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Order of Ministry of
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INSTRUCTION
for medical use

MONTULAR® KIDS

Composition:
active substance: montelukast sodium;
each chewable tablet contains montelukast sodium equivalent to montelukast 5 mg;
excipients: microcrystalline cellulose (PH 112), hydroxypropyl cellulose, croscarmellose sodium, ferric oxide red (E 172), aspartame (E 951), cherry flavor 501027AP0551, mannitol (E 951), magnesium stearate.

Pharmaceutical form. Chewable Tablets
Basic physical and chemical properties: pink to light pink colored, round, biconvex, uncoated mottled tablet, plain on both sides.

Pharmacotherapeutic group. Other systemic drugs for obstructive airway diseases. Leukotriene receptor antagonists.
ATC code: R03D C03.

Pharmacological properties.
Pharmacodynamics.
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, increased vascular permeability, and eosinophil recruitment.
Montelukast is an orally active compound which binds with high affinity and selectivity to the $CysLT_1$ receptors. In clinical studies, montelukast inhibits bronchoconstriction due to inhaled LTD_4 at doses as low as 5 mg. Bronchodilation was observed within two hours of oral administration. The bronchodilation effect caused by a β-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). In adult and paediatric patients 2 to 14 years of age, montelukast, compared with placebo, decreased peripheral blood eosinophils while improving clinical asthma control.

Pharmacokinetics.

Absorption

Montelukast is rapidly absorbed following oral administration. For the 10 mg film-coated tablet, the mean peak plasma concentration (C_{max}) is achieved three hours (T_{max}) after administration in adults in the fasted state. The mean oral bioavailability is 64%. The oral bioavailability and C_{max} are not influenced by a standard meal. Safety and efficacy were demonstrated in clinical trials where the 10 mg film-coated tablet was administered without regard to the timing of food ingestion.

For the 5 mg chewable tablet, the C_{max} is achieved in two hours after administration in adults in the fasted state. The mean oral bioavailability is 73% and is decreased to 63% by a standard meal.

After administration of the 4 mg chewable 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.

Distribution

Montelukast is more than 99% bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8–11 liters. Studies in rats with radiolabeled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabelled material at 24 hours post-dose 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 children.

Cytochrome P450 2C8 is the major enzyme in the metabolism of montelukast. Additionally, CYP 3A4, and 2C9 may have a minor contribution to the metabolism of montelukast, although itraconazole, an inhibitor of CYP 3A4, was shown not to change pharmacokinetic variables of montelukast in healthy subjects that received 10 mg montelukast daily. Based on *in vitro* results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6. The contribution of metabolites to the therapeutic effect of montelukast is minimal.

Elimination

The plasma clearance of montelukast averages 45 ml/min in healthy adults. Following an oral dose of radiolabelled montelukast, 86% of the radioactivity was recovered in 5-day faecal 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.

Pharmacokinetics in different groups of patients

No dosage adjustment is necessary in mild to moderate hepatic insufficiency. Studies in patients with renal impairment have not been undertaken. Because montelukast and its metabolites are eliminated by the biliary route, no dose adjustment is anticipated to be necessary in patients with renal impairment. There are no data on the pharmacokinetics of montelukast in patients with severe hepatic insufficiency (Child-Pugh score >9).

With high doses of montelukast (20- and 60-fold the recommended adult dose), a decrease in plasma theophylline concentration was observed. This effect was not seen at the recommended dose of 10 mg once daily.

Clinical characteristics.

Indications.

- Treatment of asthma as add-on therapy in those 6 to 14 year old 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;

- alternative treatment option to low-dose inhaled corticosteroids for 6 to 14 years old 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 (see "Administration and dosage" section);
- prophylaxis of asthma in 6 to 14 years old patients in which the predominant component is exercise-induced bronchoconstriction;
- relief of symptoms of seasonal and perennial allergic rhinitis. Because the benefits of montelukast in patients with allergic rhinitis may not outweigh the risk of psychoneurological symptoms (see "Special warnings and precautions for use" section), Montular® Kids should be used as a reserve drug in patients with inadequate response or intolerance to alternative therapies.

Contraindications.
Hypersensitivity to the component of the drug.

Interactions 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 medicinal products: 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 metabolized by CYP 3A4, 2C8, and 2C9, caution should be exercised, particularly in children, when montelukast is co-administered with inducers of CYP 3A4, 2C8, and 2C9, 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 medicinal products primarily metabolized by CYP 2C8) demonstrated that montelukast does not inhibit CYP 2C8 *in vivo*. Therefore, montelukast is not anticipated to markedly alter the metabolism of medicinal products metabolized by this enzyme (e.g., paclitaxel, rosiglitazone, and repaglinide).
In vitro studies have shown that montelukast is a substrate of CYP 2C8, and to a less significant extent, of 2C9, and 3A4. In a clinical drug-drug interaction study involving montelukast and gemfibrozil (an inhibitor of both CYP 2C8 and 2C9) gemfibrozil increased the systemic exposure of montelukast by 4.4-fold. No routine dosage adjustment of montelukast is required upon co-administration with gemfibrozil or other potent inhibitors of CYP 2C8, but the physician should be aware of the potential for an increase in adverse reactions.
Based on *in vitro* data, clinically important drug interactions with less potent inhibitors of CYP 2C8 (e.g., trimethoprim) are not anticipated. Co-administration of montelukast with itraconazole, a strong inhibitor of CYP 3A4, resulted in no significant increase in the systemic exposure of montelukast.

Special warnings and precautions for use.
Patients should be advised never to use oral Montular® Kids 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 doctors' 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 have been sometimes associated with the reduction or withdrawal of oral corticosteroid therapy. The possibility that leukotriene receptor antagonists may be associated with Churg–Strauss syndrome cannot be ruled out or confirmed. 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.
Treatment with montelukast does not alter the need for patients with aspirin-sensitive asthma to avoid taking aspirin and other non-steroidal anti-inflammatory drugs.
Neuropsychiatric events have been reported in adults, adolescents, and children taking montelukast tablets (see "Adverse reactions" section). Patients and physicians should be alert for neuropsychiatric events. Patients and/or caregivers should be instructed to notify their physician if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with Montular® Kids if such events occur.
Excipients
Montular® Kids contains aspartame (E 951), a source of phenylalanine, which is dangerous for patients with phenylketonuria.

Use during pregnancy or breastfeeding.
Pregnancy. Animal studies do not indicate harmful effects with respect to effects on pregnancy or embryonal/foetal development.
Available data from published prospective and retrospective cohort studies with montelukast use in pregnant women evaluating major birth defects have not established a drug-associated risk. Available studies have methodologic limitations, including small sample size, in some cases retrospective data collection, and inconsistent comparator groups.
Breastfeeding. Studies in rats have shown that montelukast is excreted in milk. It is unknown whether montelukast is excreted in human milk.
Montelukast may be used in breast-feeding mothers only if it is considered to be clearly essential.

Effects on the 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.

Administration and dosage.
For oral administration. The tablets should be chewed before swallowing. This medicinal product is to be given to a child under adult supervision.
Dosage
The dosage for paediatric patients 6–14 years of age is one chewable tablet (5 mg) daily to be taken in the evening. The drug should be taken 1 hour before or 2 hours after food. No dosage adjustment within this age group is necessary.
General recommendations
As an add-on therapy for bronchial asthma in patients with mild to moderate asthma.
The therapeutic effect of montelukast on parameters of asthma control occurs within one day. Patients should be advised to continue taking montelukast 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.

Montelukast an alternative treatment option to low-dose inhaled corticosteroids for mild persistent asthma.
Montelukast is not recommended as monotherapy in patients with moderate persistent asthma. The use of montelukast as an alternative treatment option to low-dose inhaled corticosteroids for children 6–14 years of age with mild persistent asthma should only be considered for patients 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 (see "Indications" section). Mild persistent asthma is defined as asthma symptoms more than once a week but less than once a day, nocturnal symptoms more than twice a month but less than once a week, normal lung function between episodes. If satisfactory control of asthma is not achieved at follow-up (usually within one month), the need for an additional or different anti-inflammatory therapy based on the step system for asthma therapy should be evaluated. Patients should be periodically evaluated for their asthma control.
Prophylaxis of asthma for 6 to 14 year old patients in whom the predominant component is exercise-induced bronchoconstriction.
Montelukast is recommended in 6 to 14 year old patients for the prophylaxis of exercise-induced bronchoconstriction which may be the predominant manifestation of persistent asthma that requires treatment with inhaled corticosteroids. Patients should be evaluated after 2 to 4 weeks of treatment with montelukast. If satisfactory response is not achieved, an additional or different therapy should be considered.
Therapy with montelukast in relation to other treatments for asthma.
When treatment with montelukast is used as add-on therapy to inhaled corticosteroids, it should not be abruptly substituted for inhaled corticosteroids (see "Special warnings and precautions for use" section).
Relief of symptoms of seasonal and perennial allergic rhinitis.
To alleviate the symptoms of allergic rhinitis, the time of montelukast administration is selected individually.
Paediatric population
The safety and efficacy of Montular® Kids, 5 mg chewable tablets in children less than 6 years of age have not been established. The drug is available for paediatric patients 6 to 14 years of age.

Overdose.
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 overdose 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 overdose reports.
Symptoms of overdose.
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.
Management of overdose.
No specific information is available on the treatment of overdose with montelukast. It is not known whether montelukast is dialysable by peritoneal- or haemodialysis.

Adverse reactions.
The incidence of adverse reactions with montelukast (5 mg chewable tablets or granules) was evaluated in clinical trials in 1750 children with persistent asthma aged 6 to 14 years.

In three placebo-controlled trials (one 8-week study; n = 201 and two 56-week study; n = 615), children 6 to 14 years of age treated with montelukast most common (≥1/100 to <1/102%) reported headache. The incidence was higher than in the placebo group.
The safety profile did not change during clinical trials with prolonged treatment in a limited number of adult patients for 2 years and children aged 6 to 14 years for 12 months.
Post-marketing period
Adverse reactions reported in the post-marketing period are listed according to organ system classes and using special terms (see table). The frequency is determined according to clinical trials.

Organ System Class	Adverse Reactions	Frequency Category*
Infections and infestations	Upper respiratory infection**	Very common
Blood and lymphatic system disorders	Increased bleeding tendency	Rare
	Thrombocytopenia	Very rare
Immune system disorders	Hypersensitivity reactions including anaphylaxis	Uncommon
	Hepatic eosinophilic infiltration	Very rare
Psychiatric disorders	Dream abnormalities including nightmares, insomnia, somnambulism, anxiety, agitation including aggressive behaviour or hostility, depression, psychomotor hyperactivity (including irritability, restlessness, tremor§)	Uncommon
	Disturbance in attention, memory impairment, tic	Rare
	Hallucinations, disorientation, suicidal thinking and behaviour (suicidality), obsessive-compulsive symptoms, dysphemia	Very rare
Nervous system disorders	Dizziness, drowsiness, paraesthesia/hypoesthesia, seizure	Uncommon
Cardiac disorders	Palpitations	Rare
Respiratory, thoracic and mediastinal disorders	Epistaxis	Uncommon
	Churg–Strauss Syndrome (CSS) (see "Special warnings and precautions for use" section), pulmonary eosinophilia	Very rare
Gastrointestinal disorders	Diarrhoea***, nausea***, vomiting***	Common
	Dry mouth, dyspepsia	Uncommon
Hepatobiliary disorders	Elevated levels of serum transaminases (ALT, AST)	Common
	Hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury)	Very rare
Skin and subcutaneous tissue disorders	Rash***	Common
	Bruising, urticaria, pruritus	Uncommon

	Angiooedema	Rare
	Erythema nodosum, erythema multiforme	Very rare
Musculoskeletal and connective tissue disorders	Arthralgia, myalgia including muscle cramps	Uncommon
Renal and urinary disorders	Enuresis in children	Uncommon
General disorders and administration site conditions	Pyrexia***	Common
	Asthenia/fatigue, malaise, oedema	Uncommon
* Frequency category is defined by the incidence reported in the clinical trials data base: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000), very rare (<1/10000). ** This adverse reaction, reported as "very common" in the patients who received montelukast, was also reported as "very common" in the patients who received placebo in clinical trials. *** This adverse reaction, reported as "common" in the patients who received montelukast, was also reported as "common" in the patients who received placebo in clinical trials. § This adverse reaction was observed with a frequency of "rare".		

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions according to the local reporting system.

Shelf-life.
3 years.

Storage conditions.
Store at the temperature below 25ºC in original pack.
Keep out of reach of children.

Package.
10 tablets in blister, 3 or 9 blisters in a carton package.

Conditions of supply.
By prescription.

Manufacturer.
KUSUM HEALTHCARE PVT LTD.

Location of manufacturer and its address of its business activity.
Plot No. M-3, Indore Special Economic Zone, Phase-II, Pithampur, Distt. Dhar, Madhya Pradesh, Pin 454774, India.

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