Montiget™

(Montelukast sodium)

Film-coated Tablets, Chewable Tablets and Pediatric Granules.

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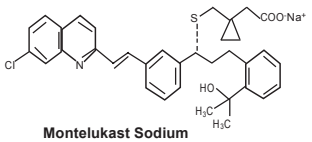
DESCRIPTION

Montiget (Montelukast sodium) is a leukotriene receptor antagonist (LTRA) used for the maintenance and treatment of asthma and to relieve symptoms of seasonal allergies rhinitis.

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 molecular formula is $C_{35}H_{35}ClNNaO_3S$ and the structural formula is:



Montelukast Sodium

QUALITATIVE AND QUANTITATIVE COMPOSITION

MONTIGET (Montelukast sodium) is available for oral administration as:

1. MONTIGET Pediatric Granules 4mg
   Each sachet contains:
   Montelukast sodium
   equivalent to Montelukast…4mg

2. MONTIGET Chewable Tablets 4mg
   Each tablet contains:
   Montelukast sodium
   equivalent to Montelukast…4mg

3. MONTIGET Chewable Tablets 5mg
   Each tablet contains:
   Montelukast sodium
   equivalent to Montelukast…5mg

4. MONTIGET Film-coated Tablets 10mg
   Each film-coated tablet contains:
   Montelukast sodium
   equivalent to Montelukast…10mg

CLINICAL PHARMACOLOGY

Mechanism of Action

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 ($CysLT_1$) 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.

Montelukast is an orally active compound that binds with high affinity and selectivity to the $CysLT_1$ receptor. Montelukast inhibits physiologic actions of LTD4 at the $CysLT_1$ receptor without any agonist activity.

Pharmacokinetics

Absorption:

Montelukast is rapidly absorbed following oral administration. After administration of the 10mg film-coated 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 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 4mg 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 4mg oral granule formulation is bioequivalent to the 4mg chewable tablet when administered to adults in the fasted state. 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.

Distribution:

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

Metabolism

Montelukast sodium is extensively metabolized in the liver by cytochrome P450 isoenzymes CYP3A4, CYP2A6 and CYP2C9. Therapeutic plasma concentrations of montelukast sodium do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6.

Excretion:

The plasma clearance of montelukast averages 45 mL/min in healthy adults. Montelukast and its metabolites are excreted almost exclusively via the bile. The mean plasma half-life of montelukast ranges from 2.7 to 5.5 hours in young adults. The pharmacokinetics of montelukast are nearly linear for oral doses up to 50mg. During once-daily dosing with 10mg montelukast, there is little accumulation of the parent drug in plasma (14%).

Special Populations:

Hepatic Insufficiency:

Patients with mild-to-moderate hepatic insufficiency and clinical evidence of cirrhosis has evidence of decreased metabolism and prolonged elimination half life of montelukast sodium resulting in 41% higher mean montelukast sodium area under the plasma concentration curve (AUC) following a single 10mg dose. The mean elimination half-life is 7.4 hours. No dosage adjustment is required in patients with mild-to-moderate hepatic insufficiency.

Pediatric Patients

In children 6 to 11 months of age, the systemic exposure to montelukast and the variability of plasma montelukast concentrations are higher than those observed in adults. Based on population analysis, the mean AUC (4296 ng•hr/mL [range 1200 to 7153]) is 60% higher and the mean Cmax (667 ng/mL [range 201 to 1058]) is 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 is less variable, but is still higher than that observed in adults. The mean AUC (3574 ng•hr/mL [range 2229 to 5408]) is 33% higher and the mean Cmax (562 ng/mL [range 296 to 814]) is 60% higher than those observed in adults.

THERAPEUTIC INDICATIONS

Asthma

MONTIGET is indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age and older.

Exercise-Induced Bronchoconstriction

MONTIGET is indicated for prevention of exercise-induced bronchoconstriction (EIB) in patients 15 years of age and older.

Allergic Rhinitis

MONTIGET is indicated for the relief of symptoms of seasonal allergic rhinitis in patients 2 years of age and older and perennial allergic rhinitis in patients 6 months of age and older.

DOSAGE AND ADMINISTRATION

Asthma

MONTIGET should be taken once daily in the evening. The following doses are recommended:

For adults and adolescents 15 years of age and older: one 10mg tablet.
For pediatric patients 6 to 14 years of age: one 5mg chewable tablet.
For pediatric patients 2 to 5 years of age: one 4mg chewable tablet or one packet of 4mg oral granules.
For pediatric patients 12 to 23 months of age: one packet of 4mg oral granules.

The pharmacokinetics of montelukast are similar whether dosed in the morning or evening.

Exercise-Induced Bronchoconstriction (EIB) in Patients 15 Years of Age and Older

For prevention of EIB, a single 10mg dose of MONTIGET should be taken at least 2 hours before exercise. An additional dose of MONTIGET should not be taken within 24 hours of a previous dose. Patients already taking MONTIGET daily for another indication (including chronic asthma) should not take an additional dose to prevent EIB. All patients should have available for rescue a short-acting □-agonist.

Allergic Rhinitis

For allergic rhinitis, MONTIGET should be taken once daily. Montelukast should be administered in the morning or the evening without regard to time of food ingestion.

The following doses for the treatment of symptoms of seasonal allergic rhinitis are recommended:

For adults and adolescents 15 years of age and older: one 10mg tablet.
For pediatric patients 6 to 14 years of age: one 5mg chewable tablet.
For pediatric patients 2 to 5 years of age: one 4mg chewable tablet or one packet of 4mg oral granules.

The following doses for the treatment of symptoms of perennial allergic rhinitis are recommended:

For adults and adolescents 15 years of age and older: one 10mg tablet.
For pediatric patients 6 to 14 years of age: one 5mg chewable tablet.
For pediatric patients 2 to 5 years of age: one 4mg chewable tablet or one packet of 4mg oral granules.
For pediatric patients 6 to 23 months of age: one packet of 4mg oral granules.

Asthma and Allergic Rhinitis
Patients with both asthma and allergic rhinitis should take only one MONTIGET dose daily in the evening.

Instructions for Administration of Oral Granules
- MONTIGET 4mg oral granules can be administered either directly in the mouth, dissolved in 1 teaspoonful (5mL) of cold or room temperature baby formula or breast milk, or mixed with a spoonful of cold or room temperature soft foods, only applesauce, carrots, rice, or ice cream should be used.
- The packet should not be opened until ready to use.
- After opening the packet, the full dose (with or without mixing with baby formula, breast milk, or food) must be administered within 15 minutes. If mixed with baby formula, breast milk, or food, MONTIGET oral granules must not be stored for future use. Discard any unused portion.
- MONTIGET oral granules are not intended to be dissolved in any liquid other than baby formula or breast milk for administration. However, liquids may be taken subsequent to administration.
- MONTIGET oral granules can be administered without regard to the time of meals.

ADVERSE REACTIONS
Montelukast sodium is generally well tolerated. However, following are the adverse effects reported which usually were mild and did not require discontinuation of therapy.
- Increased bleeding tendency.
- Hypersensitivity reactions including anaphylaxis, hepatic eosinophilic infiltration.
- Dream abnormalities including nightmares, hallucinations, insomnia, irritability, anxiety, restlessness, agitation including aggressive behaviour, tremor, depression, suicidal thinking and behaviour (suicidality) in very rare cases.
- Dizziness, drowsiness, paraesthesia/ hypoesthesia, seizure.
- Palpitations.
- Epistaxis.
- Diarrhoea, dry mouth, dyspepsia, nausea, vomiting.
- Elevated levels of serum transaminases (ALT, AST), cholestatic hepatitis.
- Angioedema, bruising, urticaria, pruritus, rash, erythema, nodosum.
- Arthralgia, myalgia including muscle cramps.
- Asthenia/fatigue, malaise, oedema, pyrexia.

CONTRAINDICATIONS
Montelukast sodium is contraindicated in a patient who has shown hypersensitivity to the drug or any of its components.
Montelukast sodium is not indicated for use in acute asthma attacks including status asthmaticus.

WARNINGS AND PRECAUTIONS
Acute Asthma
MONTIGET 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 MONTIGET can be continued during acute exacerbations of asthma. Patients who have exacerbations of asthma after exercise should have available for rescue a short-acting inhaled -agonist.

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

Aspirin Sensitivity
Patients with known aspirin sensitivity should continue avoidance of aspirin or non-steroidal antiinflammatory 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.

Neuropsychiatric Events
Neuropsychiatric events have been reported in adult, adolescent, and pediatric patients taking MONTIGET. Patients and prescribers should be alert for neuropsychiatric events. Patients should be instructed to notify their prescriber if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with MONTIGET if such events occur.

Eosinophilic Conditions
Patients with asthma on therapy with MONTIGET 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.

Phenylketonuria
Phenylketonuric patients should be informed that the 4mg and 5mg chewable tablets contain phenylalanine (a component of aspartame).

Pregnancy
Montelukast sodium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known if montelukast sodium is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when MONTIGET is given to a nursing mother.

Drug Interactions
The area under the plasma concentration curve (AUC) for montelukast is decreased approximately 40% 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.

STORAGE
Store below 30°C.
Protect from sunlight & moisture.
Keep out of reach of children.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
1. MONTIGET (Montelukast sodium) Pediatric Granules 4mg are available in pack of 14 sachets.
2. MONTIGET (Montelukast sodium) Chewable Tablets 4mg are available in blister pack of 14's.
3. MONTIGET (Montelukast sodium) Chewable Tablets 5mg are available in blister pack of 14's.
4. MONTIGET (Montelukast sodium) Film-coated Tablets 10mg are available in blister pack of 14's..

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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