MONTIKA® Tablets / Sachets

(Montelukast Sodium)

WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS

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

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

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

QUALITATIVE & QUANTITATIVE COMPOSITION

MONTIKA® 4mg Chewable Tablets	MONTIKA® 5mg Chewable Tablets	MONTIKA® 10mg Film Coated Tablets	MONTIKA® 4mg Sachets
Each chewable tablet contains:	Each chewable tablet contains:	Each film coated tablet contains:	Each sachet contains:
Montelukast Sodium USP	Montelukast Sodium USP	Montelukast Sodium USP	Montelukast Sodium USP
eq. to Montelukast Acid..... 4mg	eq. to Montelukast Acid..... 5mg	eq. to Montelukast Acid..... 10mg	eq. to Montelukast Acid..... 4mg

PHARMACEUTICAL FORM: Tablet, Sachet

CLINICAL PARTICULARS: THERAPEUTIC INDICATIONS: ● **Asthma:** MONTIKA® is indicated for the prophylaxis and chronic treatment of asthma in adults and paediatric patients 12 months of age and older. ● **Exercise-Induced Bronchoconstriction (EIB):** MONTIKA® is indicated for prevention of exercise-induced bronchoconstriction (EIB) in patients 6 years of age and older. ● **Allergic Rhinitis:** MONTIKA® 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. Because the benefits may not outweigh the risk of neuropsychiatric symptoms in patients with allergic rhinitis, reserve use for patients who have an inadequate response or intolerance to alternative therapies.

POSOLOGY AND METHOD OF ADMINISTRATION: General Recommendations: The therapeutic effect of MONTIKA® on parameters of asthma control occurs within one day. Patients should be advised to continue taking MONTIKA® even if their asthma is under control, as well as during periods of worsening asthma. No dosage adjustment is necessary for patients with renal insufficiency, or mild to moderate hepatic impairment. There are no data on patients with severe hepatic impairment. The dosage is the same for both male and female patients. **Posology:** MONTIKA® is to be given to a child under adult supervision. For children who have problems consuming a chewable tablet, a sachet formulation is available. **Asthma:** MONTIKA® 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 paediatric patients 6 to 14 years of age: one 5mg chewable tablet. ● For paediatric patients 2 to 5 years of age: one 4mg chewable tablet or one packet of 4mg oral sachet. ● For paediatric patients 12 to 23 months of age: one packet of 4mg oral sachet.

Safety and effectiveness in paediatric patients less than 12 months of age with asthma have not been established.

Patients who miss a dose should take the next dose at their regular time and should not take 2 doses at the same time.

There have been no clinical trials in patients with asthma to evaluate the relative efficacy of morning versus evening dosing. The pharmacokinetics of montelukast are similar whether dosed in the morning or evening.

Efficacy has been demonstrated for asthma when montelukast was administered in the evening without regard to time of food ingestion.

Exercise-Induced Bronchoconstriction (EIB): For prevention of EIB, a single dose of MONTIKA® should be taken at least 2 hours before exercise. The following doses are recommended: ● For adults and adolescents 15 years of age and older: one 10mg tablet. ● For paediatric patients 6 to 14 years of age: one 5mg chewable tablet.

An additional dose of MONTIKA® should not be taken within 24 hours of a previous dose.

Patients already taking MONTIKA® 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 ß-agonist.

Safety and efficacy in patients younger than 6 years of age have not been established. Daily administration of MONTIKA® for the chronic treatment of asthma has not been established to prevent acute episodes of EIB.

Allergic Rhinitis: For allergic rhinitis, MONTIKA® should be taken once daily. Efficacy was demonstrated for seasonal allergic rhinitis when montelukast was administered in the morning or the evening without regard to time of food ingestion. The time of administration may be individualized to suit patient needs. 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 paediatric patients 6 to 14 years of age: one 5mg chewable tablet. ● For paediatric patients 2 to 5 years of age: one 4mg chewable tablet or one 4mg oral sachet.

Safety and effectiveness in paediatric patients younger than 2 years of age with seasonal allergic rhinitis have not been established.

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 paediatric patients 6 to 14 years of age: one 5mg chewable tablet. ● For paediatric patients 2 to 5 years of age: one 4mg chewable tablet or one 4mg oral sachet. ● For pediatric patients 6 to 23 months of age: one 4mg oral sachet.

Safety and effectiveness in paediatric patients younger than 6 months of age with perennial allergic rhinitis have not been established.

Patients who miss a dose should take the next dose at their regular time and should not take 2 doses at the same time.

Asthma and Allergic Rhinitis: Patients with both asthma and allergic rhinitis should take only one MONTIKA® dose daily in the evening. Patients who miss a dose should take the next dose at their regular time and should not take 2 doses at the same time. **Instructions for Administration of Sachet:** MONTIKA® 4mg sachet 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 food. The sachet should not be opened until ready to use. After opening, 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, MONTIKA® sachet must not be stored for future use. Discard any unused portion. MONTIKA® oral sachet 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. MONTIKA® sachet can be administered without regard to the time of meals.

Method of Administration: Oral use.

CONTRAINDICATIONS: Hypersensitivity to the active substance.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE: Neuropsychiatric Events: Serious neuropsychiatric (NP) events have been reported with use of montelukast sodium. These post marketing reports have been highly variable and included, but were not limited to, agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, dysphemia (stuttering), hallucinations, insomnia, irritability, memory impairment, obsessive-compulsive symptoms, restlessness, somnambulism, suicidal thoughts and behavior (including suicide), tic, and tremor. NP events have been reported in adult, adolescent, and paediatric patients with and without a previous history of psychiatric disorder. NP events have been reported mostly during montelukast sodium treatment, but some were reported after montelukast sodium discontinuation. Based upon the available data, it is difficult to identify risk factors for or quantify the risk of NP events with montelukast sodium use. Due to the risk of NP events, the benefits of montelukast sodium may not outweigh the risks in some patients, particularly when the symptoms of disease may be mild and adequately treated with alternative therapies. Reserve use of montelukast sodium for patients with allergic rhinitis who have an inadequate response or intolerance to alternative therapies. In patients with asthma or exercise induced bronchoconstriction, consider the benefits and risks before prescribing montelukast sodium.

Discuss the benefits and risks of montelukast sodium use with patients and caregivers when prescribing montelukast sodium. Advise patients and/or caregivers to be alert for changes in behavior or for new NP symptoms when taking montelukast sodium. If changes in behavior are observed, or if new NP symptoms or suicidal

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thoughts and/or behavior occur, advise patients to discontinue montelukast sodium and contact a healthcare provider immediately. In many cases, symptoms resolved after stopping montelukast sodium therapy; however, in some cases symptoms persisted after discontinuation of montelukast sodium. Therefore, continue to monitor and provide supportive care until symptoms resolve. Re-evaluate the benefits and risks of restarting treatment with montelukast sodium if such events occur. **Acute Asthma:** Montelukast sodium 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 sodium 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 ß-agonist. **Concomitant Corticosteroid Use:** While the dose of inhaled corticosteroid may be reduced gradually under medical supervision, montelukast sodium 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 anti-inflammatory agents while taking montelukast sodium. **Eosinophilic Conditions:** Patients with asthma on therapy with montelukast sodium 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 have been sometimes 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 sodium and these underlying conditions has not been established. **Phenylketonuria:** Phenylketonuric patients should be informed that the 4mg and 5mg chewable tablets contain phenylalanine (a component of aspartame), 1.681 and 1.513mg per 4mg and 5mg chewable tablet, respectively.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION: No dose adjustment is needed when montelukast sodium is co-administered with theophylline, prednisone, prednisolone, oral contraceptives, terfenadine, digoxin, warfarin, gemfibrozil, itraconazole, thyroid hormones, sedative hypnotics, non-steroidal anti-inflammatory agents, benzodiazepines, decongestants, and Cytochrome P450 (CYP) enzyme inducers.

PREGNANCY AND LACTATION: Pregnancy: Animal studies do not indicate harmful effects with respect to effects on pregnancy or embryonal/fetal development. Limited data from available pregnancy databases do not suggest a causal relationship between montelukast and malformations (i.e. limb defects) that have been rarely reported in worldwide post marketing experience. Montelukast may be used during pregnancy only if it is considered to be clearly essential. **Breastfeeding:** It is unknown whether montelukast/metabolites are is excreted in human milk. Montelukast may be used in breast-feeding mothers only if it is considered to be clearly essential.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES: Montelukast has no or negligible influence on the ability to drive and use machines, however individuals have reported drowsiness or dizziness.

UNDESIRABLE EFFECTS: Post Marketing Experience: The following adverse reactions have been identified during post-approval use of Montelukast sodium. Since these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. **Blood and lymphatic system disorders:** Increased bleeding tendency, thrombocytopenia. **Immune system disorders:** Hypersensitivity reactions including anaphylaxis, hepatic eosinophilic infiltration. **Psychiatric disorders:** Including, but not limited to, agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, dysphemia (stuttering), hallucinations, insomnia, irritability, memory impairment, obsessive-compulsive symptoms, restlessness, somnambulism, suicidal thinking and behavior (including suicide), tic, and tremor. **Nervous system disorders:** Drowsiness, paresthesia/hypoesthesia, seizures. **Cardiac disorders:** Palpitations. **Respiratory, thoracic and mediastinal disorders:** Epistaxis. **Gastrointestinal disorders:** Diarrhoea, dyspepsia, nausea, pancreatitis, vomiting. **Hepatobiliary disorders:** Cases of cholestatic hepatitis, hepatocellular liver-injury, and mixed-pattern liver injury have been reported in patients treated with montelukast sodium. Most of these occurred in combination with other confounding factors, such as use of other medications, or when montelukast sodium was administered to patients who had underlying potential for liver disease such as alcohol use or other forms of hepatitis. **Skin and subcutaneous tissue disorders:** Angioedema, bruising, erythema multiforme, erythema nodosum, pruritus, Stevens-Johnson syndrome /toxic epidermal necrolysis, urticaria. **Musculoskeletal and connective tissue disorders:** Arthralgia, myalgia including muscle cramps. **Renal and urinary disorders:** Enuresis in children. **General disorders and administration site conditions:** Edema. Patients with asthma on therapy with montelukast sodium 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 have been sometimes 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.

OVERDOSE: No specific information is available on the treatment of over dosage with montelukast sodium. 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.

PHARMACOLOGICAL PROPERTIES

Montelukast sodium, the active ingredient in **MONTIKA®**, is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene $CysLT_1$ receptor.

THERAPEUTIC CLASSIFICATION & ATC CODES: Pharmacotherapeutic group: Leukotriene receptor antagonist. **ATC Code:** RO3D CO3

MECHANISM OF ACTION: The cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4) are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important pro-asthmatic mediators bind to cysteinyl leukotriene receptors (CysLT) found in the human airway and cause airway actions, including bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment.

PHARMACODYNAMIC PROPERTIES: Montelukast is an orally active compound which binds with high affinity and selectivity to the $CysLT_1$ receptor. In clinical studies, montelukast inhibits bronchoconstriction due to inhaled LTD_4 at doses as low as 5mg. Bronchodilation was observed within two hours of oral administration. The bronchodilation effect caused by a ß-agonist was additive to that caused by montelukast. Treatment with montelukast inhibited both early and late phase bronchoconstriction due to antigen challenge. Montelukast, compared with placebo, decreased peripheral blood eosinophils in adult and paediatric patients. In a separate study, treatment with montelukast significantly decreased eosinophils in the airways (as measured in sputum) and in peripheral blood while improving clinical asthma control.

PHARMACOKINETIC PROPERTIES: 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. **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 is extensively metabolized. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and paediatric 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 45ml/min in healthy adults. Following an oral dose of radio-labelled 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. **Characteristics in patients:** No dosage adjustment is necessary for the elderly or mild to moderate hepatic insufficiency. Studies in patients with renal impairment have not been undertaken.

SHELF LIFE: See expiry on the pack.

AVAILABILITY

MONTIKA® 4mg chewable tablets in a pack of 14's
MONTIKA® 5mg chewable tablets in a pack of 14's
MONTIKA® 10mg film coated tablets in a pack of 14's
MONTIKA® 4mg sachets in a pack of 14's

INSTRUCTIONS: Dosage: As advised by the physician. To be sold on the prescription of registered medical practitioner. Keep out of reach of children. Avoid exposure to heat, light and humidity. Store between 15 to 30°C. Improper storage may deteriorate the medicine.

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com
Mfg. Lic. No. 000072

مونٹیکا ٹیبلٹ/ساشے

(مونٹی لوکاسٹ سوڈیم)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔
دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری
سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی۔

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