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

# LEZYNCET M

## 1. Generic Name

Levocetirizine Dihydrochloride & Montelukast Oral Suspension

## 2. Qualitative and quantitative composition

Each 5ml contains:

Levocetirizine Dihydrochloride I.P. ...2.5mg

Excipients……...q.s.

Montelukast Sodium I.P. eq. to Anhydrous Montelukast 4.0 mg

Colour: Titanium dioxide I.P.

The excipients used are Sucrose, Methyl Paraben, Propyl Paraben, Glycerin, Polysorbate 80, Xanthan Gum, Colloidal Silicon Dioxide, Microcrystalline Cellulose, Saccharin Sodium, Aspartame, Flavour Strawberry, Citric Acid Monohydrate, Sodium Citrate and Colour Sunset Yellow.

## 3. Dosage form and strength

**Dosage Form:** Oral Suspension

**Strength:** Levocetirizine dihydrochloride 2.5 mg and Anhydrous Montelukast 4.0 mg per 5ml.

## 4. Clinical particulars

### 4.1 Therapeutic indication

For the treatment of Allergic Rhinitis in Children aged 2 years and above

### 4.2 Posology and Method of administration

**Posology**

**Children 2 years and above**

The recommended daily dose of suspension is 2.5 mg levocetirizine and 4.0 mg montelukast (5 ml solution).

For 15 years and above, Lezyncet M tablets is preferred.

**Renal impairment**

In paediatric patients suffering from renal impairment, the dose will have to be adjusted on an individual basis taking into account the renal clearance of the patient and his body weight. There are no specific data for children with renal impairment.

**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**

Shake well before use. The appropriate volume of suspension should be measured with dosing cup, and poured in a spoon or in a glass of water. The oral suspension must be taken orally, and may be taken with or without food.

## 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.

**Paediatric population**

Even if some clinical data are available in children aged 6 months to 12 years, these data are not sufficient to support the administration of the drug to infants and toddlers aged less than 2 years.

**Montelukast**

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 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.

Lezyncet M contains aspartame, a source of phenylalanine. Patients with phenylketonuria should take into account that each 5 ml solution contains phenylalanine in an amount equivalent to 0.674 mg phenylalanine per dose.

## 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 ≥1/1000, <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%).

**Paediatric population**

In two placebo-controlled studies in paediatric patients aged 6-11 months and aged 1 year to less than 6 years, 159 subjects were exposed to levocetirizine at the dose of 1.25mg daily for 2 weeks and 1.25mg twice daily respectively. The following incidence of adverse drug reactions was reported at rates of 1% or greater under levocetirizine or placebo.

| System Organ Class and Preferred Term | Placebo (n=83) | Levocetirizine (n=159) |
|---|---|---|
| **Gastrointestinal disorders** | | |
| Diarrhoea | 0 | 3(1.9%) |
| Vomiting | 1(1.2%) | 1(0.6%) |
| Constipation | 0 | 2(1.3%) |
| **Nervous system disorders** | | |
| Somnolence | 2(2.4%) | 3(1.9%) |
| **Psychiatric disorders** | | |
| Sleep disorder | 0 | 2(1.3%) |

***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 reported clinical studies were reported commonly (≥1/100 to 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 |

With prolonged treatment in clinical trials with a limited number of patients for up to 2 years for adults, and up to 12 months for paediatric patients 6 to 14 years of age, the safety profile did not change.

**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 |

| System Organ Class | Adverse Reactions | Frequency Category* |
|---|---|---|
| | 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), obsessive-compulsive symptoms, dysphemia | Very Rare |
| Nervous system disorders | dizziness, drowsiness, paraesthesia/hypoesthesia, seizure | Uncommon |
| Cardiac disorders | palpitations | Rare |
| Respiratory, thoracic and mediastinal disorders | epistaxis | Uncommon |
| | Churg-Strauss Syndrome (CSS) | Very Rare |
| | pulmonary eosinophilia | Very Rare |
| Gastro-intestinal disorders | diarrhoea‡, nausea‡, vomiting‡ | Common |
| | dry mouth, dyspepsia | Uncommon |
| | elevated levels of serum transaminases (ALT, AST) | Common |
| Hepatobiliary disorders | 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 |
| | pyrexia‡ | Common |

| System Organ Class | Adverse Reactions | Frequency Category* |
|---|---|---|
| General disorders and administration site conditions | 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 suspected adverse reactions**

If you get any side effects, talk to your doctor 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 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, decreasedperipheral 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.

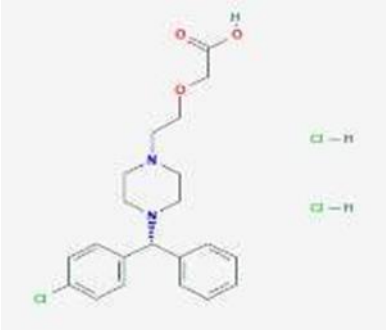
**Montelukast**

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

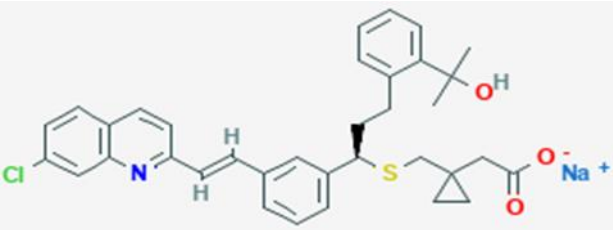
**Levocetirizine Dihydrochloride**

Levocetirizine Dihydrochloride is chemically 2-[2-[4-[(R)-(4-chlorophenyl)-phenylmethyl]piperazin-1-yl]ethoxy]acetic acid; dihydrochloride having molecular weight of 461.8 g/mol and molecular formula is $C_{21}H_{27}Cl_3N_2O_3$ and the chemical structure is:



**Montelukast Sodium**

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:



Levocetirizine Dihydrochloride & Montelukast Sodium Suspension are orange coloured, viscous suspension, 60ml filled in amber colour PET bottle. The excipients used are Sucrose, Methyl Paraben, Propyl Paraben, Glycerin, Polysorbate 80, Xanthan Gum, Colloidal Silicon Dioxide, Microcrystalline Cellulose, Saccharin Sodium, Aspartame, Flavour Strawberry, Citric Acid Monohydrate, Sodium Citrate and Colour Sunset Yellow.

## 8. Pharmaceutical Particulars

### 8.1 Incompatibilities

Not applicable

### 8.2 Shelf-life

Do not use later than the date of expiry.

### 8.3 Packing Information

LEZYNCET-M Suspension is available in bottle of 60 ml.

### 8.4 Storage and handling instructions

Store protected from light & moisture, at a temperature not exceeding 30°C.

## 9 Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness

- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

**10. Details of manufacturer**

Manufactured in India by:

Akums Drugs and Pharmaceuticals Ltd.

22, Sector-6A, I.I.E., SIDCUL, Haridwar – 249403, Uttarakhand.

**11. Details of permission or licence number with date**

Mfg Lic No. 123/UA/2007 issued on 10.08.2015

**12. Date of revision**

MAR 2025

**MARKETED BY**

TORRENT PHARMACEUTICALS LTD.

**IN/LEZYNCET-M/2.5, 4.0 mg /MAR-2025/02/PI**