MONTICOPE

(Montelukast & Levocetirizine Dihydrochloride Tablets)

1. NAME OF MEDICINAL PRODUCT

MONTICOPE (Montelukast & Levocetirizine Dihydrochloride Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated bilayered tablet contains: Montelukast Sodium USP equivalent to Montelukast 10 mg and Levocetrizine Dihydrochloride USP 5 mg

Excipients: For a full list of excipients, please refer Section 6.1.

3. PHARMACEUTICAL FORMS

MONTICOPE: Pale yellow mottled on one side and white to off-white on other side, bilayer, round shaped, biconvex, uncoated tablet plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Indicated for relief of symptoms of allergic rhinitis (seasonal and perennial).

4.2 Dosage and Administration

Adults (Above 14 years): 1Tablet once daily

Method of administration: For oral use.

4.3 Contraindications

Patients who are hypersensitive to any component of this product or to montelukast sodium, levocetirizine or cetirizine. Patients with completely impaired renal function (anuria).

4.4 Special Warning and Precautions for use

Montelukast

Montelukast is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status asthmatics. Patients should be advised to have appropriate rescue medication available. Therapy with montelukast can be continued during acute exacerbation of asthma. While the dose of inhaled corticosteroid may be reduced gradually under medical supervision, montelukast should not be abruptly substituted for inhaled or oral corticosteroid. Montelukast should not be used as monotherapy for the treatment and management of exercise-induced bronchospasm. Patients who have exacerbation of asthma after exercise should continue to use their usual regimen of inhaled (beta) agonists as prophylaxis and have available for rescue a short-acting inhaled (beta)-agonist

Eosinophilic Conditions: Patients 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. 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.

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

Neuropsychiatric Events: Agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, dream abnormalities, hallucinations, insomnia, irritability, restlessness, somnambulism, suicidal thinking and behavior (including suicide), and tremor have been reported.

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.

Levocetirizine

Literature reports revealed no evidence that levocetirizine at the recommended dose impairs mental alertness, reactivity or the ability to drive. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and motor co-ordination such as operating machinery or driving a motor vehicle after ingestion of levocetirizine. Concurrent use of levocetirizine with alcohol or other central nervous system depressants should be avoided because additional reductions in alertness and additional impairment of central nervous system performance may occur.

Urinary retention has been reported with levocetirizine. Levocetirizine should be used with caution in patients with predisposing factors of urinary retention (e.g. spinal cord lesion, prostatic hyperplasia) as levocetirizine may increase the risk of urinary retention. Discontinue, if urinary retention occurs.

Monticope contains Butylated Hydroxytoluene which may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

4.5 Interactions with other medicinal products and other form of interaction

Montelukast:

Montelukast may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma. The recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following drugs: theophylline, prednisone, prednisolone, oral contraceptives (norethindrone 1 mg/ethinyl estradiol 35 mcg), terfenadine, digoxin and warfarin in drug interaction studies.

Montelukast is metabolized by CYP 3A4, hence caution should be exercised, particularly in children, when montelukast is co-administered with inducers of CYP 3A4, such as phenytoin, phenobarbital and rifampicin.

Montelukast can be used concomitantly with a wide range of commonly prescribed drugs i.e. thyroid hormones, sedative hypnotics, non-steroidal anti-inflammatory agents, benzodiazepines, and decongestants.

Montelukast is not anticipated to markedly alter the metabolism of medicinal products metabolised by CYP 2C8 enzyme (e.g., paclitaxel, rosiglitazone, and repaglinide.)

No routine dosage adjustment of montelukast is required upon coadministration with gemfibrozil or other potent inhibitors of CYP 2C8, but the physician should be aware of the potential for an increase in adverse reactions.

Co-administration of montelukast with itraconazole, a strong inhibitor of CYP 3A4, resulted in no significant increase in the systemic exposure of montelukast.

Levocetirizine:

Levocetirizine is unlikely to produce pharmacokinetic interactions through inhibition or induction of liver drug-metabolizing enzymes. Drug interaction studies have been performed with racemic cetirizine.

Cetirizine did not interact with antipyrine, pseudoephedrine, erythromycin, glipizide and diazepam, azithromycin, ketoconazole and cimetidine. There was a small decrease (~16%) in the clearance of cetirizine caused by a 400 mg dose of theophylline. It is possible that higher theophylline doses could have a greater effect in clearance of cetirizine.

The extent of absorption of levocetirizine is not reduced with food although the rate of absorption is decreased.

Ritonavir increased the plasma AUC of cetirizine by about 42% accompanied by an increase in half-life (53%) and a decrease in clearance (29%) of cetirizine. The disposition of ritonavir was not altered by concomitant cetirizine administration.

In sensitive patients the simultaneous administration of cetirizine or levocetirizine and alcohol or other CNS depressants may have effects on the central nervous system, although it has been shown that the racemate cetirizine does not potentiate the effect of alcohol.

4.6 Pregnancy and Lactation

Pregnancy

The combination should be used in pregnancy only if clearly needed but should not be continued.

Lactation

Since levocetirizine is excreted in breast-milk the combination is not recommended during breast feeding.

4.7 Effects on ability to drive and use machines

The use of this product may lead to drowsiness, dizziness and hence it is dangerous to drive a vehicle or be in charge of machinery or do any activity that requires alertness after administration.

4.8 Undesirable Effects

Montelukast and levocetirizine are generally well tolerated. Common side effects, which might be seen with the combination, are dyspepsia, abdominal pain, rash, dizziness, headache, fatigue and somnolence, Sometimes, hypersensitivity, irritability, restlessness, insomnia, vomiting and diarrhoea may occur. In rare cases, patients may present with systemic eosinophilia, sometimes presenting with clinical features of consistent with Churg-Strauss syndrome.

4.9 Overdose

Symptoms of overdosage include dyspepsia, abdominal pain, rash, dizziness, headache, fatigue and somnolence. Sometimes, hypersensitivity, irritability, restlessness, insomnia, vomiting and diarrhoea may occur. In rare cases, patients may present with systemic eosinophilia, sometimes presenting with clinical features of consistent with Churg-Strauss Syndrome. Treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics Properties

Pharmacotherapeutic group: Combination of Antihistamine and leukotriene receptor antagonist

Levocetirizine:

Levocetirizine, the R- enantiomer of cetirizine, is a potent and selective antagonist of peripheral H1-receptors. Binding studies revealed that levocetirizine has high affinity for human H1-receptors (Ki = 3.2 nmol/l). Levocetirizine has an affinity 2-fold higher than that of cetirizine (Ki = 6.3 nmol/l). Levocetirizine dissociates from H1-receptors with a half-life of 115 ± 38 min. After single administration, levocetirizine shows receptor occupancy of 90% at 4 hours and 57% at 24 hours.

Pharmacokinetics/Pharmacodynamic relationship 5 mg levocetirizine provide a similar pattern of inhibition of histamine-induced wheal and flare than 10 mg cetirizine.

Montelukast:

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 (CysLT) receptors. The CysLT type-1 ($CysLT_1$) receptor is found in the human airway (including airway smooth muscle cells and airway macrophages) and on other proinflammatory cells (including eosinophils and certain myeloid stem cells). CysLTs have been correlated with the pathophysiology of asthma and allergic rhinitis.

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.

Montelukast is an orally active compound that binds with high affinity and selectivity to the $CysLT_1$ receptor. Montelukast inhibits physiologic actions of LTD_4 at the $CysLT_1$ receptor without any agonist activity.

5.2 Pharmacokinetics Properties

Levocetirizine

Absorption

Levocetirizine is rapidly and extensively absorbed following oral administration. In adults, peak plasma concentrations are achieved 0.9 h after dosing. Steady state is achieved after two days. Peak concentrations are typically 270 ng/ml and 308 ng/ml following a single and a repeated 5 mg o.d. dose, respectively. The extent of absorption is dose-independent and is not altered by food, but the peak concentration is reduced and delayed.

Distribution

No tissue distribution data are available in humans. Levocetirizine is 90% bound to plasma proteins. The distribution of levocetirizine is restrictive, as the volume of distribution is 0.4 l/kg.

Biotransformation

The extent of metabolism of levocetirizine in humans is less than 14% of the dose and therefore differences resulting from genetic polymorphism or concomitant intake of

enzyme inhibitors are expected to be negligible. Metabolic pathways include aromatic oxidation, N- and O- dealkylation and taurine conjugation. Dealkylation pathways are primarily mediated by CYP 3A4 while aromatic oxidation involved multiple and/or unidentified CYP isoforms. Levocetirizine had no effect on the activities of CYP isoenzymes 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 at concentrations well above peak concentrations achieved following a 5 mg oral dose.

Due to its low metabolism and absence of metabolic inhibition potential, the interaction of levocetirizine with other substances, or vice-versa, is unlikely.

Elimination

The plasma half-life in adults is 7.9 ± 1.9 hours. The half-life is shorter in small children. The mean apparent total body clearance in adults is 0.63 ml/min/kg. The major route of excretion of levocetirizine and metabolites is via urine, accounting for a mean of 85.4% of the dose. Excretion via fasces accounts for only 12.9% of the dose. Levocetirizine is excreted both by glomerular filtration and active tubular secretion.

Montelukast

Absorption

After administration of the 10-mg film coated tablet to fasted adults, the mean peak montelukast plasma concentration (Cmax) is achieved 3 hours to 4 hours (Tmax). The mean oral bioavailability is 64%. The oral bioavailability and Cmax 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 8-11 litres.

Biotransformation

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.

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 upto 50 mg. During once daily dosing with 10-mg montelukast, there is little accumulation of the parent drug in plasma (~14%).

5.3 Pre-Clinical Safety Data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Microcrystalline Cellulose, Croscarmellose Sodium, Hydroxypropyl Cellulose, Butylhydroxy Toluene, Methylene Chloride, Ferric Oxide Yellow, Silica Colloidal Anhydrous, Magnesium Stearate, Purified Water, Hypromellose.

6.2 Incompatibilities

None

6.3 Shelf Life

24 months from the date of manufacture.

6.4 Special Precautions for Storage

Store below 30°C. Protect from light & moisture.

Keep all medicines out of the reach of children.

6.5 Nature and Contents of Container

10 tablets are packed in Alu/Alu blister. 03 such blisters are packed in a unit carton along with a package insert.

6.6 Special Precautions for Disposal

No special requirements.

7. DATE OF PUBLICATION OF INSERT

Aug' 2017

Manufactured by:

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