MTnL® Tablets

1. Generic Names

Montelukast

Levocetirizine

2. Qualitative and Quantitative Composition

Montelukast 10 mg

Levocetirizine 5 mg

3. Dosage form and strength

Oral tablets containing Montelukast 10mg & Levocetirizine 5mg.

4. Clinical particulars

4.1 Therapeutic indication

MTnL Tablet is indicated for treatment of allergy associated with upper respiratory tract infection, Bronchial Asthma and Bronchitis

4.2 Posology and method of administration

One tablet once daily.

4.3 Contraindication

MTnL tablet is contraindicated in patients with:

- Known hypersensitivity to montelukast sodium, levocetirizine or cetirizine or to any other component of this product.
- Severe renal impairment at less than 10ml/min creatinine clearance.

- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

4.4 Special warnings and precautions for use

- In rare cases, 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.
- Patients should avoid engaging in hazardous occupation requiring complete mental alertness such as driving or operating machinery when taking levocetirizine. Precaution is recommended with intake of alcohol and in those who are on CNS depressants

4.5 Drug interactions

- 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.

- LEVOCETIRIZINE

✓ In vitro data indicate that levocetrizine 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 levocetrizine.

✓ 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.

✓ 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.

4.6 Use in special population

- Pediatric: Montelukast: The safety of Montelukast 4-mg chewable tablets in pediatric patients aged 2 to 14 years with allergic rhinitis is supported by data from studies conducted in pediatric patients aged 2 to 14 years with asthma. A safety study in pediatric patients 2 to 14 years of age with seasonal allergic rhinitis demonstrated a similar safety profile. The safety and effectiveness in pediatric patients below the age of 12 months with asthma and 6 months with allergic rhinitis have not been established.

  Levocetirizine: The safety and effectiveness of Levocetirizine in pediatric patients under 2 years of age have not been established. The effectiveness of Levocetirizine 2.5 mg once daily for the treatment of the symptoms of seasonal and perennial allergic rhinitis in children 2 to 6 years of age is supported by the extrapolation of demonstrated efficacy of Levocetirizine 5 mg once daily in patients 12 years of age and older and by the pharmacokinetic comparison in adults and children. In children 2 to 6 years of age the recommended dose of 2.5 mg once daily should not be exceeded.

- Geriatric: Montelukast: No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

  Levocetirizine: Clinical studies of levocetirizine for each approved indication did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy
- Liver impairment: As montelukast is mainly excreted through bile, caution is to be exercised while prescribing this combination in patients with impaired hepatic function.
- Renal failure: As levocetrizine is mainly excreted through urine, dosage adjustment may be required in patients with impaired renal function. Hence this combination should be used with caution in such patients.
- 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

4.7 Effects on ability to drive and use machine

Patients should be cautioned against engaging in activities requiring complete mental alertness, and motor coordination such as operating machinery until their response to MTnL Tablet is known.

4.8 Undesirable effects

- Montelukast

Eosinophilia, Palpitations, Tachycardia, Vertigo, Visual impairment, Nausea , Vomiting, Dry mouth, Diarrhoea, Abdominal pain, Hepatic function abnormal, Decreased appetite, Arthralgia, Myalgia, Muscle spasms, Pain in extremity, Depression, Anxiety, Insomnia, Aggression, Suicidal ideation, Rash, Urticaria, Pruritus, Hypertension.

- Levocetirizine

Anaemia, Palpitations, Vertigo, Tinnitus, Eye pruritus, Lacrimation increased, Nausea, Vomiting, Dry mouth, Diarrhoea, Abdominal pain, Constipation, Decreased appetite, Myalgia, Insomnia, Nightmare.

4.9 Overdose

There is no data to prove the overdosages of this combination. However, overdosages has been reported with individual molecules.

Montelukast: There have been reports of acute over-dosage in post-marketing experience and clinical studies with montelukast. These include reports in adults and children with a dose as high as 1000 mg. The clinical and laboratory findings observed were 6 consistent with the safety profile in adults and pediatric patients. There were no adverse experiences in the majority of over-dosage 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 initially agitation and restlessness followed by drowsiness, in children. There is no known specific antidote to levocetrizine. Should overdose occur, symptomatic or supportive treatment is recommended. Levocetrizine is not effectively removed by dialysis and dialysis will be ineffective unless a dialyzable agent has been concomitantly ingested.

5. Pharmacological properties

5.1 Mechanism of action

Montelukast selectively antagonizes leukotriene D4 (LTD4) at the cysteinyl leukotriene receptor, CysLT1, in the human airway. Montelukast inhibits the actions of LTD4 at the

CysLT1 receptor, preventing airway edema, smooth muscle contraction, and enhanced secretion of thick, viscous mucus.

Levocetirizine is an inverse agonist that decreases activity at histamine H1 receptors. This in turn prevents the release of other allergy chemicals and increased blood supply to the area, and provides relief from the typical symptoms associated with seasonal and perennial allergic rhinitis. It does not prevent the actual release of histamine from mast cells.

5.2 Pharmacodynamic properties

Montelukast, like zafirlukast, is a leukotriene receptor antagonist used as an alternative to anti-inflammatory medications in the management and chronic treatment of asthma and exercise-induced bronchospasm (EIB). Unlike zafirlukast, montelukast does not inhibit CYP2C9 or CYP3A4 and is, therefore, not expected to affect the hepatic clearance of drugs metabolized by these enzymes.

5.3 Pharmacokinetic properties

Peak plasma concentrations of montelukast are achieved in 3 to 4 hours after oral doses. The mean oral bioavailability is 64%. Montelukast is more than 99% bound to plasma proteins. It is extensively metabolised in the liver by cytochrome P450 isoenzymes CYP3A4, CYP2A6, and CYP2C9, and is excreted principally in the faeces via the bile.

Levocetirizine is rapidly and extensively absorbed following oral administration. In adults, peak plasma concentrations are achieved 0.9 hour after administration of the oral tablet. Levocetirizine is poorly metabolized and undergo renal excretion.

6. Nonclinical properties

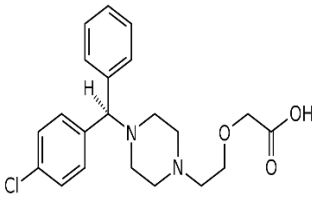
6.1 Animal Toxicology or Pharmacology

No mortality occurred following a single oral administration of montelukast sodium at doses up to 5000 mg/kg, in mice and rats, (15 000 mg/m2 and 29 500 mg/m2 in mice and rats, respectively) the maximum dose tested (oral aLD50 >5000 mg/kg). This dose is equivalent to

25 000 times the recommended daily adult human dose (determined using mg/kg/day values) .

7. Description

Levocetirizine is in a class of medications called antihistamines. Its chemical name is 2-(2-{4-[(R)-(4-chlorophenyl)(phenyl)methyl]piperazin-1-yl}ethoxy)acetic acid dihydrochloride and its structural formula is:



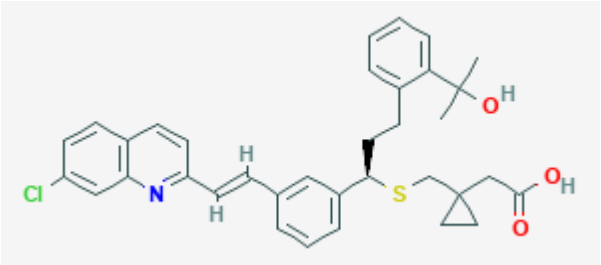
Its empirical formula is C21H25ClN2O3, and its molecular weight is 388.8878 g/mol.

Montelukast is a drug which is used for the treatment of asthma. Montelukast is considered to be a practically insoluble (in water) and relatively neutral molecule. Montelukast has been detected in multiple biofluids, such as urine and blood. Within the cell, montelukast is primarily located in the cytoplasm and membrane (predicted from logP). Montelukast can be converted into montelukast nitrile.

Molecular Formula: $C_{35}H_{36}ClNO_3S$

Molecular Weight: 586.2 g/mol

Structure:



8. Pharmaceutical particulars

8.1 Incompatibilities

There are no known incompatibilities.

8.2 Shelf-life

18 months.

8.3 Packaging Information

MTnL Tablet is available in strip of 10 tablets.

8.4 Storage and handling instructions

Store in a cool dry place. Protect from moisture and light.

9. Patient Counselling Information

9.1 Adverse Reactions

Refer part 4.8

9.2 Drug Interactions

Refer part 4.5

9.3 Dosage

Refer part 4.2

9.4 Storage

Refer part 8.4

9.5 Risk Factors

Refer part 4.4

9.6 Self-monitoring information

NA

9.7 Information on when to contact a health care provider or seek emergency help

Patient is advised to be alert for the emergence or worsening of the adverse reactions and contact the prescribing physician.

9.8 Contraindications

Refer part 4.3

10. Manufactured by Ravenbhel Biotech

11. Details of permission or license number with date

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12. Date of revision: January 2022