# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Montelukast and Levocetirizine dihydrochloride

Allercet M

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Montelukast sodium IP equivalent to Montelukast ……10mg

Levocetirizine Dihydrochloride IP …….5mg

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film **c**oated Tablets

Yellow, circular, biconvex film-coated tablets with MICRO/MICRO engraved on both sides

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Montelukast and Levocetirizine is indicated for the relief of symptoms of allergic rhinitis (Seasonal and Pernnial) Montelukast and Levocetirizine is also indicated in the treatment of asthma as add-on therapy in those patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom "as-needed" short acting β-agonists provide inadequate clinical control of asthma. In those asthmatic patients in whom Montelukast is indicated in asthma, Montelukast can also provide symptomatic relief of seasonal allergic rhinitis.

Montelukast and Levocetirizine are also indicated for relief of prophylaxis in seasonal allergic rhinitis and treatment of comorbid asthma in patients 15 years of age and over.

## 4.2 Posology and method of administration

Posology

Montral Tablets

Adults and Adolescents 15 years of age and older)

1 tablet once daily

The recommended dose for adults and adolescents 15 years of age and older with asthma, or with asthma and concomitant seasonal allergic rhinitis is one tablet once daily.

Montral tablets can be added to a patient's existing treatment regimen.

General recommendations

Montral tablets may be taken with or without food.

The dosage is the same for both male and female patients

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients

Patients with severe renal impairment at less than 10 ml/min creatinine clearance

## 4.4 Special warnings and precautions for use

***Montelukast***

Patients should be advised never to use oral montelukast to treat acute asthma attacks and to keep their usual appropriate rescue medication for this purpose readily available. If an acute attack occurs, a short-acting inhaled β-agonist should be used. Patients should seek their doctors' advice as soon as possible if they need more inhalations of short-acting β-agonists than usual.

Montelukast should not be substituted abruptly for inhaled or oral corticosteroids.

There are no data demonstrating that oral corticosteroids can be reduced when montelukast is given concomitantly.

In rare cases, patients on therapy with anti-asthma agents including 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.

Treatment with montelukast does not alter the need for patients with aspirin-sensitive asthma to avoid taking aspirin and other non-steroidal anti-inflammatory drugs.

***Levocetirizine***

*Paediatric Population*

The use of the film-coated tablet formulation is not recommended in children aged less than 6 years since this formulation does not allow for appropriate dose adaptation. It is recommended to use a paediatric formulation of 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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**4.5 Interaction with other medicinal products and other forms of interaction**

***Montelukast***

Montelukast may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma. In drug-interactions studies, the recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following medicinal products: theophylline, prednisone, prednisolone, oral contraceptives (ethinyl estradiol/norethindrone 35/1), terfenadine, digoxin and warfarin.

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.

*In vitro* studies have shown that montelukast is a potent inhibitor of CYP 2C8. However, data from a clinical drug-drug interaction study involving montelukast and rosiglitazone (a probe substrate representative of medicinal products primarily metabolized by CYP 2C8) demonstrated that montelukast does not inhibit CYP 2C8 *in vivo.* Therefore, montelukast is not anticipated to markedly alter the metabolism of medicinal products metabolised by this enzyme (e.g., paclitaxel, rosiglitazone, and repaglinide).

*In vitro* studies have shown that montelukast is a substrate of CYP 2C8, and to a less significant extent, of 2C9, and 3A4. In a clinical drug-drug interaction study involving montelukast and gemfibrozil (an inhibitor of both CYP 2C8 and 2C9) gemfibrozil increased the systemic exposure of montelukast by 4.4-fold. No routine dosage adjustment of montelukast is required upon co-administration with gemfibrozil or other potent inhibitors of CYP 2C8, but the physician should be aware of the potential for an increase in adverse reactions.

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.

***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.

**4.6 Pregnancy and lactation**

***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.

Montelukast may be used in breast-feeding only if it is considered to be clearly essential.

***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.

**4.7 Effects on ability to drive and use machines**

It has no or negligible influence on the ability to drive and use machines. However, individuals have reported drowsiness or dizziness.

**4.8 Undesirable effects**

***Montelukast***

Montelukast has been evaluated in clinical studies as follows:

- 10 mg film-coated tablets in approximately 4,000 adult and adolescent asthmatic patients 15 years of age and older.
- 10 mg film-coated tablets in approximately 400 adult and adolescent asthmatic patients with seasonal allergic rhinitis 15 years of age and older.
- 5 mg chewable tablets in approximately 1,750 paediatric asthmatic patients 6 to 14 years of age.

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

| **Body System Class** | **Adult and Adolescent Patients** | **Paediatric Patients** |
|---|---|---|

| | **15 years and older (two 12-week studies; n=795)** | **6 to 14 years old (one 8-week study; n=201) (two 56-week studies; n=615)** |
|---|---|---|
| **Nervous system disorders** | headache | headache |
| **Gastro-intestinal disorders** | abdominal pain | |

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 |
| 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, | Uncommon |

| | | |
|---|---|---|
| | restlessness, tremor[§]) | |
| | disturbance in attention, memory impairment | Rare |
| | hallucinations, disorientation, suicidal thinking and behaviour (suicidality) | 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 |
| Gastrointestinal 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 |

| | | |
|---|---|---|
| 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

***Levocetirizine***

*Adults and adolescents above 12 years of age:*

In 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 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%).

***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%) |

In children aged 6-12 years double blind placebo controlled studies were performed where 243 children were exposed to 5mg Levocetirizine daily for variable periods ranging from less than 1 week to 13 weeks. The following incidence of adverse drug reactions was reported at rates of 1% or greater under Levocetirizine or placebo.

| **Preferred Term** | **Placebo (n=240)** | **Levocetirizine 5mg (n=243)** |
|---|---|---|
| Headache | 5(2.1%) | 2(0.8%) |

| | | |
|---|---|---|
| Somnolence | 1(0.4%) | 7(2.9%) |

***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

• 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

• 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

**4.9 Overdose**

***Montelukast***

In chronic asthma studies, montelukast has been administered at doses up to 200 mg/day to adult patients for 22 weeks and in short term studies, up to 900 mg/day to patients for approximately one week without clinically important adverse experiences.

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 dialyzable by peritoneal- or hemodialysis.

***Levocetirizine***

Symptoms

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

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 hemodialysis.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

***Montelukast***

The cysteinyl Leukotrienes ($LTC_4$, $LTD_4$, $LTE_4$) are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important pro-asthmatic mediators bind to cysteinyl leukotriene (CysLT) receptors. The CysLT type-1 ($CysLT_1$) receptor is found in the human airway (including airway smooth muscle cells and airway macrophages) and on other pro-inflammatory cells (including eosinophils and certain myeloid stem cells). CysLTs have been correlated with the pathophysiology of asthma and allergic rhinitis. In asthma, leukotriene-mediated effects include bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment. In allergic rhinitis, CysLTs are released from the nasal mucosa after allergen exposure during both early- and late-phase reactions and are associated with symptoms of allergic rhinitis. Intranasal challenge with CysLTs has been shown to increase nasal airway resistance and symptoms of nasal obstruction.

***Levocetirizine***

Levocetirizine, the (R) enantiomer of cetirizine, is a potent and selective antagonist of peripheral H1-receptors.

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 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.

## 5.2 Pharmacokinetic properties

***Absorption***

*Montelukast*

Montelukast is rapidly absorbed following oral administration. For the 10 mg film-coated tablet, the mean peak plasma concentration ($C_{max}$) is achieved 3 hours ($T_{max}$) after administration in adults in the fasted state. The mean oral bioavailability is 64%. The oral bioavailability and $C_{max}$ 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.

For the 5 mg chewable tablet, the $C_{max}$ is achieved in 2 hours after administration in adults in the fasted state. The mean oral bioavailability is 73% and is decreased to 63% by a standard meal.

*Levocetirizine*

Levocetirizine is rapidly and extensively absorbed following oral administration. 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***

*Montelukast*

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.

*Levocetirizine*

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 Human, levocetirizine is 90% bound to plasma proteins. The distribution of levocetirizine is restrictive, as the volume of distribution is 0.4 l/kg.

***Biotransformation***

*Montelukast*

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.

*Levocetirizine*

The extent of metabolism of levocetirizine in humans is less than 14% of the dose and therefore differences resulting from genetic polymorphism or concomitant intake of enzyme inhibitors are expected to be negligible. Metabolic pathways include aromatic oxidation, N- and O-dealkylation and taurine conjugation. Dealkylation pathways are primarily mediated by CYP 3A4 while aromatic oxidation involved multiple and/or unidentified CYP isoforms. Levocetirizine had no effect on the activities of CYP isoenzymes 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 at concentrations well above peak concentrations achieved following a 5 mg oral dose.

Due to its low metabolism and absence of metabolic inhibition potential, the interaction of levocetirizine with other substances, or vice-versa, is unlikely.

***Elimination***

*Montelukast*

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 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.

*Levocetirizine*

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.

***Characteristics in Patients***

*Montelukast*

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), decrease in plasma theophylline concentration was observed. This effect was not seen at the recommended dose of 10 mg once daily.

***Levocetirizine***

***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 $C_{max}$ and AUC values are about 2-fold greater than that reported in healthy adult subjects in a cross-study comparison. The mean $C_{max}$ 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 324 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.

Older people: 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.

**5.3 Preclinical safety data**

***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. In monkeys, the adverse effects appeared at doses from 150 mg/kg/day (>232-fold the systemic exposure seen at the clinical dose). In animal studies, montelukast did not affect fertility or reproductive performance at systemic exposure exceeding the clinical systemic exposure by greater than 24-fold. A slight decrease in pup body weight was noted in the female fertility study in rats at 200 mg/kg/day (>69-fold the clinical systemic exposure). In studies in rabbits, a higher incidence of incomplete ossification, compared with concurrent control animals, was seen at systemic exposure>24-fold the clinical systemic exposure seen at the clinical dose.

No abnormalities were seen in rats. Montelukast has been shown to cross the placental barrier and is excreted in breast milk of animals.

No deaths occurred following a single oral administration of montelukast sodium at doses up to 5000 mg/kg in mice and rats (15,000 mg/m2 and 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 determined not to be phototoxic in mice for UVA, UVB or visible light spectra at doses up to 500 mg/kg/day (approximately>200-fold based on systemic exposure). Montelukast was neither mutagenic in in vitro and in vivo tests nor tumorigenic in rodent species.

***Levocetrizine***

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.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

LACTOSE IP(PHARMATOSE DCL 15)

PREGE.STARCH (STARCH 1500)

CROSS POVIDONE TYPE-A (POLYPLASDONE-XL)

TALC

MAGNESIUM STEARATE

H.P.M.C 15 CPS

TITANIUM DIOXIDE

IRON OXIDE YELLO

### 6.2 Incompatibilities

Not Applicable

### 6.3 Shelf life

The Shelf life is 36 months from the date of manufacture

### 6.4 Special precautions for storage

Store below 30˚C. Keep out from the reach of the children

### 6.5 Nature and contents of container

Blister Pack of 10 tablets

### 6.6 Special precautions for disposal and other handling

No Special requirements.

### 7. Marketing Authorization Holder

**MICRO LABS LIMITED**

31, Race course road

Bangalore-560001

INDIA

## 8. Number from the register of medicinal product.

Not applicable

## 9. Date of authorization or of the last renewal of the authorization

Not applicable

## 10. Date of revision of the text

July 2020