Pharmacode position may change as per Supplier's m/c requirement & additional small pharma code may appear on the front / back panel

SUMMARY OF PRODUCT CHARACTERISTICS

M-KAST 4

Montelukast Chewable Tablets 4 mg

Rx Only

NAME OF DRUG PRODUCT: Montelukast Chewable Tablets 4 mg

(TRADE) NAME OF PRODUCT: M-KAST 4

STRENGTH: 4 mg

PHARMACEUTICAL DOSAGE FORM: Chewable Tablet.

QUALITATIVE AND QUANTITATIVE COMPOSITION:
Each chewable tablet contains Montelukast Sodium Ph.Eur. equivalent to Montelukast 4 mg.

PHARMACEUTICAL FORM:
Pink coloured, mottled, oval, biconvex, uncoated tablets, debossed with 'X' on one side and '52' on the other side.

CLINICAL PARTICULARS:

Therapeutic indications:
Montelukast is indicated in pediatric patients 2 year of age and older for the prophylaxis and chronic treatment of asthma, including the prevention of day- and nighttime symptoms, the treatment of aspirin-sensitive asthmatic patients, and the prevention of exercise-induced bronchoconstriction.

Montelukast is indicated for the relief of daytime and nighttime symptoms of allergic rhinitis (seasonal allergic rhinitis in pediatric patients 2 years of age and older, and perennial allergic rhinitis in pediatric patients 2 year of age and older). Because the benefits of Montelukast 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:
Posology
This medicinal product is to be given to a child under adult supervision. For children who have problems consuming a chewable tablet, a granule formulation is available. The recommended dose for paediatric patients 2-5 years of age is one 4 mg chewable tablet daily to be taken in the evening.

General recommendations:
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.

Therapy with Montelukast in relation to other treatments for asthma.
Montelukast can be added to a patient's existing treatment regimen.

Reduction in Concomitant Therapy:

Bronchodilator Treatments: Montelukast can be added to the treatment regimen of patients who are not adequately controlled on bronchodilator alone. When a clinical response is evident (usually after the first dose), the patient's bronchodilator therapy can be reduced as tolerated.

Inhaled Corticosteroids: Treatment with Montelukast provides additional clinical benefit to patients treated with inhaled corticosteroids. A reduction in the corticosteroid dose can be made as tolerated. The dose should be reduced gradually with medical supervision. In some patients, the dose of inhaled corticosteroids can be tapered off completely. Montelukast should not be abruptly substituted for inhaled corticosteroids.

10 mg film-coated tablets are available for adults 15 years of age and older.

Paediatric population
Do not give Montelukast 4 mg chewable tablets to children less than 2 years of age. The safety and efficacy of Montelukast 4 mg chewable tablets in children less than 2 years of age has not been established.
5 mg chewable tablets are available for paediatric patients 6 to 14 years of age.

Method of administration
Oral use.
The tablets are to be chewed before swallowing.

Contraindications:
Hypersensitivity to the active substance or to any of the excipients.

Special warnings and precautions for use:
Patients should be advised never to use oral montelukast 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.

In rare cases, patients on therapy with anti-asthma agents including montelukast may present with one or more of the following: eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications and/or neuropathy sometimes diagnosed as Churg- Strauss syndrome, a systemic eosinophillic vasculitis. These cases have been sometimes associated with the reduction or withdrawal of oral corticosteroid therapy. Although a causal relationship with leukotriene receptor antagonism has not been established, caution and appropriate clinical monitoring are recommended in patients receiving montelukast.

Neuropsychiatric events have been reported in patients taking Montelukast (see SIDE EFFECTS). Post-marketing reports with Montelukast use include agitation including aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, dysphemia (stuttering), hallucinations, insomnia, memory impairment, obsessive-compulsive symptoms, psychomotor hyperactivity (including irritability, restlessness and tremor), somnambulism, suicidal thinking and behavior (suicidality) and tic. The clinical details of some post-marketing reports involving Montelukast appear consistent with a drug-induced effect.

These neuropsychiatric events have been reported in patients with and without a previous history of psychiatric disorder. Neuropsychiatric events have been reported mostly during Montelukast treatment, but some were reported after Montelukast discontinuation. Based upon the available data, it is difficult to identify risk factors for or quantify the risk of neuropsychiatric events with Montelukast use.

Physicians should discuss the benefits and risks of Montelukast use with patients and caregivers when prescribing Montelukast. Patients and/or caregivers should be advised to be alert for changes in behavior or for new neuropsychiatric symptoms when taking Montelukast. If changes in behavior are observed, or if new neuropsychiatric symptoms or suicidal thoughts and/or behavior occur, patients should be advised to contact a healthcare provider immediately. In many cases, symptoms resolved after stopping Montelukast therapy; however, in some cases symptoms persisted after discontinuation of Montelukast. Therefore, patients should be monitored and provided supportive care until symptoms resolve.

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 β-agonists as prophylaxis and have available for rescue a short-acting inhaled β-agonist.

Prescribers should carefully evaluate the risks and benefits of continuing treatment with Montelukast if such events occur.

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. 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 NSAIDs in aspirin-sensitive asthmatic patients.

Montelukast contains aspartame, a source of phenylalanine. Patients with phenylketonuria should take into account that each 4 mg chewable tablet contains phenylalanine in an amount equivalent to 0.674 mg phenylalanine per dose.

Interaction 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 and in the treatment of allergic rhinitis.

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. No dosage adjustment for montelukast is recommended.

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 metabolised 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 metabolised by this enzyme (e.g., paclitaxel, rosiglitazone, and repaglinide).

In vitro studies have shown that montelukast is a substrate of CYP 2C8, 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. Co-administration of itraconazole, a strong CYP 3A4 inhibitor, with gemfibrozil and montelukast did not further increase the systemic exposure of montelukast. The effect of gemfibrozil on systemic exposure of montelukast is not considered to be clinically meaningful based on clinical safety data with doses greater than the 10 mg approved dose in adults (e.g., 200 mg/day to adult patients for 22 weeks, and up to 900 mg/day to patients for approximately one week) where clinically important adverse experiences were not observed. Therefore, no dosage adjustment of montelukast is required upon co-administration with gemfibrozil.
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.

Fertility, pregnancy and lactation:
Pregnancy
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.

During worldwide marketing experience, congenital limb defects have been rarely reported in the offspring of women being treated with Montelukast during pregnancy. Most of these women were also taking other asthma medications during their pregnancy. A causal relationship between these events and Montelukast has not been established

Montelukast may be used during pregnancy only if it is considered to be clearly essential.

Breast-feeding
It is unknown whether montelukast/metabolites are 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:
Montelukast has been generally well tolerated. Side effects, which usually were mild, generally did not require discontinuation of therapy. The overall incidence of side effects reported with Montelukast was comparable to placebo.

Pediatric Patients 2 to 5 Years of Age with Asthma
Montelukast has been evaluated in 573 pediatric patients 2 to 5 years of age. In a 12-week, placebo-controlled clinical study, the only adverse experience reported as drug related in > 1% of patients treated with Montelukast and at a greater incidence than in patients treated with placebo was thirst. The incidence of thirst was not significantly different in the two treatment groups.

A/s: 210 x 300 mm ■ Black

AUROBINDO Packaging Development	Product Name: M-KAST 4 mg	Component: Leaflet	Item Code: P1523933	Date & Time: 25.10.2021 & 06.00 pm
	Customer / Country: Singapore_Unit 7	Version No.: 05	Reason Of Issue: Submission	Reviewed / Approved by
Team Leader: Kiran K	Dimensions: 210 x 300 mm	No. of Colours : 01		
Initiator: Shirisha N		23933		
Artist: SCD	Pharmacode: 23933			
Additional Information : Dimension Changed 17-08-2021				Sign / Date

Cumulatively, 426 pediatric patients 2 to 5 years of age were treated with Montelukast for at least 3 months, 230 for 6 months or longer, and 63 patients for 12 months or longer. With prolonged treatment, the adverse experience profile did not change.

Pediatric Patients 2 to 14 Years of Age with Seasonal Allergic Rhinitis

Montelukast has been evaluated in 280 pediatric patients 2 to 14 years of age for the treatment of seasonal allergic rhinitis in a 2-week, placebo-controlled, clinical study. Montelukast administered once daily in the evening was generally well tolerated with a safety profile similar to that of placebo. In this study, no adverse experiences reported as drug related in ≥ 1% of patients treated with Montelukast and at a greater incidence than in patients treated with placebo were observed.

Pediatric Patients 1 to 14 Years of Age with Perennial Allergic Rhinitis

The safety in patients 2 to 14 years of age with perennial allergic rhinitis is supported by the established safety in patients 2 to 14 years of age with seasonal allergic rhinitis. The safety in patients 12 to 23 months of age is supported by data from pharmacokinetic and safety and efficacy studies in asthma in this pediatric population and from adult pharmacokinetic studies.

Pooled Analyses of Clinical Trials Experience

A separate pooled analysis of 46 placebo-controlled clinical studies (35 studies in patients 15 years of age and older; 11 studies in pediatric patients 3 months to 14 years of age) assessing behavior-related adverse experiences (BRAEs) was performed. Among the 11,673 patients who received montelukast and 8827 patients who received placebo in these studies, the frequency of patients with at least one BRAE was 2.73% in patients who received Montelukast and 2.27% in patients who received placebo; the odds ratio was 1.12 (95% CI [0.93; 1.36]).

The clinical trials included in these pooled analyses were not designed specifically to examine suicidality or BRAEs.

Post-Marketing Experience
The following side effects have been reported in post-marketing use:
Infections and infestations: upper respiratory infection
Blood and lymphatic system disorders: increased bleeding tendency, thrombocytopenia
Immune system disorders: hypersensitivity reactions including anaphylaxis, very rarely hepatic eosinophilic infiltration
Psychiatric disorders: agitation including aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, dysphemia (stuttering), hallucinations, insomnia, memory impairment, obsessive-compulsive symptoms, psychomotor hyperactivity (including irritability, restlessness and tremor), somnambulism, suicidal thinking and behavior (suicidality), tic
Nervous system disorders: dizziness, drowsiness, paraesthesia/hypoesthesia, very rarely seizure
Cardiac disorders: palpitations
Respiratory, thoracic and mediastinal disorders: epistaxis; pulmonary eosinophilia
Gastrointestinal disorders: diarrhea, dyspepsia, nausea, vomiting
Hepatobiliary disorders: increased ALT and AST, very rarely hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury)
Skin and subcutaneous tissue disorders: angioedema, bruising, erythema multiforme, erythema nodosum, pruritus, rash, Steven 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: asthenia/fatigue, edema, pyrexia

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 1,000 mg. 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 haemo-dialysis.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: Pharmacotherapeutic group: Leukotriene receptor antagonist ATC-Code: R03D C03

Mechanism of action
The cysteinyl leukotrienes (LTC_4, LTD_4, LTE4) 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.

In allergic rhinitis, CysLTs are released from the nasal mucosa after allergen exposure during both early- and late-phase reactions and are associated with symptoms of allergic rhinitis. Intranasal challenge with CysLTs has been shown to increase nasal airway resistance and symptoms of nasal obstruction.

Pharmacodynamic effects
Montelukast is a potent, orally active compound with anti-inflammatory properties which significantly improves parameters of asthmatic inflammation. Based on biochemical and pharmacological bioassays, it binds with high affinity and selectivity to the CysLT1 receptor (in preference to other pharmacologically important airway receptors such as the prostanoid, cholinergic, or β-adrenergic receptor). Montelukast potently inhibits physiologic actions of LTC4, LTD4, and LTE4 at the CysLT1 receptor without any agonist activity.
In asthmatic patients, montelukast causes potent inhibition of airway cysteinyl leukotriene receptors as demonstrated by the ability to inhibit bronchoconstriction due to inhaled LTD4. Doses as low as 5 mg cause substantial blockage of LTD4-induced bronchoconstriction. Montelukast causes bronchodilation within 2 hours of oral administration; these effects were additive to the bronchodilation caused by a β-agonist.

Clinical Studies – Asthma

In clinical studies, montelukast is effective in adult and pediatric patients for the prophylaxis and chronic treatment of asthma, including the prevention of day- and night time symptoms, the treatment of aspirin-sensitive asthmatic patients, and the prevention of exercise-induced bronchoconstriction. Montelukast is effective alone or in combination with other agents used in the maintenance treatment of chronic asthma. Montelukast and inhaled corticosteroid may be used concomitantly with additive effects to control asthma or to reduce the inhaled corticosteroid dose while maintaining clinical stability.

Pediatric patients 6 months to 5 years of age

In a 12-week, placebo-controlled study in pediatric patients 2 to 5 years of age, montelukast 4 mg once daily consistently improved parameters of asthma control irrespective of concomitant controller therapy use compared with placebo. Sixty percent of patients were not on any other controller therapy. Montelukast significantly improved daytime symptoms (including coughing, wheezing, trouble breathing and activity limitation) and nighttime symptoms compared with placebo. Montelukast also significantly decreased “as-needed” β-agonist use and corticosteroid rescue compared with placebo. Patients receiving Montelukast had significantly more days without asthma than those receiving placebo. A treatment effect was achieved after the first dose. In addition, total blood eosinophil counts were significantly decreased.

Clinical Studies - Allergic Rhinitis

The efficacy of Montelukast for the treatment of seasonal allergic rhinitis was investigated in similarly designed randomized, 2-week, double-blind, placebo-controlled trials including 4924 patients (1751 patients were treated with SINGULAIR). Patients were 15 years of age and older with a history of seasonal allergic rhinitis, a positive skin test to at least one relevant seasonal allergen, and active symptoms of seasonal allergic rhinitis at study initiation.

In a combined analysis of three pivotal studies, Montelukast 10-mg tablets administered to 1189 patients once daily in the evening resulted in a statistically significant improvement in the primary endpoint, daytime nasal symptoms score, and its individual components (nasal congestion, rhinorrhea, nasal itching and sneezing); nighttime symptoms score, and its individual components (nasal congestion upon awakening, difficulty going to sleep, and nighttime awakenings); composite symptoms score (composed of the daytime nasal and nighttime symptoms scores); and global evaluations of allergic rhinitis by patients and by physicians, compared with placebo.

In a separate 4-week study in which Montelukast was administered once daily in the morning, the efficacy over the initial 2 weeks was significantly different from placebo and consistent with the effect observed in studies using evening dosing. Additionally, the effect over the entire 4 weeks was consistent with the 2-week results.

In patients with seasonal allergic rhinitis aged 15 years and older who received SINGULAIR, a median decrease of 13% in peripheral blood eosinophil counts was noted, compared with placebo, over the double-blind treatment periods.

The efficacy of Montelukast for the treatment of perennial allergic rhinitis was investigated in two, similarly designed randomized, 6-week, double-blind, placebo-controlled studies including 3235 patients (1632 patients were treated with Montelukast). Patients were 15 to 82 years of age with a history of perennial allergic rhinitis, positive skin test results to relevant perennial allergens (including dust mites, animal dander, and mold spores), and active symptoms of perennial allergic rhinitis at study initiation.

In one study, Montelukast 10-mg tablets administered to 1000 patients once daily resulted in a statistically significant improvement in the primary endpoint, Daytime Nasal Symptoms score, and its individual components (nasal congestion, rhinorrhea, and sneezing), compared with placebo. SINGULAIR also demonstrated patient-perceived improvement of allergic rhinitis as assessed by the secondary endpoints of Global Evaluation of Allergic Rhinitis by Patient, and Rhinoconjunctivitis Quality-of-Life overall score (average of scores for the 7 domains of activity, sleep, non-nose/non-eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotions), compared with placebo.

The efficacy of Montelukast for the treatment of seasonal allergic rhinitis in pediatric patients 2 to 14 years of age, and for the treatment of perennial allergic rhinitis in pediatric patients 1 year to 14 years of age is supported by extrapolation from the demonstrated efficacy in patients 15 years of age and older with allergic rhinitis as well as the assumption that the disease course, pathophysiology and the drug’s effect are substantially similar among these populations.

Pharmacokinetic properties
Absorption:
Montelukast is rapidly absorbed following oral administration. For the 10 mg film-coated tablet, the mean peak plasma concentration (C_{max}) is achieved 3 hours (T_{max}) after administration in adults in the fasted state. The mean oral bioavailability is 64%. The oral bioavailability and Cmax 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.
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.

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 radiolabelled 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.

Biotransformation:
Montelukast is extensively metabolised. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and children.
In vitro studies using human liver microsomes indicate that cytochrome P450 3A4, 2C8, and 2C9 are involved in the metabolism of montelukast. Based on further in vitro results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6.

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.

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. There are no data on the pharmacokinetics of montelukast in patients with severe hepatic insufficiency (Child-Pugh score>9).
The safety and effectiveness in pediatric patients younger than 1 year of age with perennial allergic rhinitis and in patients below the age of 12 months with asthma have not been established.

PHARMACEUTICAL PARTICULARS
List of excipients
Mannitol, Microcrystalline cellulose, Hydroxypropyl cellulose, Croscarmellose sodium, Ferric oxide, Aspartame, Artificial cherry flavor, Magnesium Stearate.

Incompatibilities
None known.

Shelf life:
24 months

Special precautions for storage
Store below 30 °C. Protect from light & moisture.

Nature and contents of container
M-KAST 4 mg tablets packed in a carton of 30 tablets [30's (10's Blister x3)].

DISTRIBUTED IN SINGAPORE BY:
Apotheca Marketing Pte. Ltd.,
63 Hillview Avenue #09-16,
Lam Soon Industrial Building,
Singapore 669569.

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