LETISTOR

Instructions for the medicinal product

Trade name: Letistor.
International Nonproprietary Name: Levocetirizine + Montelukast.
Dosage form: Film coated tablets.
Composition: Each film-coated tablet contains:
Levocetirizine Hydrochloride 5 mg;
Montelukast Sodium USP eq. to Montelukast 10 mg;
Colour: Titanium Dioxide BP
Pharmacotherapeutic group: Leukotriene receptor antagonists and selective antagonist of peripheral H 1 - receptors.
ATC Classification: R06AE09 **(**Levocetirizine**);** R03DC03 (Montelukast).
Pharmacologic property:
Pharmacodynamics:
As Letistor is a combination of Levocetirizine and Montelukast; the pharmacological properties of both the molecules are given separately:
Levocetirizine - the active component of Letistor , is the R enantiomer of cetirizine hydrochloride, a racemic compound with antihistaminic properties. It is an orally active and selective H_1-receptor antagonist. Histamines act on H_1 receptors, causing the symptoms commonly seen in allergic reactions. Levocetirizine inhibits these H_1 receptors.
Montelukast - the cysteinyl leukotrienes (LTC4, LTD4, and LTE4) 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 (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 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 CysLT1 receptor. Montelukast inhibits physiologic actions of LTD4 at the CysLT1 receptor without any agonist activity.
Pharmacokinetics:
Levocetirizine.
Absorption - Levocetirizine is rapidly and extensively absorbed following oral administration. Peak plasma concentrations are achieved 0.9 g 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, neither concerning the passage of levocetirizine through the blood-brain-barrier. 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 mean apparent total body clearance 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 faeces 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 in 3 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 to 11 liters.
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.
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 is 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%).
Indications:
- relief of symptoms of allergic rhinitis (seasonal or perennial), as prophylaxis in seasonal allergic rhinitis;
- treatment of comorbid asthma and allergic rhinitis.

Contraindications:
patients with known hypersensitivity to montelukast sodium, levocetirizine or cetirizine or to any other component of this product;
patients with severe renal impairment at less than10ml/min creatinine clearance;
children less than 6 years of age.
Pregnancy and Lactation:
There are no adequate and well-controlled studies of either montelukast or levocetrizine in pregnant women. Hence this combination should not be used during pregnancy.
Since levocetirizine is excreted in breast-milk the combination is not recommended during lactation.
With caution should be used in patients with impaired renal function and with impaired hepatic function.
Dosage and directions for use:
For adults and children over 15 years of age: 1 tablet per day.
For children 6-14 years of age: ½ tablet per day.
Side-effects:
Montelukast.
Common side effects include dyspepsia, abdominal pain, rash, dizziness, headache, fatigue, fever, trauma, cough, nasal congestion.
Levocetirizine.
Use of levocetirizine has been associated with somnolence, fatigue, nasopharyngitis, dry mouth, and pharyngitis in subjects 12 years of age and older.
Further uncommon incidences of adverse reactions like asthenia or abdominal pain were observed.
Overdose:
There is no data reported on the overdosage of this combination. However, overdosage has been reported with individual molecules.
Montelukast.
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.
Levocetirizine.
Symptoms of overdose may include drowsiness in adults, and in children, initially agitation and restlessness, followed by drowsiness. There is no known specific antidote to levocetirizine. Should overdose occur, consider standard measures to remove any unabsorbed drug. Gastric lavage should be considered following short-term ingestion. Levocetirizine is not effectively removed by haemodialysis.
Drug interactive:
Levocetirizine: In vitro data indicate that levocetirizine is unlikely to produce pharmacokinetic interactions through inhibition or induction of liver drug-metabolizing enzymes. No in vivo drug-drug interaction studies have been performed with levocetirizine. Drug interaction studies have been performed with racemic cetirizine. Pharmacokinetic interaction studies performed with racemic cetirizine demonstrated that cetirizine did not interact with antipyrine, pseudoephedrine, erythromycin, 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. 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.
Montelukast: In drug-interaction studies, 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.
Although additional specific interaction studies were not performed, montelukast was used concomitantly with a wide range of commonly prescribed drugs in clinical studies without evidence of clinical adverse interactions. These medications included thyroid hormones, sedative hypnotics, non-steroidal anti-inflammatory agents, benzodiazepines, and decongestants.
Phenobarbital, which induces hepatic metabolism, decreased the AUC of montelukast approximately 40% following a single 10-mg dose of montelukast. No dosage adjustment for montelukast is recommended. It is reasonable to employ appropriate clinical monitoring when potent cytochrome P450 enzyme inducers, such as phenobarbital or rifampin, are co-administered with montelukast.
Cautions:
*Levocetirizine***.** Comparative clinical trials have revealed no evidence that levocetirizine at the recommended dose impairs mental alertness, reactivity or the ability to drive. In clinical trials the occurrence of somnolence, fatigue, and asthenia has been reported in some patients under therapy with levocetirizine. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness, and motor coordination 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.
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. Therapy with montelukast can be continued during acute exacerbations 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 corticosteroids.
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 (beta)-agonists as prophylaxis and have available for rescue a short-acting inhaled (beta)-agonist. Patients with known aspirin sensitivity should continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking Letistor. 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 non-steroidal anti-inflammatory drugs in aspirin-sensitive asthmatic patients.
Presentation:
10 film-coated tablets in each alu/alu blister. 2 blisters with instructions for use in a cardboard box.
Storage:
Keep in dry place, protected from light at a temperature below 30°C. Keep out of reach of children.
Shelf life:
Labeled. Do not use after expiry date.
Distribution Condition:
Prescribed medicine.

SPEY
Manufactured for:
SPEY MEDICAL
London, United Kingdom
Manufactured by:
Akums Drugs & Pharmaceuticals Ltd.
19,20,21, Sector-6A, I.I.E., SIDCUL,
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