SUMMARY OF PRODUCT CHARACTERISTIC

1. Name of the Medicinal Product

Montemac 5 (Montelukast Sodium Chewable Tablet 5mg)

2. Qualitative and Quantitative Composition

Each Chewable tablet contains:

Montelukast Sodium USP 5.2 mg

equivalent to Montelukast……..5 mg

For Excipients see point 6.1

3. Pharmaceutical Form

Chewable Tablet

4. Clinical Particulars

4.1 Therapeutic indications

- **Asthma:** Montelukast is indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age and older.

- **Exercise-Induced Bronchoconstriction (EIB):** Montelukast is indicated for prevention of exercise-induced bronchoconstriction (EIB) in patients 6 years of age and older.

- **Allergic Rhinitis:** Montelukast 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.

4.2 Posology and method of administration

Asthma: Montelukast should be taken once daily in the evening. The recommended dose is 5 mg for pediatric patients 6 to 14 years of age.

Exercise-Induced Bronchoconstriction (EIB) in Pediatric Patients 6 to 14 Years of Age: For prevention of EIB, a single dose of Montelukast should be taken at least 2 hours before exercise. The recommended dose is 5 mg for pediatric patients 6 to 14 years of age.

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. Daily administration of montelukast for the chronic treatment of asthma has not been established to prevent acute episodes of EIB.

Allergic Rhinitis: For allergic rhinitis, Montelukast should be taken once daily. The time of administration may be individualized to suit patient needs. For Seasonal & Perennial allergic rhinitis: The recommended dose is 5 mg for pediatric patients 6 to 14 years of age.

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

Method of administration: Oral use.

The tablets are to be chewed before swallowing.

4.3 Contraindications

Hypersensitivity to any component of this product.

4.4 Special warnings and precautions for use

Acute Asthma

Montelukast is not indicated for use in the reversal of bronchospasm in acuteasthma attacks, including status asthmaticus. Patients should be advised to have appropriate rescue medication available. Therapy with Montelukast 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 β-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.

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Aspirin Sensitivity

Patients with known aspirin sensitivity should continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking Montelukast. Although Montelukast is effective in improving airway function in asthmatics with documented aspirin sensitivity, it has not been shown to truncatebronchoconstrictor 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 Montelukast. Post-marketing reports with Montelukast use include agitation, 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. The clinical details of some post-marketing reports involving Montelukast appear consistent with a drug-induced effect.

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 Montelukast if such events occur.

Eosinophilic Conditions

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 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 and these underlying conditions has not been established.

Phenylketonuria: Phenylketonuric patients should be informed that the chewable tablets contain phenylalanine (a component of aspartame).

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4.5 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. 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 metabolised 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 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, 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.

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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 has no or negligible influence on the ability to drive and use machines. However, individuals have reported drowsiness or dizziness.

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, anxiety, disturbance in attention, dream abnormalities, hallucinations, insomnia, irritability, memory impairment,

restlessness, somnambulism, suicidal thinking and behavior (including suicide), and tremor.

Nervous system disorders: dizziness, drowsiness, paraesthesia/hypoesthesia, seizures.

Cardiac disorders: palpitations

Respiratory, thoracic and mediastinal disorders: epistaxis, pulmonary eosinophilia, Churg-Strauss Syndrome.

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.

Musculoskeletal, connective tissue and bone disorders: arthralgia, myalgia including muscle cramps.

Renal and urinary disorders: enuresis in children.

General disorders and administration site conditions: edema

4.9 Overdose

No specific information is available on the treatment of overdosage with Montelukast. Montelukast has been administered at doses up to 200 mg/day to adult chronic asthma patients for 22 weeks and, in short-term studies, up to 900 mg/day to chronic asthma patients for approximately a week without clinically important adverse experiences. 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 have been reports of acute overdosage with Montelukast. These include reports in adults and children with a dose as high as 1000 mg. The clinical and laboratory findings observed were consistent with the safety profile in adults and pediatric patients. 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. For the 5-mg chewable tablet, the mean Cmax 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.

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 vitro studies using human liver microsomes indicate that cytochromes P450 3A4 and 2C9 are involved 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. In several studies, the mean plasma half-life of montelukast ranged from 2.7 to 5.5 hours in healthy young adults. The pharmacokinetics of montelukast are nearly linear for oral doses up to 50 mg.

Special Populations:

Hepatic Insufficiency: No dosage adjustment is required in patients with mild-to-moderate hepatic insufficiency. The pharmacokinetics of Montelukast in patients with more severe hepatic impairment or with hepatitis have not been evaluated

Renal Insufficiency: Since montelukast and its metabolites are not excreted in the urine, the pharmacokinetics of montelukast was not evaluated in patients with renal insufficiency. No dosage adjustment is recommended in these patients.

Gender: The pharmacokinetics of montelukast is similar in males and females.

Race: Pharmacokinetic differences due to race have not been studied

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, Microcrystalline cellulose (Avicel PH 101), Croscarmellose sodium, Hydroxypropyl cellulose, Disodium edentate, Magnesium Stearate

6.2 Incompatibilities

NA

6.3 Shelf life

2 years

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 in a carton along with pack insert.

Following minimum batch details is coded on foil and Carton

Batch No., Mfg. Date and Exp. Date.

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. Manufactured By

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References:

- SPC of Singulair tablet available on https://www.medicines.org.uk/emc/ medicine/ 17717
- http://www.rxlist.com/singulair-drug/indications-dosage.htm