SUMMARY OF PRODUCT CHARACTERISITICS

1. NAME OF THE MEDICINAL PRODUCT:

Brand name: BREATHEZY-L (10/5)
Generic name: Montelukast sodium 10 mg and Levocetirizine Dihydrochloride 5 mg tablets
Strength: Montelukast sodium 10 mg and Levocetirizine Dihydrochloride 5 mg
Dosage form: Film coated bilayered tablets.

2. QUALITATIVE & QUANTITATIVE COMPOSITION

Label claim
Each film coated tablet contains Montelukast sodium Ph.Eur equivalent to Montelukast 10 mg
Levocetirizine Dihydrochloride 5 mg
Excipients (please refer section 6.1)

3. PHARMACEUTICAL FORM

Film coated bilayered tablets

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Montelukast sodium is 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.
Levocetirizine Dihydrochloride is indicated for Symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis) and urticaria.

4.2 Posology and method of administration

Montelukast

The dosage for paediatric patients 6-14 years of age is one 5 mg tablet daily to be taken in the evening. If taken in connection with food, should be taken 1 hour before or 2 hours after food. No dosage adjustment within this age group is necessary.
General recommendations:
The therapeutic effect of Montelukast on parameters of asthma control occurs within one day. Patients should be advised to continue taking Montelukast even if their asthma is under control, as well as during periods of worsening asthma.
No dosage adjustment is necessary for patients with renal insufficiency, or mild to moderate hepatic impairment. There are no data on patients with severe hepatic impairment. The dosage is the same for both male and female patients.
Montelukast as an alternative treatment option to low-dose inhaled corticosteroids for mild persistent asthma:
Montelukast is not recommended as monotherapy in patients with moderate persistent asthma. The use of montelukast as an alternative treatment option to low-dose inhaled corticosteroids for children with mild persistent asthma should only be considered for patients who do not have a recent history of serious asthma attacks that required oral corticosteroid use and who have demonstrated that they are not capable of using inhaled corticosteroids (see section 4.1). Mild persistent asthma is defined as asthma symptoms more than once a week but less than once a day, nocturnal symptoms more than twice a month but less than once a week, normal lung

function between episodes. If satisfactory control of asthma is not achieved at follow-up (usually within one month), the need for an additional or different anti-inflammatory therapy based on the step system for asthma therapy should be evaluated. Patients should be periodically evaluated for their asthma control.

Therapy with Montelukast in relation to other treatments for asthma.

When treatment with Montelukast is used as add-on therapy to inhale corticosteroids, Montelukast should not be abruptly substituted for inhaled corticosteroids.

10 mg tablets are available for adults 15 years of age and older.

Levocetirizine Dihydrochloride:

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.

Adults and adolescents 12 years and above:

The daily recommended dose is 5 mg (1 film-coated tablet).

Elderly:

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

Children aged 6 to 12 years:

The daily recommended dose is 5 mg (1 film-coated tablet).

For children aged 2 to 6 years no adjusted dosage is possible with the film-coated tablet formulation. It is recommended to use a paediatric formulation of levocetirizine.

Patients with renal impairment:

The dosing intervals must be individualized 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.

Group	Creatinine clearance (ml/min)	Dosage and frequency
Normal	≥80	1 tablet once daily
Mild	50 – 79	1 tablet once daily
Moderate	30 – 49	1 tablet once every 2 days
Severe	< 30	1 tablet once every 3 days
End-stage renal disease – Patients undergoing dialysis	< 10-	Contra-indicated

In pediatric 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.

Patients with 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 Patients with renal impairment above).

Duration of use:

Intermittent allergic rhinitis (symptoms <4days/week or during less than 4 weeks) has to be treated according to the disease and its history; it can be stopped once the symptoms have disappeared and can be restarted again when symptoms reappear. In case of persistent allergic rhinitis (symptoms >4days/week and during more than 4 weeks), continuous therapy can be

proposed to the patient during the period of exposure to allergens. Clinical experience with 5 mg levocetirizine as a filmcoated tablet formulation is currently available for a 6-month treatment period. For chronic urticaria and chronic allergic rhinitis, up to one year's clinical experience is available for the racemate.

Legal Category: POM

4.3 Contraindications

Montelukast:
Hypersensitivity to the active substance or to any of the excipients.
Levocetirizine Dihydrochloride:
Hypersensitivity to levocetirizine, to other piperazine derivatives, or to any of the excipients.
Patients with severe renal impairment at less than 10 ml/min creatinine clearance.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use
Montelukast sodium 10 mg
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 doctor's advice as soon as possible if they need more inhalations of short-acting β-agonists than usual.
Montelukast should not be abruptly substituted 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 usually, but not always, have been associated with the reduction or withdrawal of oral corticosteroid therapy. The possibility that leukotriene receptor antagonists may be associated with emergence of Churg-Strauss syndrome can neither be excluded nor 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.

Levocetirizine Dihydrochloride 5 mg
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.
The administration of levocetirizine to infants and toddlers aged less than 2 years is not recommended. Precaution is recommended with intake of alcohol (see Interactions).

4.5 Interaction with other medicinal products and other forms of interaction

Montelukast sodium:
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 oestradiol/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, caution should be exercised, particularly in children, when montelukast is co-administered with inducers of CYP 3A4, 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 metabolised 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 (eg., paclitaxel, rosiglitazone, and repaglinide).

Levoxetirizine Dihydrochloride:
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 pseudoephedrine, cimetidine, ketoconazole, erythromycin, azithromycin, glipizide and diazepam). 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.
The extent of absorption of levocetirizine is not reduced with food, although the rate of absorption is decreased.
In sensitive patients the simultaneous administration of cetirizine or levocetirizine and alcohol or other CNS depressants may have effects on the central nervous system, although it has been shown that the racemate cetirizine does not potentiate the effect of alcohol.

4.6 Pregnancy and lactation

Montelukast:
Use during 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 Motelukast and malformations (i.e. limb defects) that have been rarely reported in worldwide post marketing experience.
Motelukast may be used during pregnancy only if it is considered to be clearly essential.
Use during lactation
Studies in rats have shown that montelukast is excreted in milk. It is not known if montelukast is excreted in human milk.
Motelukast may be used in breast-feeding mothers only if it is considered to be clearly essential.

Levoxetirizine Dihydrochloride:
For levocetirizine no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. Caution should be exercised when prescribing to pregnant or lactating women.

4.7 Effects on ability to drive and use machines

Montelukast:
Montelukast is not expected to affect a patient's ability to drive a car or operate machinery.
However, in very rare cases, individuals have reported drowsiness or dizziness.

Levocetirizine Dihydrochloride:
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 cetirizine. 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
Montelukast sodium:
Montelukast has been evaluated in clinical studies as follows:
• 10 mg film-coated tablets in approximately 4,000 adult patients 15 years of age and older, and
• 5 mg chewable tablets in approximately 1,750 paediatric patients 6 to 14 years of age.
The following drug-related adverse reactions in clinical studies were reported commonly (01/100 to <1/10) in patients treated with montelukast and at a greater incidence than in patients treated with placebo:

Body System Class	**Adult 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)**
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.
The following adverse reactions have been reported in post-marketing use:

Infections and infestations: upper respiratory infection.

Blood and lymphatic system disorders: increased bleeding tendency.

Immune system disorders: hypersensitivity reactions including anaphylaxis, hepatic eosinophilic infiltration.

Psychiatric disorders: dream abnormalities including nightmares, hallucinations, insomnia, somnambulism, irritability, anxiety, restlessness, agitation including aggressive behaviour or hostility, tremor, depression, suicidal thinking and behaviour (suicidality) in very rare cases.

Nervous system disorders: dizziness, drowsiness, paraesthesia/hypoesthesia, seizure.

Cardiac disorders: palpitations.

Respiratory, thoracic and mediastinal disorders: epistaxis.

Gastro-intestinal disorders: diarrhoea, dry mouth, dyspepsia, nausea, vomiting.

Hepatobiliary disorders: elevated levels of serum transaminases (ALT, AST), hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury).

Skin and subcutaneous tissue disorders: angio-oedema, bruising, urticaria, pruritus, rash, erythema nodosum.

Musculoskeletal and connective tissue disorders: arthralgia, myalgia including muscle cramps.

General disorders and administration site conditions: asthenia/fatigue, malaise, oedema, pyrexia.
Very rare cases of Churg-Strauss Syndrome (CSS) have been reported during montelukast treatment in asthmatic patients. ***Levocetirizine Dihydrochloride:***
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 drug 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, <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 were altogether more common (8.1%) under levocetirizine 5 mg than under placebo (3.1%).
In addition to the adverse reactions reported during clinical studies and listed above, very rare cases of the following adverse drug reactions have been reported in post-marketing experience.
• Immune system disorders: hypersensitivity including anaphylaxis
• Psychiatric disorders: aggression, agitation
• Nervous system disorders: convulsion
• Eyes disorders: visual disturbances
• Cardiac disorders: palpitations
• Respiratory, thoracic, and mediastinal disorders: dyspnoea
• Gastrointestinal disorders: nausea
• Hepatobiliary disorders: hepatitis

- Skin and subcutaneous tissue disorders: angioneurotic oedema, fixed drug eruption, pruritus, rash, urticaria
- Musculoskeletal, connective tissues, and bone disorders: myalgi**a**
- Investigations: weight increased, abnormal liver function tests

4.9 Overdose

Montelukast sodium

No specific information is available on the treatment of overdose with montelukast. In chronic asthma studies, montelukast has been administered at doses up to 200 mg/day to 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 1000 mg (approximately 61 mg/kg in a 42month 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. The most frequently occurring adverse experiences were consistent with the safety profile of montelukast and included abdominal pain, somnolence, thirst, headache, vomiting, and psychomotor hyperactivity.

It is not known whether montelukast is dialysable by peritoneal- or haemo-dialysis.

Levocetirizine Dihydrochloride: a) Symptoms

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

There is no known specific antidote to levocetirizine.

Should overdose occur, symptomatic or supportive treatment is recommended. Gastric lavage should be considered following short-term ingestion. Levocetirizine is not effectively removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties *Montelukast Sodium*

Pharmacotherapeutic group: Leukotriene receptor antagonist

ATC Code: RO3D CO3

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 receptors (CysLT) found in the human airway and cause airway actions, including bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment. Montelukast is an orally active compound which binds with high affinity and selectivity to the $CysLT_1$ receptor. In clinical studies, montelukast inhibits bronchoconstriction due to inhaled LTD_4 at doses as low as 5 mg. Bronchodilation was observed within two 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) and in peripheral blood while improving clinical asthma control.

In studies in adults, montelukast 10 mg once daily, compared with placebo, demonstrated significant improvements in morning FEV_1 (10.4% vs 2.7% change from baseline), AM peak expiratory flow rate (PEFR) (24.5 L/min vs 3.3 L/min change from baseline), and significant decrease in total β-agonist use (-26.1% vs -4.6% change from baseline). Improvement in

patientreported daytime and nighttime asthma symptoms scores was significantly better than placebo.
Studies in adults demonstrated the ability of montelukast to add to the clinical effect of inhaled corticosteroid (% change from baseline for inhaled beclometasone plus montelukast vs beclometasone, respectively for FEV_1 : 5.43% vs 1.04%; β-agonist use: -8.70% vs 2.64%). Compared with inhaled beclometasone (200 μg twice daily with a spacer device), montelukast demonstrated a more rapid initial response, although over the 12-week study, beclometasone provided a greater average treatment effect (% change from baseline for montelukast vs beclometasone, respectively for FEV_1 : 7.49% vs 13.3%; β-agonist use: -28.28% vs -43.89%). However, compared with beclometasone, a high percentage of patients treated with montelukast achieved similar clinical responses (e.g. 50% of patients treated with beclometasone achieved an improvement in FEV_1 of approximately 11% or more over baseline while approximately 42% of patients treated with montelukast achieved the same response).
In an 8-week study in paediatric patients 6 to 14 years of age, montelukast 5 mg once daily, compared with placebo, significantly improved respiratory function (FEV_1 8.71% vs 4.16% change from baseline; AM PEFR 27.9 L/min vs 17.8 L/min change from baseline) and decreased 'asneeded' β-agonist use (-11.7% vs +8.2% change from baseline).
In a 12-month study comparing the efficacy of montelukast to inhaled fluticasone on asthma control in paediatric patients 6 to 14 years of age with mild persistent asthma, montelukast was non-inferior to fluticasone in increasing the percentage of asthma rescue-free days (RFDs), the primary endpoint. Averaged over the 12-month treatment period, the percentage of asthma RFDs increased from 61.6 to 84.0 in the montelukast group and from 60.9 to 86.7 in the fluticasone group. The between group difference in LS mean increase in the percentage of asthma RFDs was statistically significant (-2.8 with a 95% CI of -4.7, -0.9), but within the limit pre-defined to be clinically not inferior. Both montelukast and fluticasone also improved asthma control on secondary variables assessed over the 12-month treatment period:

- FEV_1 increased from 1.83 L to 2.09 L in the montelukast group and from 1.85 L to 2.14 L in the fluticasone group. The between-group difference in LS mean increase in FEV_1 was -0.02 L with a 95% CI of -0.06, 0.02. The mean increase from baseline in % predicted FEV_1 was 0.6% in the montelukast treatment group, and 2.7% in the fluticasone treatment group. The difference in LS means for the change from baseline in the % predicted FEV_1 was -2.2% with a 95% CI of -3.6, -0.7.
- The percentage of days with β-agonist use decreased from 38.0 to 15.4 in the montelukast group, and from 38.5 to 12.8 in the fluticasone group. The between group difference in LS means for the percentage of days with β-agonist use was 2.7 with a 95% CI of 0.9, 4.5.
- The percentage of patients with an asthma attack (an asthma attack being defined as a period of worsening asthma that required treatment with oral steroids, an unscheduled visit to the doctor's office, an emergency room visit, or hospitalisation) was 32.2 in the montelukast group and 25.6 in the fluticasone group; the odds ratio (95% CI) being significant: equal to 1.38 (1.04, 1.84).
- The percentage of patients with systemic (mainly oral) corticosteroid use during the study period was 17.8% in the montelukast group and 10.5% in the fluticasone group. The between group difference in LS means was significant: 7.3% with a 95% CI of 2.9; 11.7.

Significant reduction of exercise-induced bronchoconstriction (EIB) was demonstrated in a 12-week study in adults (maximal fall in FEV_1 22.33% for montelukast vs 32.40% for placebo; time to recovery to within 5% of baseline FEV_1 44.22 min vs 60.64 min). This effect was consistent throughout the 12-week study period. Reduction in EIB was also demonstrated in a short-term study in paediatric patients (maximal fall in FEV_1 18.27% vs 26.11%; time to recovery to within 5% of baseline FEV_1 17.76 min vs 27.98 min). The effect in both studies was demonstrated at the end of the once-daily dosing interval.

In aspirin-sensitive asthmatic patients receiving concomitant inhaled and/or oral corticosteroids, treatment with montelukast, compared with placebo, resulted in significant improvement in asthma control (FEV_1 8.55% vs -1.74% change from baseline and decrease in total β-agonist use -27.78% vs 2.09% change from baseline).

Levocetirizine Dihydrochloride:

Pharmacotherapeutic group: antihistamine for systemic use, piperazine derivative

ATC Code: R06A E09

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 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.

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

In a study comparing the effects of levocetirizine 5mg, desloratadine 5mg, 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.

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.

A 6-month clinical study in 551 adult patients (including 276 levocetirizine-treated patients) suffering from persistent allergic rhinitis (symptoms present 4 days a week for at least 4 consecutive weeks) and sensitized to house dust mites and grass pollen demonstrated that levocetirizine 5 mg was clinically and statistically significantly more potent than placebo on the relief from the total symptom score of allergic rhinitis throughout the whole duration of the study, without any tachyphylaxis. During the whole duration of the study, levocetirizine significantly improved the quality of life of the patients.

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 a placebo-controlled clinical trial including 166 patients suffering from chronic idiopathic urticaria, 85 patients were treated with placebo and 81 patients with levocetirizine 5mg once daily over six weeks. Treatment with levocetirizine resulted in significant decrease in pruritus severity over the first week and over the total treatment period as compared to placebo. Levocetirizine also resulted in a larger improvement of health-related quality of life as assessed by the Dermatology Life Quality Index as compared to placebo.
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.
Pharmacokinetic / pharmacodynamic relationship:

The action on histamine-induced skin reactions is out of phase with the plasma concentrations. ECGs did not show relevant effects of levocetirizine on QT interval.

5.2 Pharmacokinetic properties *Montelukast Sodium*

Absorption: Montelukast is rapidly absorbed following oral administration. For the 10 mg filmcoated tablet, the mean peak plasma concentration (Cmax) is achieved three hours (Tmax) 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 two hours after administration in adults in the fasted state. The mean oral bioavailability is 73% and is decreased to 63% by a standard meal.
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.
In vitro studies using human liver microsomes indicate that cytochromes P450 3A4, 2A6 and 2C9 are involved in the metabolism of montelukast. Based on further *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. This effect was not seen at the recommended dose of 10 mg once daily.

Levocetirizine Dihydrochloride:

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

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

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

Biotransformation:

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

Elimination:

The plasma half-life in adults is 7.9 ± 1.9 hours. The mean apparent total body clearance is 0.63 ml/min/kg. The major route of excretion of levocetirizine and metabolites is via urine, accounting for a mean of 85.4% of the dose. Excretion via feces accounts for only 12.9% of the dose.

Levocetirizine is excreted both by glomerular filtration and active tubular secretion.

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%.

5.3 Preclinical safety data

Montelukast Sodium:

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/m^2 and 30,000 mg/m^2 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.

Levocetirizine Dihydrochloride:
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
Core: Lactose monohydrate, Microcrystalline cellulose pH 112, Croscarmellose sodium, Hydroxy propyl cellulose, Magnesium stearate,, Yellow oxide of iron, Colloidal silicon dioxide, *Coating:* Instacoat aqua IC-A-329, Purified water.

6.2 Incompatibilities
Not Applicable.

6.3 Shelf life
24Months

6.4 Special precautions for storage
Do not store above 30°C Protect from moisture. Keep out of reach of children

6.5 Nature and contents of container
10 tablets of Montelukast Sodium 10 mg and Levocetirizine 5 mg tablets are sealed with Plain aluminium Base foil on one side and printed Aluminium lid foil on the other side in the form of a Alu-Alu Blister pack and 1 or 3 such Alu-Alu Blister packs are further packed in a printed carton along with a leaflet.

6.6 Special precautions for disposal and other handling
No special requirements.

7. MARKETING AUTHORIZATION HOLDER:

MSN Laboratories Private Limited - Formulation Division
MSN House, Plot No. : C-24, Industrial Estate, Sanath Nagar, Hyderabad – 500 018 Telangana, India.

8. MARKETING AUTHORISATION NUMBER

144/RWANDA FDA/2018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First Authorization: 31 December 2018

10. DATE OF REVISION OF THE TEXT

March 2017