MONTELUKAST (Systemic)

Category

Antiasthmatic (leukotriene receptor antagonist).

**Indications**

Accepted

Asthma, bronchial, chronic (prophylaxis and treatment)¾Montelukast is indicated for prophylaxis and chronic treatment of asthma 1.

Unaccepted

Montelukast is not indicated for treatment of bronchospasm in acute asthma attacks, including status asthmaticus 1.

Pharmacology

Mechanism of action/Effect:

Montelukast inhibits bronchoconstriction due to antigen challenge. Montelukast is a selective leukotriene receptor antagonist of the cysteinyl leukotriene CysLT 1 receptor. The cysteinyl leukotrienes (LTC 4, LTD 4, LTE 4) are products of arachidonic acid metabolism that are released from various cells, including mast cells and eosinophils. They bind to cysteinyl leukotriene receptors (CysLT) found in the human airway. Binding of cysteinyl leukotrienes to leukotriene receptors has been correlated with the pathophysiology of asthma, including airway edema, smooth muscle contraction, and altered cellular activity associated with the inflammatory process, factors that contribute to the signs and symptoms of asthma. Montelukast binding to the CysLT 1 receptor is high-affinity and selective, preferring the CysLT 1 receptor to other pharmacologically important airway receptors, such as the prostanoid, cholinergic, or beta-adrenergic receptor. Montelukast inhibits physiologic actions of LTD 4 at the CysLT 1 receptors, without any agonist activity. 1

**Precautions to Consider**

Carcinogenicity

A 2-year study in Sprague Dawley rats at oral (gavage) doses of up to 200 mg per kg of body weight per day (mg/kg/day) (approximately 160 and 190 times the maximum recommended daily oral dose in adults and children, respectively, on a mg per square meter of body surface area basis) and a 92-week study in mice at oral doses of up to 100 mg/kg/day (approximately 40 and 50 times the maximum recommended daily oral dose in adults and children, respectively, on a mg per square meter of body surface area basis) found no evidence of carcinogenicity or tumorigenicity 1.

Mutagenicity

Montelukast was not found to be mutagenic or clastogenic in 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 the in vivo mouse bone marrow chromosomal aberration assay 1.

Pregnancy/Reproduction

Fertility¾A reduction in fertility was seen in female rats on oral doses of montelukast of 200 mg/kg (approximately 160 times the maximum recommended daily oral dose in adults, on a mg per square meter of body surface area basis). 1 However, no effects on fertility were seen in female rats on oral doses of montelukast of 100 mg/kg (approximately 80 times the maximum recommended daily oral dose in adults, on a mg per square meter of body surface area basis). 1 No reduction in fertility was seen in male rats at oral doses of up to 800 mg/kg (approximately 650 times the maximum recommended daily oral dose in adults, on a mg per square meter of body surface area basis). 1

Pregnancy¾Adequate and well-controlled studies in humans have not been done 1.

Studies in rats at oral doses of up to 400 mg/kg/day (approximately 320 times the maximum recommended daily oral dose in adults on a mg per square meter of body surface area basis) and in rabbits at oral doses of up to 300 mg/kg/day (approximately 490 times the maximum recommended daily oral dose in adults on a mg per square meter of body surface area basis) found no evidence of teratogenicity. Montelukast crosses the placenta in rats and rabbits. 1

Risk-benefit should be considered before use of montelukast during pregnancy 1.

FDA Pregnancy Category B 1.

Breast-feeding

It is not known whether montelukast is distributed into breast milk in humans. However, it is distributed into breast milk in rats. Risk-benefit should be considered before breast-feeding during treatment with montelukast. 1

Pediatrics

Safety and efficacy in children younger than 6 years of age have not been established 1.

Studies in children 6 to 14 years of age have found a similar efficacy and side effects profile to that in adults 1.

Adverse reactions, such as diarrhea, laryngitis, pharyngitis, nausea, otitis, sinusitis, and viral infection were slightly more frequent in the pediatric group. 1 The pharmacokinetics of the 5-mg chewable tablet in children 6 to 14 years of age are similar to the pharmacokinetics of the 10-mg tablet in adults; use of the 5-mg chewable tablet is recommended for children 6 to 14 years of age 1.

The chewable tablet contains aspartame, which has phenylalanine as a component. Individuals with phenylketonuria should be informed that there is 0.842 mg of phenylalanine per 5-mg tablet.

Adolescents

The pharmacokinetics of the 10-mg tablet are similar in adolescents 15 years of age and older and young adults; the pharmacokinetics of the 5-mg chewable tablet in children 6 to 14 years of age are similar to those of the 10-mg tablet in adults. The 5-mg chewable tablet is recommended for children 6 to 14 years of age and the 10-mg tablet is recommended for adolescents 15 years of age and older. 1

Geriatrics

The pharmacokinetics and oral bioavailability of montelukast are similar in elderly and younger adults. The plasma half-life is slightly longer in the elderly, but no dosage adjustment is necessary. 1

No information is available comparing the use of montelukast in elderly patients with its use in younger adults. However, a small percentage of the patients in clinical trials were 65 years of age and over, and no differences in efficacy or adverse effects were observed. 1

**Drug interactions and/or related problems**

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Although studies have not been done, because of the potential for interactions, monitoring is recommended during concurrent use with potent cytochrome P450 enzyme inducers, such as rifampin 1.

Studies have not found that montelukast causes significant changes in the pharmacokinetics of theophylline, warfarin, immunoreactive digoxin, terfenadine, fexofenadine, oral contraceptives containing norethindrone 1 mg and ethinyl estradiol 35 mcg, prednisone, or prednisolone 1.

Combinations containing any of the following medications, depending on the amount present, may also interact with this medication 1.

Phenobarbital

(concurrent use results in significant decreases [approximately 40%] in the area under the curve [AUC] for montelukast, as a result of induction of hepatic metabolism; however, no dosage adjustment is necessary 1 )

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With physiology/laboratory test values

Alanine aminotransferase (ALT [SGPT]) and

Aspartate aminotransferase (AST [SGOT])

(serum values may infrequently be increased 1 )

Eosinophils

(mean peripheral eosinophils may be increased by approximately 13 to 15% from baseline 1 )

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Risk-benefit should be considered when the following medical problems exist

Hepatic function impairment

(metabolism of montelukast may be decreased in patients with mild to moderate hepatic function impairment and clinical evidence of cirrhosis; half-life may be slightly prolonged [to a mean of 7.4 hours]; however, dosage adjustment is not necessary; montelukast has not been evaluated in patients with severe hepatic function impairment 1 )

Sensitivity to montelukast 1

**Side/Adverse Effects**

Note: Systemic eosinophilia has occurred rarely in patients taking montelukast, sometimes presenting with the clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. 2 These events have usually, but not always, occurred in association with the reduction of oral corticosteroid therapy. 2 It is recommended that physicians be alert for signs of eosinophilia, vasculitic rash, worsening of pulmonary symptoms, cardiac complications, and/or neuropathy in these patients. 2 A causal association between montelukast and these underlying conditions has not been established. 2

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence less frequent

Elevated hepatic enzymes 1 asymptomatic)

Note: Elevated hepatic enzymes include alanine aminotransferase (ALT [SGPT]) and aspartate aminotransferase (AST [SGOT]) 1.

Incidence rare

Pyuria pus in the urine)
Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Headache 1
Incidence less frequent

Abdominal or stomach pain 1; asthenia or fatigue 1 (weakness or unusual tiredness); cough 1; dental pain 1; dizziness 1; dyspepsia 1 (heartburn); fever 1; gastroenteritis, infectious 1 (abdominal or stomach pain); nasal congestion 1 (stuffy nose); skin rash 1

Overdose

Clinical effects of overdose

No information is available on the clinical effects of overdose 1.

Treatment of overdose

Treatment may include removal of unabsorbed material from the gastrointestinal tract, clinical monitoring, and supportive therapy if required 1.

It is not known if montelukast can be removed by peritoneal dialysis or hemodialysis. 1

Patients in whom intentional overdose is confirmed or suspected should be referred for psychiatric consultation.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Montelukast (Systemic)¾Introductory Version .
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Sensitivity to montelukast
Proper use of this medication

>> Importance of not using this medicine to treat acute asthma symptoms

>> Proper dosing
Missed dose: Taking as soon as remembered; not taking if almost time for next dose; not doubling doses
>> Proper storage
Precautions while using this medication

>> Compliance with therapy; using every day, even during symptom-free periods

>> Importance of not discontinuing montelukast without discussing with physician

>> Checking with physician if condition becomes worse

>> Importance of not discontinuing any concurrent antiasthmatic medication without physician's advice

Side/adverse effects

Signs of potential side effects, especially pus in the urine

General Dosing Information

Patients should be instructed to have appropriate rescue treatment available while being treated with montelukast. 1 Therapy with montelukast may be continued during acute exacerbations of asthma. 1

Montelukast should not be abruptly substituted for inhaled or oral corticosteroids. 1 If appropriate, the dose of corticosteroids should be tapered gradually under medical supervision. 1 Rarely, the reduction of systemic corticosteroids in patients on another leukotriene antagonist has been followed by the occurrence of eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy sometimes presenting as Churg-Strauss syndrome, a systemic eosinophilic vasculitis. 1 A causal relationship between this phenomenon and leukotriene receptor antagonism has not been established and the problem was not observed during clinical trials with montelukast. 1 However, caution and appropriate clinical monitoring is recommended when systemic corticosteroid dose reduction is considered in patients receiving montelukast. 1

Montelukast should not be used as monotherapy for the treatment or management of exercise-induced bronchospasm. 1 The patient should be instructed to continue with the usual regimen of an inhaled beta-agonist for prophylaxis of exercise-induced bronchospasm and to have a short-acting inhaled beta-agonist available for rescue treatment. 1

Oral Dosage Forms

MONTELUKAST SODIUM TABLETS

Note: The chewable tablets are recommended for use in children 6 to 15 years of age and the tablets are recommended for use in children 15 years of age and over and in adults 1.

Usual adult and adolescent 1 dose

Asthma, bronchial, chronic¾
Oral, 10 mg once a day in the evening 1.

Usual pediatric dose

Asthma, bronchial, chronic¾
Children younger than 6 years of age: Safety and efficacy have not been established 1.

Children 6 to 15 years of age: See Montelukast Sodium Chewable Tablets 1.

Children 15 years of age and over: See Usual adult and adolescent dose 1.

Usual geriatric dose

Asthma, bronchial, chronic¾
See Usual adult and adolescent dose 1.

Strength(s) usually available

U.S.¾10 mg (Rx)[Singulair (lactose monohydrate)]

Note: This product contains 10.4 mg of montelukast sodium, which is equivalent to 10 mg of the free acid.

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F) 1.

Protect from light 1.

Protect from moisture 1.

MONTELUKAST SODIUM CHEWABLE TABLETS

Note: The chewable tablets are recommended for use in children 6 to 15 years of age and the tablets are recommended for use in children 15 years of age and over and in adults 1.

Usual adult and adolescent dose

Asthma, bronchial, chronic¾
See Montelukast Sodium Tablets 1.

Usual pediatric dose

Asthma, bronchial, chronic¾
Children younger than 6 years of age: Safety and efficacy have not been established 1.

Children 6 to 15 years of age: Oral, 5 mg once a day in the evening 1.

Children 15 years of age and over: See Montelukast Sodium Tablets 1.

Usual geriatric dose

Asthma, bronchial, chronic¾
See Montelukast Sodium Tablets 1.

Strength(s) usually available

U.S.¾5 mg (Rx)[Singulair (aspartame [contains 0.842 mg of phenylalanine]) (cherry flavor)]

Note: This product contains 5.2 mg of montelukast sodium which is equivalent to 5 mg of the free acid. 1

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F) 1.

Protect from light 1.

Protect from moisture 1.

References

1 Singulair package insert (MSD¾US), Rev 2/98, Rec 3/13/98.

2 Merck & Co., Inc.: Dear Doctor Letter, 12/98.