For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

LEZYNCET-M

1. Generic Name

Montelukast Sodium & Levocetirizine Hydrochloride Tablets IP

2. Qualitative and quantitative composition

Each film coated bilayer tablet contains:
Levocetirizine Hydrochloride I.P. ……5mg
Montelukast Sodium I.P.
equivalent to Montelukast ……..10mg
Colour : Sunset Yellow Lake.

The excipients used are Microcrystalline Cellulose Powder, Lactose, PVPK-30, Talcum, Magnesium Stearate, Sunset Yellow Lake colour, Croscarmellose Sodium, ICS 329 Transparent, Isopropyl Alcohol and Methylene Chloride.

3. Dosage form and strength

Dosage form: Film coated bilayer tablet

Strength: Levocetirizine hydrochloride 5 mg and Montelukast 10 mg.

4. Clinical particulars

4.1 Therapeutic indication

For the treatment of allergic rhinitis in 15 years and above.

4.2 Posology and method of administration

Posology

The daily recommended dose is one film-coated tablet for children aged 15 years and above and adults.

Elderly
Adjustment of the dose is recommended in elderly patients with moderate to severe renal impairment (see Renal impairment below).

Renal impairment
The dosing intervals must be individualised according to renal function. Refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in ml/min is needed. The CLcr (ml/min) may be estimated from serum creatinine (mg/dl) determination using the following formula:

$$CL_{cr} = \frac{[140 - age\,(years)] * weight\,(kg)}{72 * serum\ creatinine\,(mg/dl)} (* 0.85\ for\ women)$$

Hepatic impairment

No dose adjustment is needed in patients with solely hepatic impairment. In patients with hepatic impairment and renal impairment, adjustment of the dose is recommended (see Renal impairment above).

Method of administration

The film-coated tablet must be taken orally, swallowed whole with liquid and may be taken with or without food. It is recommended to take the daily dose in one single intake.

4.3 Contraindications

Hypersensitivity to the active substance, or to any of the other excipients.

Severe renal impairment at less than 10 ml/min creatinine clearance.

4.4 Special warnings and precautions for use

Levocetirizine

Precaution is recommended with concurrent intake of alcohol.

Caution should be taken in patients with predisposing factors of urinary retention (e.g. spinal cord lesion, prostatic hyperplasia) as levocetirizine may increase the risk of urinary retention.

Caution should be taken in patients with epilepsy and patients at risk of convulsion as levocetirizine may cause seizure aggravation.

Response to allergy skin tests are inhibited by antihistamines and a wash-out period (of 3 days) is required before performing them.

Pruritus may occur when levocetirizine is stopped even if those symptoms were not present before treatment initiation. The symptoms may resolve spontaneously. In some cases, the symptoms may be intense and may require treatment to be restarted. The symptoms should resolve when the treatment is restarted.

Montelukast

In rare cases, patients on 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 cases have been sometimes associated with the reduction or withdrawal of oral corticosteroid therapy. Although a causal relationship with leukotriene receptor antagonism has not been established, physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. Patients who develop these symptoms should be reassessed and their treatment regimens evaluated.
Patients and physicians should be alert for neuropsychiatric events. Patients and/or caregivers should be instructed to notify their physician if these changes occur.

4.5 Drugs interactions

Levocetirizine

No interaction studies have been performed with levocetirizine (including no studies with CYP3A4 inducers); studies with the racemate compound cetirizine demonstrated that there were no clinically relevant adverse interactions (with antipyrine, azithromycin, cimetidine, diazepam, erythromycin, glipizide, ketoconazole and pseudoephedrine). A small decrease in

the clearance of cetirizine (16%) was observed in a multiple dose study with theophylline (400 mg once a day); while the disposition of theophylline was not altered by concomitant cetirizine administration.

In a multiple dose study of ritonavir (600 mg twice daily) and cetirizine (10 mg daily), the extent of exposure to cetirizine was increased by about 40% while the disposition of ritonavir was slightly altered (-11%) further to concomitant cetirizine administration.

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

In sensitive patients, the concurrent administration of cetirizine or levocetirizine and alcohol or other CNS depressants may cause additional reductions in alertness and impairment of performance.

Montelukast

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.

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.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Levocetirizine

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of levocetirizine in pregnant women. However, for cetirizine, the racemate of levocetirizine, a large amount of data (more than 1000 pregnancy outcomes) on pregnant women indicate no malformative or feto/neonatal toxicity. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition or postnatal development. The use of levocetirizine may be considered during pregnancy, if necessary.

Breast-feeding

Cetirizine, the racemate of levocetirizine, has been shown to be excreted in human. Therefore, the excretion of levocetirizine in human milk is likely. Adverse reactions associated with levocetirizine may be observed in breastfed infants. Therefore, caution should be exercised when prescribing levocetirizine to lactating women.

Fertility

For levocetirizine no clinical data are available

Montelukast

Pregnancy

Animal studies do not indicate harmful effects with respect to effects on pregnancy or embryonal/foetal development. Limited data from available pregnancy databases do not suggest a causal relationship between montelukast and malformations (i.e. limb defects) that have been rarely reported in worldwide post-marketing experience. Montelukast may be used during pregnancy only if it is considered to be clearly essential.

Breast-feeding

Studies in rats have shown that montelukast is excreted in milk. It is unknown whether montelukast/metabolites are excreted in human milk.

4.7 Effects on ability to drive and use machines

Comparative clinical trials have revealed no evidence that levocetirizine at the recommended dose impairs mental alertness, reactivity or the ability to drive.

Nevertheless, some patients could experience somnolence, fatigue and asthenia under therapy with levocetirizine. Therefore, patients intending to drive, engage in potentially hazardous activities or operate machinery should take their response to the medicinal product into account.

4.8 Undesirable effects

Levocetirizine

Adults and adolescents above 12 years of age

In reported therapeutic studies in women and men aged 12 to 71 years, 15.1% of the patients in the levocetirizine 5 mg group had at least one adverse drug reaction compared to 11.3% in the placebo group. 91.6 % of these adverse drug reactions were mild to moderate. In therapeutic trials, the dropout rate due to adverse events was 1.0% (9/935) with levocetirizine 5 mg and 1.8% (14/771) with placebo.

Clinical therapeutic trials with levocetirizine included 935 subjects exposed to the medicinal product at the recommended dose of 5 mg daily. From this pooling, following incidence of adverse drug reactions were reported at rates of 1% or greater (common: ≥1/100 to <1/10) under levocetirizine 5 mg or placebo:

Preferred Term (WHOART)	**Placebo (n =771)**	**Levocetirizine 5 mg (n = 935)**
Headache	25 (3.2%)	24 (2.6%)
Somnolence	11 (1.4%)	49 (5.2%)
Mouth dry	12 (1.6%)	24 (2.6%)
Fatigue	9 (1.2%)	23 (2.5%)

Further uncommon incidences of adverse reactions (uncommon ≥1/1,000 to <1/100) like asthenia or abdominal pain were observed. The incidence of sedating adverse drug reactions

such as somnolence, fatigue, and asthenia was altogether more common (8.1%) under levocetirizine 5 mg than under placebo (3.1%).

Post-marketing experience

Adverse reactions from post-marketing experience are per System Organ Class and per frequency. The frequency is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

• Immune system disorders:

Not known: hypersensitivity including anaphylaxis

• Metabolism and nutrition disorders:

Not known: increased appetite

• Psychiatric disorders:

Not known: aggression, agitation, hallucination, depression, insomnia, suicidal ideation, nightmare

• Nervous system disorders:

Not known: convulsion, paraesthesia, dizziness, syncope, tremor, dysgeusia

• Ear and labyrinth disorders:

Not known: vertigo

• Eyes disorders:

Not known: visual disturbances, blurred vision, oculogyration

• Cardiac disorders:

Not known: palpitations, tachycardia

• Respiratory, thoracic and mediastinal disorders:

Not known: dyspnoea

• Gastrointestinal disorders:

Not known: nausea, vomiting, diarrhoea

• Hepatobiliary disorders:

Not known: hepatitis

• Renal and urinary disorders:

Not known: dysuria, urinary retention

• Skin and subcutaneous tissue disorders:

Not known: angioneurotic oedema, fixed drug eruption, pruritus, rash, urticaria

• Musculoskeletal, connective tissues, and bone disorders:

Not known: myalgia, arthralgia

• General disorders and administration site conditions:

Not known: oedema

• Investigations:

Not known: weight increased, abnormal liver function tests

Description of selected adverse reactions

After levocetirizine discontinuation, pruritus has been reported.

Montelukast

The following drug-related adverse reactions in clinical studies were reported commonly (≥1/100 to <1/10) in patients treated with montelukast and at a greater incidence than in patients treated with placebo:

Body System Class	**Adult and Adolescent Patients 15 years and older (two 12-week studies; n=795)**	**Paediatric Patients 6 to 14 years old (one 8-week study; n=201) (two 56 week studies; n=615)**	**Paediatric Patients 2 to 5 years old (one 12-week study; n=461) (one 48-week study; n=278)**
Nervous system disorders	headache	headache	
Gastro-intestinal disorders	abdominal pain		abdominal pain
General disorders and administration site conditions			thirst

Tabulated list of Adverse Reactions

Adverse reactions reported in post-marketing use are listed, by System Organ Class and specific Adverse Reactions, in the table below. Frequency Categories were estimated based on relevant clinical trials.

System Organ Class	**Adverse Reactions**	**Frequency Category***
Infections and infestations	upper respiratory infection[†]	Very Common
Blood and lymphatic system disorders	increased bleeding tendency	Rare
	thrombocytopenia	Very Rare
Immune system disorders	hypersensitivity reactions including anaphylaxis	Uncommon
	hepatic eosinophilic infiltration	Very Rare
Psychiatric disorders	dream abnormalities including nightmares, insomnia, somnambulism, anxiety, agitation including aggressive behaviour or hostility, depression, psychomotor hyperactivity (including irritability, restlessness, tremor[§])	Uncommon
	disturbance in attention, memory impairment, tic	Rare
	hallucinations, disorientation, suicidal thinking and behaviour (suicidality),	Very Rare

	obsessive-compulsive symptoms, dysphemia	
Nervous system disorders	dizziness, drowsiness, paraesthesia/hypoesthesia, seizure	Uncommon
Cardiac disorders	palpitations	Rare
Respiratory, thoracic and mediastinal disorders	epistaxis	Uncommon
	Churg-Strauss Syndrome (CSS) (see section 4.4)	Very Rare
	pulmonary eosinophilia	Very Rare
Gastro-intestinal disorders	diarrhoea‡, nausea‡, vomiting‡	Common
	dry mouth, dyspepsia	Uncommon
Hepatobiliary disorders	elevated levels of serum transaminases (ALT, AST)	Common
	hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury).	Very Rare
Skin and subcutaneous tissue disorders	rash‡	Common
	bruising, urticaria, pruritus	Uncommon
	angiooedema	Rare
	erythema nodosum, erythema multiforme	Very Rare
Musculoskeletal and connective tissue disorders	arthralgia, myalgia including muscle cramps	Uncommon
Renal and urinary disorders	enuresis in children	Uncommon
General disorders and administration site conditions	pyrexia‡	Common
	asthenia/fatigue, malaise, oedema	Uncommon

*Frequency Category: Defined for each Adverse Reaction by the incidence reported in the clinical trials data base: Very Common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very Rare (<1/10,000).
†This adverse experience, reported as Very Common in the patients who received montelukast, was also reported as Very Common in the patients who received placebo in clinical trials.
‡This adverse experience, reported as Common in the patients who received montelukast, was also reported as Common in the patients who received placebo in clinical trials.
§ Frequency Category: Rare

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

4.9 Overdose

Levocetirizine

Symptoms of overdose may include drowsiness in adults. In children, agitation and restlessness may initially occur, followed by drowsiness.

Management of overdoses

There is no known specific antidote to levocetirizine. Should overdose occur, symptomatic or supportive treatment is recommended. Gastric lavage may be considered shortly after ingestion of the drug. Levocetirizine is not effectively removed by haemodialysis.

Montelukast

There have been reports of acute overdose in post-marketing experience and clinical studies with montelukast. These include reports in adults and children with a dose as high as 1,000 mg (approximately 61 mg/kg in a 42 month old child). The clinical and laboratory findings observed were consistent with the safety profile in adults and paediatric patients. There were no adverse experiences in the majority of overdose reports.

Symptoms of overdose
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.

Management of overdose
No specific information is available on the treatment of overdose with montelukast. It is not known whether montelukast is dialysable by peritoneal- or haemodialysis.

5. Pharmacological properties

5.1 Mechanism of Action

Levocetirizine

Levocetirizine, the (R) enantiomer of cetirizine, is a potent and selective antagonist of peripheral histamine (H1)-receptors. H1 receptors are activated by the biogenic amine histamine. Levocetirizine prevent binding of histamine to this receptors and this in turn prevent relief from the typical symptoms of allergic rhinitis.

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 a receptor occupancy of 90% at 4 hours and 57% at 24 hours. 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.

Montelukast

The cysteinyl leukotrienes (LTC4, LTD4, LTE4) are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important pro-asthmatic mediators bind to cysteinyl leukotriene receptors (CysLT) found in the human airway and cause airway actions, including bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment.

5.2 Pharmacodynamic properties

Levocetirizine

Pharmacotherapeutic group: antihistamine for systemic use, piperazine derivatives, ATC code: R06A E09.

The pharmacodynamic activity of levocetirizine has been studied in randomised, controlled trials:

In a reported study comparing the effects of levocetirizine 5 mg, desloratadine 5 mg, and placebo on histamine-induced wheal and flare, levocetirizine treatment resulted in significantly decreased wheal and flare formation which was highest in the first 12 hours and lasted for 24 hours, ($p<0.001$) compared with placebo and desloratadine. The onset of action of levocetirizine 5 mg in controlling pollen-induced symptoms has been observed at 1 hour post drug intake in placebo controlled trials in the model of the allergen challenge chamber.

In vitro studies (Boyden chambers and cell layers techniques) show that levocetirizine inhibits eotaxin-induced eosinophil transendothelial migration through both dermal and lung cells. A pharmacodynamic experimental study in vivo (skin chamber technique) showed three main inhibitory effects of levocetirizine 5 mg in the first 6 hours of pollen-induced reaction, compared with placebo in 14 adult patients: inhibition of VCAM-1 release, modulation of vascular permeability and a decrease in eosinophil recruitment.

Clinical efficacy and safety

The efficacy and safety of levocetirizine has been demonstrated in several double-blind, placebo controlled, clinical trials performed in adult patients suffering from seasonal allergic rhinitis, perennial allergic rhinitis, or persistent allergic rhinitis. Levocetirizine has been shown to significantly improve symptoms of allergic rhinitis, including nasal obstruction in some studies.

Chronic idiopathic urticaria was studied as a model for urticarial conditions. Since histamine release is a causal factor in urticarial diseases, levocetirizine is expected to be effective in providing symptomatic relief for other urticarial conditions, in addition to chronic idiopathic urticaria. ECGs did not show relevant effects of levocetirizine on QT interval.

Paediatric population

The paediatric safety and efficacy of levocetirizine tablets has been studied in two placebo controlled clinical trials including patients aged 6 to 12 years and suffering from seasonal and perennial allergic rhinitis, respectively. In both trials, levocetirizine significantly improved symptoms and increased health-related quality of life.

In children below the age of 6 years, clinical safety has been established from several short- or long -term therapeutic studies:

- one clinical trial in which 29 children 2 to 6 years of age with allergic rhinitis were treated with levocetirizine 1.25 mg twice daily for 4 weeks

- one clinical trial in which 114 children 1 to 5 years of age with allergic rhinitis or chronic idiopathic urticaria were treated with levocetirizine 1.25 mg twice daily for 2 weeks

- one clinical trial in which 45 children 6 to 11 months of age with allergic rhinitis or chronic idiopathic urticaria were treated with levocetirizine 1.25 mg once daily for 2 weeks

- one long-term (18 months) clinical trial in 255 levocetirizine - treated atopic subjects aged 12 to 24 months at inclusion.

The safety profile was similar to that seen in the short-term studies conducted in children 1 to 5 years of age.

Montelukast

Pharmacotherapeutic group: Leukotriene receptor antagonist
ATC-Code: R03D C03

Pharmacodynamic effects
Montelukast is an orally active compound which binds with high affinity and selectivity to the CysLT1 receptor. In clinical studies, montelukast inhibits bronchoconstriction due to inhaled LTD4 at doses as low as 5 mg. Bronchodilation was observed within 2 hours of oral administration. The bronchodilation effect caused by a β-agonist was additive to that caused by montelukast. Treatment with montelukast inhibited both early- and late-phase bronchoconstriction due to antigen challenge. Montelukast, compared with placebo, decreased peripheral blood eosinophils in adult and paediatric patients. In a separate study, treatment with montelukast significantly decreased eosinophils in the airways (as measured in sputum). In adult and paediatric patients 2 to 14 years of age, montelukast, compared with placebo, decreased peripheral blood eosinophils while improving clinical asthma control.

5.3 Pharmacokinetic properties

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. 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, neither concerning the passage of levocetirizine through the blood-brain-barrier. In rats and dogs, the highest tissue levels are found in liver and kidneys, the lowest in the CNS compartment.

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.

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 faeces accounts for only 12.9% of the dose. Levocetirizine is excreted both by glomerular filtration and active tubular secretion.

Special population

Renal impairment

The apparent body clearance of levocetirizine is correlated to the creatinine clearance. It is therefore recommended to adjust the dosing intervals of levocetirizine, based on creatinine clearance in patients with moderate and severe renal impairment. In anuric end stage renal disease subjects, the total body clearance is decreased by approximately 80% when compared to normal subjects. The amount of levocetirizine removed during a standard 4-hour hemodialysis procedure was < 10%.

Paediatric population

Data from a paediatric pharmacokinetic study with oral administration of a single dose of 5 mg levocetirizine in 14 children age 6 to 11 years with body weight ranging between 20 and 40 kg show that Cmax and AUC values are about 2-fold greater than that reported in healthy adult subjects in a cross-study comparison. The mean Cmax was 450 ng/ml, occurring at a mean time of 1.2 hours, weight-normalized, total body clearance was 30% greater, and the elimination half-life 24% shorter in this paediatric population than in adults. Dedicated pharmacokinetic studies have not been conducted in paediatric patients younger than 6 years of age. A retrospective population pharmacokinetic analysis was conducted in 323 subjects (181 children 1 to 5 years of age, 18 children 6 to 11 years of age, and 124 adults 18 to 55 years of age) who received single or multiple doses of levocetirizine ranging from 1.25 mg to 30 mg. Data generated from this analysis indicated that administration of 1.25 mg once daily to children 6 months to 5 years of age is expected to result in plasma concentrations similar to those of adults receiving 5 mg once daily.

Elderly

Limited pharmacokinetic data are available in elderly subjects. Following once daily repeat oral administration of 30 mg levocetirizine for 6 days in 9 elderly subjects (65–74 years of age), the total body clearance was approximately 33% lower compared to that in younger adults. The disposition of racemic cetirizine has been shown to be dependent on renal function rather than on age. This finding would also be applicable for levocetirizine, as levocetirizine and cetirizine are both predominantly excreted in urine. Therefore, the levocetirizine dose should be adjusted in accordance with renal function in elderly patients.

Gender

Pharmacokinetic results for 77 patients (40 men, 37 women) were evaluated for potential effect of gender. The half-life was slightly shorter in women (7.08 ± 1.72 hr) than in men (8.62 ± 1.84 hr); however, the body weight-adjusted oral clearance in women (0.67 ± 0.16 ml/min/kg) appears to be comparable to that in men (0.59 ± 0.12 ml/min/kg). The same daily doses and dosing intervals are applicable for men and women with normal renal function.

Race

The effect of race on levocetirizine has not been studied. As levocetirizine is primarily renally excreted, and there are no important racial differences in creatinine clearance, pharmacokinetic characteristics of levocetirizine are not expected to be different across races. No race-related differences in the kinetics of racemic cetirizine have been observed.

Hepatic impairment

The pharmacokinetics of levocetirizine in hepatically impaired subjects have not been tested. Patients with chronic liver diseases (hepatocellular, cholestatic, and biliary cirrhosis) given 10 or 20 mg of the racemic compound cetirizine as a single dose had a 50% increase in half life along with a 40% decrease in clearance compared to healthy subjects.

Montelukast

Absorption

Montelukast is rapidly absorbed following oral administration. The mean oral bioavailability is 64%. The oral bioavailability and Cmax are not influenced by a standard meal. Safety and efficacy were demonstrated in clinical trials where the 10 mg film-coated tablet was administered without regard to the timing of food ingestion.

Distribution

Montelukast is more than 99% bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8-11 litres. Studies in rats with radiolabelled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabelled material at 24 hours post-dose were minimal in all other tissues.

Biotransformation

Montelukast is extensively metabolised. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and children.

Cytochrome P450 2C8 is the major enzyme in the metabolism of montelukast. Additionally CYP 3A4 and 2C9 may have a minor contribution, although itraconazole, an inhibitor of CYP 3A4, was shown not to change pharmacokinetic variables of montelukast in healthy subjects that received 10 mg montelukast daily. Based on in vitro results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6. The contribution of metabolites to the therapeutic effect of montelukast is minimal.

Elimination

The plasma clearance of montelukast averages 45 ml/min in healthy adults. Following an oral dose of radiolabelled montelukast, 86% of the radioactivity was recovered in 5-day faecal 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.

Characteristics in Patients

No dosage adjustment is necessary for the elderly or mild to moderate hepatic insufficiency. Studies in patients with renal impairment have not been undertaken. Because montelukast and its metabolites are eliminated by the biliary route, no dose adjustment is anticipated to be necessary in patients with renal impairment. There are no data on the pharmacokinetics of montelukast in patients with severe hepatic insufficiency (Child-Pugh score >9).

With high doses of montelukast (20- and 60-fold the recommended adult dose), a decrease in plasma theophylline concentration was observed.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Levocetirizine

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.

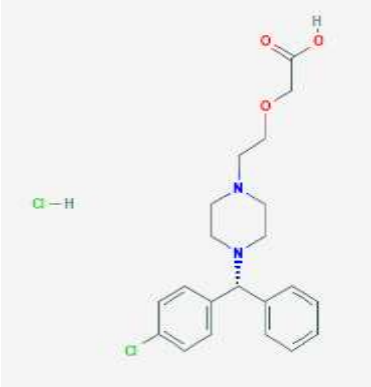
Montelukast

In animal toxicity studies, minor serum biochemical alterations in ALT, glucose, phosphorus and triglycerides were observed which were transient in nature. The signs of toxicity in animals were increased excretion of saliva, gastro-intestinal symptoms, loose stools and ion imbalance. These occurred at dosages which provided >17-fold the systemic exposure seen at the clinical dosage. No deaths occurred following a single oral administration of montelukast sodium at doses up to 5,000 mg/kg in mice and rats (15,000 mg/m2 and 30,000 mg/m2 in mice and rats, respectively), the maximum dose tested. This dose is equivalent to 25,000 times the recommended daily adult human dose (based on an adult patient weight of 50 kg). Montelukast was neither mutagenic in in vitro and in vivo tests nor tumorigenic in rodent species.

7. Description

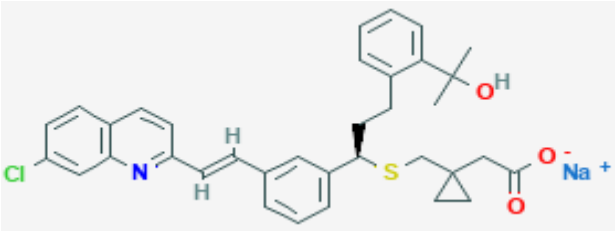
<u>Levocetirizine Hydrochloride</u>

Levocetirizine Hydrochloride is chemically 2-[2-[4-[(R)-(4-chlorophenyl)-phenylmethyl]piperazin-1-yl]ethoxy]acetic acid; hydrochloride having molecular weight of 425.3 g/mol and molecular formula is $C_{21}H_{26}Cl_2N_2O_3$ and the chemical structure is:



<u>Montelukast Sodium</u>

Montelukast Sodium is sodium;2-[1-[[(1R)-1-[3-[(E)-2-(7-chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(2-hydroxypropan-2-yl)phenyl]propyl]sulfanylmethyl] cyclopropyl] acetate having molecular weight of 608.2 g/mol and molecular formula is $C_{35}H_{35}ClNNaO_3S$ and the chemical structure is:



Montelukast Sodium & Levocetirizine Hydrochloride Tablets are White (Levocetirizine Dihydrochloride)/ Orange (Montelukast) coloured, round shaped, biconvex, film coated bilayered tablets having both sides plain. The excipients used are Microcrystalline Cellulose Powder, Lactose, PVPK-30, Talcum, Magnesium Stearate, Sunset Yellow Lake colour, Croscarmellose Sodium, ICS 329 Transparent, Isopropyl Alcohol and Methylene Chloride.

8. Pharmaceutical particulars

8.1 Incompatibilities

None stated

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

LEZYNCET-M is available in strip of 10 tablets.

8.4 Storage and handing instructions

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

Keep the medicines out of reach of children.

9. Patient counselling information

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• **This medicine has been prescribed for you only.** Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.3.How to take LEZYNCET-M

9.4.Possible side effects

9.5.How to store LEZYNCET-M

9.6.Contents of the pack and other information

9.1 What LEZYNCET-M is and what it is used for

LEZYNCET-M contains the active substance Levocetirizine Dihydrochloride and Montelukast.

LEZYNCET-M is used for the treatment of allergic rhinitis in adults only.

9.2 What you need to know before you take LEZYNCET-M

Do not take LEZYNCET-M:

– if you are allergic to Levocetirizine Hydrochloride & Montelukast, or to any of the other ingredients of this medicine.

– if you have a severe impairment of kidney function (severe renal failure with creatinine clearance below 10 ml/min).

Warnings and precautions

Talk to your doctor before taking LEZYNCET-M:

If you are likely to be unable to empty your bladder (with conditions such as spinal cord injury or enlarged prostate), please ask your doctor for advice.

If you suffer from epilepsy or are at risk of convulsions, please ask your doctor for advice as use of LEZYNCET-M may cause seizure aggravation.

If you are scheduled for allergy testing, ask your doctor if you should stop taking LEZYNCET-M for several days before testing. This medicine may affect your allergy test result.

Patients should be aware that various neuropsychiatric events (for example behaviour and mood-related changes) have been reported in adults with Montelukast.

Children

The use of LEZYNCET-M is not recommended for infants and children.

Other medicines and LEZYNCET-M

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines including those obtained without a prescription.

Tell your doctor if you are taking the following medicines before starting LEZYNCET-M: phenobarbital, phenytoin and rifampicin.

LEZYNCET-M with food, drink and alcohol

Caution is advised if LEZYNCET-M is taken at the same time as alcohol or other agents acting on the brain.

In sensitive patients, the concurrent administration of LEZYNCET-M and alcohol or other agents acting on the brain may cause additional reductions in alertness and impairment of performance. LEZYNCET-M can be taken with or without food.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

Some patients being treated with LEZYNCET-M may experience somnolence/drowsiness, tiredness and exhaustion. Use caution when driving or operating machinery untill you know how this medicine affects you. However, special tests have revealed no impairment of mental alertness, the ability to react or the ability to drive in healthy test persons after taking levocetirizine in the recommended dosage.

9.3 How to take LEZYNCET-M

Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist have told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one tablet per day.

Method of administration: The film-coated tablet must be taken orally, swallowed whole with liquid and may be taken with or without food. It is recommended to take the daily dose in one single intake.

Special dosage instructions for specific populations:
Renal and hepatic impairment

Patients with impaired kidney function may be given a lower dose according to the severity of their kidney disease, and the dose will be determined by your doctor.

Patients who have severe impairment of kidney function must not take LEZYNCET-M.

Patients who only have impaired liver function should take the usual prescribed dose.

Patients who have both impaired liver and kidney function may be given a lower dose depending on the severity of the kidney disease, the dose will be determined by your doctor.

Elderly patients aged 65 years and above
No adaptation of the dose is necessary in elderly patients, provided their renal function is normal.

If you take more LEZYNCET-M than you should

Tell your doctor or pharmacist if you have taken more than the recommended dose. If possible take your medicine and this leaflet with you.

If you forget to take LEZYNCET-M

Do not take a double dose to make up for the forgotten dose. Take your next, normal dose, the next day, at your usual time.

If you have any further questions on the use of this medicine ask your doctor or pharmacist.

9.4 Possible side effects

Levocetirizine

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Common: may affect up to 1 in 10 people

Dry mouth, headache, tiredness and somnolence/drowsiness

Uncommon: may affect up to 1 in 100 people

Exhaustion and abdominal pain

Not known: frequency cannot be estimated from the available data

Other side effects such as palpitations, increased heart rate, fits, pins and needles, dizziness, syncope, tremor, dysgeusia (distortion of the sense of taste), sensation of rotation or movement, visual disturbances, blurred vision, oculogyration (eyes having uncontrolled circular movements), painful or difficult urination, inability to completely empty the bladder, oedema, pruritus (itchiness), rash, urticaria (swelling, redness and itchiness of the skin), skin eruption, shortness of breath, weight increase, muscular pain, joint pain, aggressive or agitated behaviour, hallucination, depression, insomnia, recurring thoughts of or preoccupation with suicide, nightmare, hepatitis, abnormal liver function, vomiting, increased appetite, nausea and diarrhoea have also been reported. Pruritus (intense itching) upon discontinuation.

Montelukast

In clinical studies with montelukast, most commonly reported side effects (may affect up to 1 in 10 people) thought to be related to montelukast were abdominal pain, headache and thirst.

Talk with your doctor immediately if you notice any of the following side effects, which may be serious, and for which you may need urgent medical treatment.

Uncommon: the following may affect up to 1 in 100 people

• allergic reactions including swelling of the face, lips, tongue, and/or throat which may cause difficulty in breathing or swallowing, behaviour and mood related changes: agitation including aggressive behaviour or hostility, depression, seizure

Rare: the following may affect up to 1 in 1,000 people

• increased bleeding tendency, tremor, palpitations

Very rare: the following may affect up to 1 in 10,000 people

• combination of symptoms such as flu-like illness, pins and needles or numbness of arms and legs, worsening of pulmonary symptoms and/or rash (Churg-Strauss syndrome) (see section 2), low blood platelet count, behaviour and mood related changes: hallucinations, disorientation, suicidal thoughts and actions, swelling (inflammation) of the lungs, severe skin reactions (erythema multiforme) that may occur without warning, inflammation of the liver (hepatitis)

Other side effects while the medicine has been on the market.

Very common: the following may affect more than 1 in 10 people

• upper respiratory infection

Common: the following may affect up to 1 in 10 people

• diarrhoea, nausea, vomiting, rash, fever, elevated liver enzymes

Uncommon: the following may affect up to 1 in 100 people

• behaviour and mood related changes: dream abnormalities, including nightmares, trouble sleeping, sleepwalking, irritability, feeling anxious, restlessness, dizziness, drowsiness, pins and needles/numbness, nosebleed, dry mouth, indigestion, bruising, itching, hives, joint or muscle pain, muscle cramps, weakness/tiredness, feeling unwell, swelling

Rare: the following may affect up to 1 in 1,000 people

• behaviour and mood related changes: disturbance in attention, memory impairment, uncontrolled muscle movements

Very rare: the following may affect up to 1 in 10,000 people

• tender red lumps under the skin, most commonly on your shins (erythema nodosum), behaviour and mood related changes: obsessive-compulsive symptoms, stuttering

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting. By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store LEZYNCET-M

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

9.6 Contents of the pack and other information

What **LEZYNCET-M** contains

The active substances **LEZYNCET-M** is Levocetirizine Hydrochloride and Montelukast.

The excipients used are Microcrystalline Cellulose Powder, Lactose, PVPK-30, Talcum, Magnesium Stearate, Sunset Yellow Lake colour, Croscarmellose Sodium, ICS 329 Transparent, Isopropyl Alcohol and Methylene Chloride.

10. Details of manufacturer

Manufactured in India by:

Ravenbhel Healthcare Pvt Ltd.

(WHO & cGMP Certified Company)

16-17, EPIP, SIDCO, Kartholi, Bari-Brahmana, Jammu – 181133.

11. Details of permission or licence number with date

Mfg Lic No. JK/01/56 issued on 24.05.2018

12. Date of revision

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/LEZYNCET-M/5, 10 mg/APR-20/01/PI