ROMILAST

(Montelukast Sodium Tablets)

COMPOSITION

ROMILAST TABLETS 4 MG

Each uncoated tablet contains
Montelukast sodium
equivalent to Montelukast 4 mg

ROMILAST TABLETS 5 MG

Each uncoated tablet contains
Montelukast sodium
equivalent to Montelukast 5 mg

ROMILAST TABLETS 10 MG

Each film-coated tablet contains:
Montelukast sodium
equivalent to Montelukast 10 mg

Inactive Ingredients : Mannitol, Microcrystalline Cellulose, Aspartame, Croscarmellose Sodium, Fruit Gum Flavour, Magnesium Stearate

DESCRIPTION

ROMILAST (montelukast sodium) is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene CysLT1 receptor. Montelukast sodium is chemically designated 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 for montelukast sodium is $C_{35}H_{35}ClNNaO_3S$, and its molecular weight is 608.18.

PHARMACOLOGY[1]

Mechanism of action

The cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4) 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 ß-adrenergic receptor). Montelukast inhibits physiologic actions of LTD_4 at the $CysLT_1$ receptor without any agonist activity.

Pharmacokinetics

Montelukast is rapidly absorbed following oral administration. After administration of the 10-mg film-coated tablet to fasted adults, the mean peak 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.

The comparative pharmacokinetics of montelukast when administered as two 5-mg mouth dissolving tablets versus one 10-mg film-coated tablet have not been evaluated.

Montelukast is more than 99% bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8 to 11 liters. Distribution across the blood-brain barrier is minimal. In addition, concentrations at 24 hours postdose are minimal in all other tissues. 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. Therapeutic plasma concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6 (see **Drug Interactions**).

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%).

Special Populations

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

Geriatrics: The pharmacokinetic profile and the oral bioavailability of a single 10-mg 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.

Hepatic Insufficiency: Patients with mild-to-moderate hepatic insufficiency and clinical evidence of cirrhosis had evidence of decreased metabolism of montelukast resulting in 41% higher mean montelukast area under the plasma concentration curve (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.

Renal Insufficiency: 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.

Adolescents and Pediatric Patients: The plasma concentration profile of montelukast following administration of montelukast 10-mg 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 (in terms of AUC) of the 5-mg mouth dissolving tablet and the 4-mg mouth dissolving tablet in pediatric patients 6 to 14 years of age and 2 to 5 years of age, respectively, is similar to that of the 10-mg tablet in adults. The 5-mg mouth dissolving tablet should be used in pediatric patients 6 to 14 years of age and the 4-mg mouth dissolving tablet should be used in pediatric patients 2 to 5 years of age.

CLINICAL STUDIES[2]

In clinical studies in adults, montelukast 10 mg once daily, compared with placebo, demonstrated significant improvements in morning FEV1 (forced expiratory volume in 1 second) (10.4% vs 2.7% change from baseline), AM peak expiratory flow rate (PEFR) (24.5 L/min vs 3.3 L/min change from baseline), and significant decrease in total ß-agonist use (-26.1% vs -4.6% change from baseline). Improvement in patient-reported daytime and nighttime asthma symptoms scores was significantly better than placebo.

Studies in adults demonstrated the ability of montelukast to add to the clinical effect of inhaled corticosteroid (% change from baseline for inhaled beclomethasone plus montelukast vs beclomethasone, respectively for FEV1 : 5.43% vs 1.04%; ß-agonist use: -8.7% vs 2.64%). Compared with inhaled beclomethasone (200 ug twice daily with a spacer device), montelukast demonstrated a more rapid initial response, although over the 12-week study, beclomethasone provided a greater average treatment effect (% change from baseline for montelukast vs beclomethasone, respectively for FEV1 : 7.49% vs 13.3%; ß-agonist use: -28.28% vs -43.89%). However, compared with beclomethasone, a high percentage of patients treated with montelukast achieved similar clinical responses (e.g. 50% of patients treated with beclomethasone achieved an improvement in FEV1 of approximately 11% or more over baseline while approximately 42% of patients treated with montelukast achieved the same response).

In an 8-week study in pediatric patients, montelukast 5 mg once daily, compared with placebo, significantly improved respiratory function (FEV1 8.71% vs 4.16% change from baseline; AM PEFR 27.9 L/min vs 17.8 L/min change from baseline) and decreased 'as needed' ß-agonist use (-11.7% vs +8.2% change from baseline).

Significant reduction of exercise-induced bronchoconstriction (EIB) was demonstrated in a 12-week study in adults (maximal fall in FEV1 22.33% for montelukast vs 32.40% for placebo; time to recovery to within 5% of baseline FEV1 44.22 min vs 60.64 min). This effect was consistent throughout the 12-week study period. Reduction in EIB was also demonstrated in a short term study in pediatric patients (maximal fall in FEV1 18.27% vs 26.11%; time to recovery to within 5% of baseline FEV1 17.76 min vs 27.98 min). The effect in both studies was demonstrated at the end of the once-daily dosing interval.

In aspirin-sensitive asthmatic patients receiving concomitant inhaled and/or oral corticosteroids, treatment with montelukast, compared with placebo resulted in significant improvement in asthma control (FEV1 8.55% vs -1.74% change from baseline and decrease in total ß-agonist use -27.78% vs 2.09% change from baseline).

INDICATIONS[1]

ROMILAST (montelukast sodium) is indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 2 years of age and older.

DOSAGE AND ADMINISTRATION[1]

Adolescents and Adults 15 Years of Age and Older: One ROMILAST TABLETS 10 MG daily to be taken in the evening.

Pediatric Patients 6 to 14 Years of Age: One ROMILAST TABLETS 5 MG daily to be taken in the evening.

Pediatric Patients 2 to 5 Years of Age: One ROMILAST TABLETS 4 MG daily to be taken in the evening.

Safety and effectiveness in pediatric patients younger than 2 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.

DIRCETIONS FOR USE OF ROMILAST TABLETS 4 MG AND 5 MG (Mouth Dissolving)

ROMILAST TABLETS (Mouth Dissolving) should be placed on the tongue following which it will disintegrate in seconds. Alternatively, ROMILAST TABLETS (Mouth Dissolving) may be chewed or swallowed with water.

PRECAUTIONS[1,2]

*** General**

Montelukast is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus.

Patients should be advised to have appropriate rescue medication available. Therapy with montelukast can be continued during acute exacerbations of asthma.

While the dose of inhaled corticosteroid may be reduced gradually under medical supervision, montelukast should not be abruptly substituted for inhaled or oral corticosteroids.

Montelukast should not be used as monotherapy for the treatment and management of exercise-induced bronchospasm. Patients who have exacerbations of asthma after exercise should continue to use their usual regimen of inhaled ß-agonists as prophylaxis and have available for rescue a short-acting inhaled ß-agonist.

Patients with known aspirin sensitivity should continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking montelukast. Although montelukast is effective in improving airway function in asthmatics with documented aspirin sensitivity, it has not been shown to truncate bronchoconstrictor response to aspirin and other non-steroidal anti-inflammatory drugs in aspirin-sensitive asthmatic patients.

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. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between montelukast and these underlying conditions has not been established.

• Contraindications

ROMILAST (montelukast sodium) is contraindicated in patients with a history of hypersensitivity to any component of this product.

• Pregnancy

There are no adequate and well-controlled studies in pregnant women. No teratogenicity was observed in rats at oral doses up to 400 mg/kg/day (estimated exposure approximately 100 times the AUC for adults at the maximum recommended daily oral dose) and in rabbits at oral doses up to 300 mg/kg/day (estimated exposure approximately 110 times the AUC for adults at the maximum recommended daily oral dose). Montelukast crosses the placenta following oral dosing in rats and rabbits. Because animal reproduction studies are not always predictive of human response, montelukast should be used during pregnancy only if clearly needed.

• Lactation

It is not known if montelukast is excreted in human milk. However, montelukast is excreted in the milk of lactating rats. Because many drugs are excreted in human milk, caution should be exercised when montelukast is given to a nursing mother.

• Pediatrics

Safety and effectiveness in patients below the age of 2 years have not been established.

Long-term trials evaluating the effect of chronic administration of montelukast on linear growth in pediatric patients have not been conducted.

• Geriatrics

In clinical trials, no overall differences in safety or effectiveness have been observed between subjects 75 years of age and over 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.

• Carcinogenicity/ Mutagenicity/ Impairment of Fertility

No evidence of tumorigenicity was seen in either a 2-year carcinogenicity study in Sprague-Dawley rats at oral gavage doses up to 200 mg/kg/day (estimated exposure was approximately 120 times the area under the plasma concentration versus time curve (AUC) for adults and children at the maximum recommended daily oral dose) or in a 92-week carcinogenicity study in mice at oral gavage doses up to 100 mg/kg/day (estimated exposure was approximately 45 times the AUC for adults and children 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).

• Drug Interactions

Montelukast has been administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma with no apparent increase in adverse reactions. 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, fexofenadine, digoxin, and warfarin.

Montelukast, at a dose of 10 mg once daily dosed to pharmacokinetic steady state, did not influence the effect of a single 30-mg oral dose of warfarin on prothrombin time or the INR (International Normalized Ratio), and did not prolong the QTc interval following co-administration with terfenadine 60 mg twice daily.

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.

• Adverse reactions

Side effects, which usually were mild, generally did not require discontinuation of therapy.

Adults

Montelukast has been evaluated in approximately 2,600 adult patients 15 years of age and older in clinical studies. In two similarly designed, 12-week placebo-controlled clinical trials, only abdominal pain and headache were reported as drug-related in ≥1% of patients treated with montelukast and at a greater incidence than in patients treated with placebo. The incidences of these events were not significantly different in the two treatment groups.

Although a causal relationship with montelukast was not established, the following adverse events were reported in ≥1% of patients and at an incidence equal to or greater than in placebo in clinical trials:

Body as a whole: asthenia/fatigue, fever, abdominal pain, trauma.
Digestive system disorders: diarrhoea, dyspepsia, infectious gastro-enteritis, dental pain.
Nervous system/psychiatric: dizziness, headache, insomnia.
Respiratory system disorders: nasal congestion, cough, influenza.
Skin/skin appendages disorder: rash.

With prolonged treatment in clinical trials with a limited number of patients for up to 2 years, the adverse experience profile did not change.

Pediatrics

Montelukast has also been evaluated in approximately 320 pediatric patients 6 to 14 years of age. In an 8-week, placebo-controlled clinical trial, only headache was reported as drug-related in >1% of patients treated with montelukast and at a greater incidence than in patients treated with placebo. The incidence was not significantly different in the two treatment groups.

Although a causal relationship with montelukast was not established the following adverse events were reported in ≥3% of pediatric patients and at an incidence greater than in placebo in clinical trials:

Body as a whole: fever.
Digestive system disorders: diarrhoea, nausea.
Respiratory system disorders: influenza, pharyngitis, sinusitis.

With prolonged treatment in clinical trials with a limited number of patients for 1 year and longer, the adverse experience profile did not change.

Adults and Pediatrics

The following have been reported in post-marketing use: asthenia/fatigue, dizziness, dream abnormalities including nightmares, drowsiness, insomnia, irritability, restlessness, arthralgia, diarrhoea, dry mouth, dyspepsia, hypersensitivity reactions (including anaphylaxis, angioedema, urticaria, pruritus, rash and very rarely, hepatic eosinophilic infiltration), malaise, myalgia, nausea and vomiting.

OVERDOSAGE[1]

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 patients for 22 weeks and, in short-term studies, up to 900 mg/day to patients for approximately a week without clinically important adverse experiences. In the event of overdose, it is reasonable to employ the usual supportive measures; e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required. There have been reports of acute overdosage in pediatric patients in post-marketing experience and clinical studies of up to at least 150 mg/day with montelukast. The clinical and laboratory findings observed were consistent with the safety profile in adults and older pediatric patients. There were no adverse experiences reported in the majority of overdosage reports. The most frequent adverse experiences observed were thirst, somnolence, mydriasis, hyperkinesia, and abdominal pain. It is not known whether montelukast is removed by peritoneal dialysis or hemodialysis.

STORAGE : Store below 25°C, protected from moisture.

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN.

SUPPLY : Strip of 10's, Box of 10's.

REFERENCES

1. Prescribing Information of SINGULAIR, Merck & Co., USA, February 2001.
2. ABPI Compendium of Data Sheets and Summaries of Product Characteristics SINGULAIR, Merck Sharp & Dohme Limited, UK, June 2000.

Information compiled in Dec' 2001.

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