SUMMARY OF PRODCUT CHARACTERISTICS

1. Name of the Medicinal Product

Montemac 10 (Montelukast Sodium 10mg Tablet).

2. Qualitative and Quantitative Composition

Each film coated tablet contains montelukast sodium equivalent to 10 mg montelukast.

Excipients with known effect:

Each tablet contains 115.9 mg of lactose monohydrate

For the full list of excipients, see section 6.1

3. Pharmaceutical Form

Tablet

Beige colour, rounded square shaped. biconvex, film coated tablet debossed with 'CL 26' on one side and plain on the other side.

4. Clinical Particulars

4.1 Therapeutic indications

Montelukast is indicated for:

- The prophylaxis and chronic treatment of asthma in adults and adolescent patients 15 years of age and older.
- Prevention of exercise-induced broncho constriction in patients 15 years of age and older.
- Relief of symptoms of allergic rhinitis (seasonal allergic rhinitis and perennial allergic rhinitis in patients 15 years of age and older).

4.2 Posology and method of administration

Asthma:

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

For adults and adolescents 15 years of age and older: 10mg.

Exercise-Induced Bronchoconstriction (EIB) in Patients 15 Years of Age and Older: For prevention of EIB, a single 10 mg dose of Montelukast should be taken at least 2 hours before exercise. An additional dose of Montelukast should

not be taken within 24 hours of a previous dose. Patients already taking montelukast 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 β-agonist. Safety and efficacy in patients younger than 6 years of age have not been established.

Allergic Rhinitis:

For allergic rhinitis, Montelukast should be taken once daily.

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

For adults and adolescents 15 years of age and older: 10mg

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

For adults and adolescents 15 years of age and older: 10-mg

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

4.3 Contraindications

Hypersensitivity to any component of this product.

4.4 Special warnings and precautions for use

Montelukast 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.

While the dose of inhaled corticosteroid may be reduced gradually under medical supervision.

Montelukast should not be abruptly substituted for inhaled or oral corticosteroids.

Patients with known aspirin sensitivity should continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking Montelukast.

Neuropsychiatric events have been reported in adult, adolescent, and pediatric patients taking Montelukast. These include agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, dream abnormalities, hallucinations, insomnia, irritability, restlessness, somnambulism, suicidal thinking and behavior (including suicide), and tremor.

Patients with asthma on therapy with 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 events usually, but not always, have been associated with the reduction of oral corticosteroid therapy.

4.5 Interaction with other medicinal products and other forms of interaction

No dose adjustment is needed when Montelukast is co-administered with theophylline, prednisone, prednisolone, oral contraceptives, terfenadine, digoxin, warfarin, itraconazole, gemfibrozil, ,thyroid hormones, sedative, hypnotics, non-steroidal anti-inflammatory agents, benzodiazepines, decongestants, and Cytochrome P450 (CYP) enzyme inducers. It is reasonable to employ appropriate clinical monitoring when potent cytochrome P450 enzyme inducers, such as phenobarbital or rifampin, are co-administered with Montelukast. *In vitro* studies have shown that montelukast is a potent inhibitor of CYP2C8; however, data from a clinical drug-drug interaction study involving montelukast and rosiglitazone (a probe substrate representative of drugs primarily metabolized by CYP2C8) demonstrated that montelukast does not inhibit CYP2C8 *in vivo*, and therefore is not anticipated to alter the metabolism of drugs metabolized by this enzyme.

4.6 Pregnancy and lactation

Pregnancy

Pregnancy Category B: There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Montelukast should be used during pregnancy only if clearly needed.

Lactation

Studies in rats have shown that montelukast is excreted in milk. It is not known if montelukast is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Montelukast is given to a nursing mother.

4.7 Effects on ability to drive and use machines

Montelukast may cause drowsiness or dizziness. These effects may be worse if you take it with alcohol or certain medicines. Use montelukast with caution.

Patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medicinal product affects their ability to perform these activities.

4.8 Undesirable effects

The most common adverse reactions are upper respiratory infection, fever, headache, pharyngitis, cough, abdominal pain, diarrhea, otitis media, influenza, rhinorrhea, sinusitis, otitis.

Body as a whole: Asthenia/fatigue, Fever, Abdominal Pain, Trauma.

Digestive System Disorders: Dyspepsia, Infectious Gastroenteritis, Dental Pain.

Nervous System/Psychiatric: Dizziness, Headache.

Respiratory System Disorders: Nasal Congestion, Cough, Influenza.

Skin/Skin Appendages Disorder: Rash

Laboratory Adverse Experiences: Increased ALT,

Increased AST, Pyuria.

The following additional adverse reactions with montelukast use:

Blood and lymphatic system disorders: increased bleeding tendency

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, hallucinations, insomnia, irritability, memory impairment, restlessness, somnambulism, suicidal thinking and behavior (including suicide), and tremor.

Nervous system disorders: drowsiness, paraesthesia/hypoesthesia, seizures

Cardiac disorders: palpitations

Respiratory, thoracic and mediastinal disorders: epistaxis, pulmonary eosinophilia.

Gastrointestinal disorders: diarrhea, dyspepsia, nausea, very rarely pancreatitis, vomiting.

Hepatobiliary disorders: Rare cases of cholestatic hepatitis, hepatocellular liver-injury, and mixed-pattern liver injury. Most of these occurred in combination with other confounding factors, such as use of other medications, or when montelukast 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.

General disorders and administration site conditions: edema.

4.9 Overdose:

No specific information is available on the treatment of overdosage with Montelukast. 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.

There were no adverse experiences in the majority of overdosage reports. 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.

It is not known whether montelukast is removed by peritoneal dialysis or hemodialysis.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

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 (CysLT1) 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. In asthma, leukotriene-mediated effects include airway edema, smooth muscle contraction, and altered cellular activity associated with the inflammatory process. 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.

Montelukast is an orally active compound that 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 inhibits physiologic actions of LTD4 at the CysLT1 receptor without any agonist activity.

Montelukast causes inhibition of airway cysteinyl leukotriene receptors as demonstrated by the ability to inhibit bronchoconstriction due to inhaled LTD4 in asthmatics.

5.2 Pharmacokinetic properties

Absorption

Montelukast is rapidly absorbed following oral administration. After administration of the 10-mg 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.

Distribution

Montelukast is more than 99% bound to plasma proteins. The steady state volume of distribution of montelukast averages 8 to 11 liters. Studies in rats with radiolabeled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabeled 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 pediatric 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 45 mL/min in healthy adults. Following an oral dose of radiolabeled 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.

The pharmacokinetics of montelukast are nearly linear for oral doses up to 50 mg. During once-daily dosing with 10-mg montelukast, there is little accumulation of the parent drug in plasma (14%).

5.3 Preclinical safety data

No evidence of tumorigenicity was seen in carcinogenicity studies of either 2 years in Sprague-Dawley rats or 92 weeks in mice at oral gavage doses up to 200 mg/kg/day or 100 mg/kg/day, respectively. The estimated exposure in rats was approximately 120 and 75 times the AUC for adults and children, respectively, at the maximum recommended daily oral dose. The estimated exposure in mice was approximately 45 and 25 times the AUC for adults and children, respectively, at the maximum recommended daily oral dose.

Montelukast demonstrated no evidence of mutagenic or clastogenic activity in the following assays: 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 in the in vivo mouse bone marrow chromosomal aberration assay.

In fertility studies in female rats, montelukast produced reductions in fertility and fecundity indices at an oral dose of 200 mg/kg (estimated exposure was approximately 70 times the AUC for adults at the maximum recommended daily oral dose). No effects on female fertility or fecundity were observed at an oral dose of 100 mg/kg (estimated exposure was approximately 20 times the AUC for adults at the maximum recommended daily oral dose). Montelukast had no effects on fertility in male rats at oral doses up to 800 mg/kg (estimated exposure was approximately 160 times the AUC for adults at the maximum recommended daily oral dose).

6. Pharmaceutical Particulars

6.1 List of Excipients

Lactose monohydrate

Hydroxypropyl cellulose

Crospovidone Type A

Povidone (PVPK-30)

Sodium lauryl sulfate

Purified water

Magnesium stearate

6.2 Incompatibilities

None

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Do not store above 30°C. Protect from moisture.

Keep out of reach of children.

6.5 Nature and contents of container

Alu/Alu Blister pack of 10 Tablets. Such 3 blisters packed in a carton along with pack insert.

6.6 Special Precaution for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

07745/08940/NMR/2021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05 September 2022

10. Date of Revision of the Text:

August 2023

References:

1. Prescription Information of Montelukast sodium Tablets available at http://www.accessdata. fda.gov/drugsatfda_docs/label/2012/021409s036lbl.pdf
2. Montelukast sodium Tablets available at http://www.drugs.com/pro/montelukast-oral-granules.html