MTnL Tablet/ MTnL Kid Tablet

Montelukast & Levocetirizine dihydrochloride

COMPOSITION

MTnL Tablets

Each film-coated tablet contains:

Montelukast sodium equivalent to montelukast	10 mg
Levocetirizine dihydrochloride	5 mg
Excipients	q.s.

MTnL Kid Tablets

Each tablet contains:

Montelukast sodium equivalent to montelukast	4 mg
Levocetirizine dihydrochloride	2.5 mg
Excipients	q.s.

DESCRIPTION

Montelukast sodium is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene ($CysLT_1$), receptor.

Levocetirizine is the R-enantiomer of cetirizine. Levocetirizine is an orally active, potent, selective and long acting H_1 -histamine receptor antagonist with no anticholinergic activity.

Recent studies have demonstrated that Allergic Rhinitis [AR] when treated concomitantly with an antileukotriene (montelukast) and an antihistamine (levocetrizine), shows significantly better symptom relief compared with the modest improvement of rhinitis symptoms with each of the treatments alone.

PHARMACOLOGY

As **MTnL** is a combination of Montelukast and Levocetrizine; the pharmacological properties of both the molecules are given separately:

Pharmacodynamics

MONTELUKAST

Montelukast causes inhibition of airway cysteinyl leukotriene receptors as demonstrated by the ability to inhibit bronchoconstriction due to inhaled LTD4 in asthmatics. Doses as low as 5 mg cause substantial blockage of LTD4 -induced bronchoconstriction.

LEVOCETIRIZINE

Levocetirizine, the (R) enantiomer of cetirizine, is a potent and selective antagonist of peripheral H_1 -receptors.

Binding studies revealed that levocetirizine has high affinity for human H_1-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 H_1-receptors with a half-life of 115 ± 38 min.

Pharmacodynamic studies in healthy volunteers demonstrate that, at half the dose, levocetirizine has comparable activity to cetirizine, both in the skin and in the nose.

Pharmacokinetic/pharmacodynamic relationship 5 mg levocetirizine provide a similar pattern of inhibition of histamine-induced wheal and flare than 10 mg cetirizine. As for cetirizine, the action on histamine-induced skin reactions was out of phase with the plasma concentrations. ECGs did not show relevant effects of levocetirizine on QT interval.

Pharmacokinetics

MONTELUKAST

Absorption

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

LEVOCETIRIZINE

The pharmacokinetics of levocetirizine are linear with dose and time-independent with low inter-subject variability. The pharmacokinetic profile is the same when given as the single enantiomer or when given as cetirizine. No chiral inversion occurs during the process of absorption and elimination.

Absorption

Levocetirizine is rapidly and extensively absorbed following oral administration. Peak plasma concentrations are achieved 0.9h 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.

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 sec.

INDICATIONS

MTnL Tablets are indicated for relief of symptoms of allergic rhinitis [seasonal or perennial], as prophylaxis in seasonal allergic rhinitis and treatment of comorbid asthma and allergic rhinitis in patients 15 years of age and over.

MTnL Kid Tablets are indicated for the relief of symptoms of allergic rhinitis [seasonal or perennial], as prophylaxis in seasonal allergic rhinitis and treatment of comorbid asthma and allergic rhinitis in patients 2 to 5 years of age.

DOSAGE & ADMINISTRATION

Adults [>15years]: 1 MTnL Tablet once daily
Children (2-5years): One MTnL Kid Tablet once daily

Due to the lack of clinical data, the administration of this product to infants less than 2 years of age is not recommended.

CONTRAINDICATIONS

MTnL is contraindicated in patients with known hypersensitivity to montelukast sodium, levocetirizine or cetirizine or to any other component of this product. MTnL is also contraindicated in patients with 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 should not take this medication.

WARNINGS & PRECAUTIONS

MONTELUKAST

Eosinophilic Conditions

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.

LEVOCETIRIZINE

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

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 cetrizine.

Pharmacokinetic interaction studies performed with racemic cetrizine demonstrated that cetrizine did not interact with antipyrine, pseudoephedrine, erythromycin, azithromycin, ketoconazole and cimetidine. There was a small decrease (~16%) in the clearance of cetrizine 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 cetrizine by about 42% accompanied by an increase in half-life (53%) and a decrease in clearance (29%) of cetrizine. The disposition of ritonavir was not altered by concomitant cetrizine administration.

Renal Impairment

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.

Hepatic Impairment

As montelukast is mainly excreted through bile, caution is to be exercised while prescribing this combination in patients with impaired hepatic function.

Pregnancy

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.

Lactation

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

Pediatric Use:
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 Use
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.

UNDESIRABLE 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.

OVERDOSAGE
There is no data to prove the overdosage of this combination. However, overdosage 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

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.

PRESENTATION
MTnL Tablet is available in a strip of 10 tablets
MTnL Kid Tablet is available in a strip of 10 tablets

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