dizziness, dream abnormalities including nightmares, hallucinations, drowsiness, insomnia, paraesthesia/ hypoesthesia, irritability, agitation including aggressive behaviour, restlessness, seizure

Musculo-skeletal disorders: arthralgia, myalgia including muscle cramps

Digestive system disorders: diarrhoea, dry mouth, dyspepsia, nausea, vomiting.

Hepato-biliary disorders: elevated levels of serum transaminases (ALT, AST), cholestatic hepatitis.

Cardiovascular disorders: increased bleeding tendency, bruising, palpitations.

Very rare cases of Churg-Strauss Syndrome (CSS) have been reported during montelukast treatment in asthmatic patients.

DOSAGE AND ADMINISTRATION

Adolescents and Adults 15 Years of Age and Older

The dosage for adolescents and adults 15 years of age and older is one 10-mg tablet daily to be taken in the evening.

Pediatric Patients 6 To 14 Years of Age

The dosage for pediatric patients 6 to 14 years of age is one 5-mg tablet daily to be taken in the evening. No dosage adjustment within this age group is necessary. Safety and effectiveness in pediatric patients younger than 6 years of age have not been established.

The safety and efficacy of montelukast was demonstrated in clinical trials, where it was administered in the evening without regard to the time of food ingestion. There have been no clinical trials evaluating the relative efficacy of morning versus evening dosing.

OVERDOSAGE

No specific information is available on the treatment of overdosage with montelukast. In chronic asthma studies, montelukast has been administered at doses up to 200 mg/day to adult 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 overdosage 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 overdosage 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 dialyzable by peritoneal- or haemo-dialysis.

STORAGE

Store below 30^{o}C, Protected from moisture & light.

PRESENTATION

Asthator uncoated tablets 5mg and 10mg are packed in Alu/Alu blister pack of 10 tablets.

5mg - Pink colored, round shaped, uncoated tablets, with break line on both the sides.

10mg - Light brown colored, round biconvex shaped, uncoated tablets, with break line on both the sides.

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