SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Glemont L (Montelukast Sodium & Levocetirizine Dihydrochloride Tablets (10mg + 5mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:
Montelukast Sodium equivalent to Montelukast 10 mg
Levocetirizine Dihydrochloride 5 mg
Colours: Ferric Oxide Yellow USPNF, Ferric Oxide Red USPNF & Titanium Dioxide USP

3. PHARMACEUTICAL FORM

Film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Montelukast Sodium/Levocetirizine dihydrochloride 10/5mg film-coated tablets are indicated for the relief of symptoms associated with seasonal allergic rhinitis.

4.2 Posology and Method of Administration

Adult Patient (≥18 years of age): The recommended dose is one tablet to be taken orally, in the evening. The tablets should be swallowed whole with or without food.

Paediatric and Adolescent (<18 years): Since this product has not been studied in the adolescent and paediatric population this medicinal product is not recommended in this age group.

Patients with renal impairment: No dose adjustment is needed in patients with mild renal impairment (creatinine clearance >79 ml/min). For patients with moderate to severe renal impairment (creatinine clearance <79 ml/min - >10ml/min), this product is to be used with caution and under strict medical supervision.

Patients with hepatic impairment: No dose adjustment is needed in patients with hepatic impairment.

4.3 Contraindications

- Hypersensitivity to the active substance, to cetirizine, to hydroxyzine, to any 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
Patients should be advised never to use this fixed dose combination of Montelukast and Levocetirizine to treat acute asthma attacks and to keep their usual appropriate rescue medication for this purpose readily available. If an acute attack occurs, 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 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.

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

Neuropsychiatric events have been reported in adults, adolescents, and children taking montelukast. Patients and physicians should be alert for neuropsychiatric events. Patients and/or caregivers should be instructed to notify their physician if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with montelukast if such events occur.

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.

The fixed dose combination of Montelukast and Levocetirizine contains lactose as an inactive ingredient so 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

No specific drug-drug interaction studies have been performed with the fixed dose combination of Montelukast and Levocetirizine. The data is complied with the available information from the individual components of the fixed dose combination. Also since both Montelukast and Levocetirizine metabolizes with different receptors there are no drug-drug interaction anticipated with the use of this fixed dose combination.

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 pseudoephedrine, antipyrine, 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.

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 Fertility, Pregnancy and lactation

No specific studies have been performed with the FDC of Montelukast and Levocetirizine on pregnant and lactating females.

Use during pregnancy
***Montelukast*:** Animal studies do not indicate harmful effects with respect to effects on pregnancy or embryonal/foetal development. Available data from published prospective and retrospective cohort studies with montelukast use in pregnant women evaluating major birth defects have not established a drug-associated risk. Available studies have methodologic limitations, including small sample size, in some cases retrospective data collection, and inconsistent comparator groups.

Montelukast may be used during pregnancy only if it is considered to be clearly essential.

***Levocetirizine*:** 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, embryonal/ fetal development, parturition or postnatal development. The use of levocetirizine may be considered during pregnancy, if necessary.

Use during lactation
***Montelukast*:** Studies in rats have shown that montelukast is excreted in milk. It is not known if montelukast is excreted in human milk.
Montelukast may be used in breast-feeding only if it is considered to be clearly essential.

***Levocetirizine*:** 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 FDC of Montelukast and levocetirizine and individuals no clinical data are available.

4.7 Effects on ability to drive and use machines

No studies on the effect of fixed dose combination of Montelukast and Levocetirizine on the ability to drive or use machines have been performed. In the pivotal efficacy study conducted, this fixed dose combination did not show any adverse event like dizziness or impairment of mental alertness. However, montelukast have reported drowsiness or dizziness. 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

FDC of Montelukast and Levocetirizine
The following listing of undesirable effects is based on data from a double blind controlled trial (279 patients) and from post-marketing surveillance study of individual components of the FDC with reporting rates classified as adverse reactions are ranked under heading of frequency, using the following convention:

- 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) including isolated cases

In a double blind study conducted in 279 patients with seasonal allergic rhinitis, 93 patients were exposed to FDC of Montelukast and Levocetirizine for a mean duration of 13.28 days. Except for one adverse event (1.1%) of hypersomnia, all other adverse events were considered to be unrelated to FDC of Montelukast and Levocetirizine by the investigator. The adverse events reported during conduct of the study were mild to moderate in nature.
Below are the adverse drug reactions reported with the individual components of the fixed dose combination.

Montelukast
Montelukast has been evaluated in clinical studies as follows:

- 10 mg film-coated tablets in approximately 4000 adult asthmatic patients 15 years of age and older.
- 10 mg film-coated tablets in approximately 400 adult asthmatic patients with seasonal allergic rhinitis 15 years of age and older.
- 5 mg chewable tablets in approximately 1750 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 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.

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

System Organ Class	Adverse Experience Term	Frequency Category*
Infections and infestations	upper respiratory infection[†]	Very Common
Blood and lymphatic system disorders	increased bleeding tendency	Rare
	thrombocytopenia	Very Rare
Immune system disorder	hypersensitivity reactions including anaphylaxis	Uncommon
	hepatic eosinophilic infiltration	Very Rare
Psychiatric disorders	dream abnormalities including nightmares, insomnia, somnambulism, anxiety, agitation including aggressive behaviour or hostility, depression, psychomotor hyperactivity (including irritability, restlessness, tremor[§])	Uncommon
	disturbance in attention, memory impairment, tic	Rare
	hallucinations, disorientation, suicidal thinking and behaviour (suicidality), obsessive-compulsive symptoms, dysphemia	Very Rare
Nervous system disorder	dizziness, drowsiness paraesthesia/ hypoesthesia, seizure	Uncommon
Cardiac disorders	palpitations	Rare
	epistaxis	Uncommon

System Organ Class	Adverse Experience Term	Frequency Category*
Respiratory, thoracic and mediastinal disorders	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, connective tissue and bone disorders	arthralgia, myalgia including muscle cramps	Uncommon
Renal and urinary disorders	enuresis in children	Uncommon
General disorders and administration site conditions	pyrexia‡	Common
	asthenia/fatigue, malaise, oedema	Uncommon

*Frequency Category: Defined for each Adverse Experience Term by the incidence reported in the clinical trials data base: Very Common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1000 to <1/100), Rare (≥1/10,000 to <1/1000), 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

Clinical studies

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:

Undesirable effects of Levocetrizine in adults and adolescents above 12 years of age

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.

Undesirable effects of Levocetrizine in paediatric patients aged 6-11 months and aged 1 year to less than 6 years

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)

Adverse reactions from post-marketing experience of Levocetrizine

System Organ Class	Adverse Experience Term	Frequency Category*
Immune system disorders	hypersensitivity including anaphylaxis	Not known
Metabolism and nutrition disorders	increased appetite	Not known
Psychiatric disorders	aggression, agitation, hallucination, depression, insomnia, suicidal ideation, nightmare	Not known
Nervous system disorders	convulsion, paraesthesia, dizziness, syncope, tremor, dysgeusia	Not known
Ear and labyrinth disorders	Vertigo	Not known
Eyes disorders	visual disturbances, blurred vision, oculogyration	Not known
Cardiac disorders	palpitations, tachycardia	Not known
Respiratory, thoracic, and mediastinal disorders	Dyspnea	Not known
Gastrointestinal disorders	nausea, vomiting, diarrhea	Not known
Hepatobiliary disorders	Hepatitis	Not known
Renal and urinary disorders	dysuria, urinary retention	Not known
Skin and subcutaneous tissue disorders	angioneurotic oedema, fixed drug eruption, pruritus, rash, urticarial	Not known
Musculoskeletal, connective tissues, and bone disorders	myalgia, arthralgia	Not known
General disorders and administration site conditions	Oedema	Not known
Investigations	weight increased, abnormal liver function tests	Not known

Description of selected adverse reactions

After levocetirizine discontinuation, pruritus has been reported.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

No specific information is available on the treatment of overdose with FDC of Montelukast 10mg and Levocetirizine 5mg tablet.

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

Levocetirizine
Symptoms of overdoses
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 should be considered following short-term ingestion. Levocetirizine is not effectively removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic groups: An agents acting as a leukotriene receptor antagonist and an antihistamine for systemic use, piperazine derivative.

Montelukast

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

The cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4) are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important mediators bind to cysteinyl leukotriene (CysLT) receptors. The CysLT type-1 (CysLT1) receptor is found in the pro-inflammatory cells (including eosinophils and certain myeloid stem cells). CysLTs have been correlated with the pathophysiology of asthma and allergic rhinitis. 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.

Pharmacodynamic effects

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 2 hours of oral administration. The bronchodilation effect caused by a β-agonist was additive to that caused by montelukast. Treatment with montelukast inhibited both early- and late-phase bronchoconstriction due to antigen challenge. Montelukast, compared with placebo, decreased peripheral blood eosinophils in adult and paediatric patients. In a separate study, treatment with montelukast significantly decreased eosinophils in the airways (as measured in sputum) and in peripheral blood while improving clinical asthma control.

Levocetirizine

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 H_1-receptors.

Binding studies revealed that levocetirizine has high affinity for human H_1-receptors (Ki = 3.2 nmol/l). Levocetirizine has an affinity 2-fold higher than that of cetirizine (Ki = 6.3 nmol/l). Levocetirizine dissociates from H_1-receptors with a half-life of 115 ± 38 min.

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.

Pharmacodynamic effects
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.

Clinical Study- FDC of Montelukast and Levocetirizine

In a double-blind, randomized, comparative study of 14 days treatment duration the FDC of montelukast/levocetirizine dihydrochloride 10/5mg film-coated tablet was compared with Montelukast 10mg tablet monotherapy and Levocetirizine Dihydrochloride 5mg tablet monotherapy in the treatment of patients with seasonal allergic rhinitis.

A total of 279 subjects (mean age of 35.29± 11.58 years) were enrolled in the study and randomized to treatment with equal randomization (n=93) among three treatment arms. All subjects were Asian and 58% were male.

There was a statistically significant difference for the primary end point, mean change in the day time nasal symptom score (DTNSS) [composite score of rhinorrhoea, nasal congestion, nasal itching and sneezing] between the FDC and Montelukast ($p<0.05$) and Levocetirizine ($p< 0.05$) for both PP and ITT populations.

Mean Change in Daytime Nasal Symptoms Score (Both ITT and PP Population)

Visit	**Statistics**	**Montelukast 10mg + Levocetirizine 5mg (N=82)**	**Montelukast 10mg (N=82)**	**Levocetirizine 5mg (N=84)**	**p-value[1]**
Mean Change from Baseline (Day 1 to Day14) – PP Population	LSM (SE)	-1.09 (0.053)	-0.95 (0.053)	-0.96 (0.055)	0.0483
95% CI			[-0.279 - -0.017]	[-0.266 - -0.006]	
p-value[2]			0.0266	0.0409	
Visit	**Statistics**	**Montelukast 10mg + Levocetirizine 5mg (N=92)**	**Montelukast 10mg (N=92)**	**Levocetirizine 5mg (N=90)**	**p-value[1]**
Mean Change from Baseline (Day 1 to Day14) –ITT Population	LSM (SE)	-1.10 (0.056)	-0.93 (0.053)	-0.98 (0.057)	0.0159
95% CI			[-0.295 - -0.052]	[-0.250 - -0.004]	
p-value[2]			0.0054	0.0425	

[1]p-value is calculated for the comparison of treatment groups using ANCOVA with baseline Daytime Nasal Symptoms Score as covariate.
[2]p-value is calculated for the comparison between treatment groups by using ANCOVA with Estimate Statement

Overall, the study indicated that FDC of Montelukast 10mg and Levocetirizine Dihydrochloride 5mg was safe and well tolerated; and safety profile is comparable to Montelukast 10mg monotherapy and Levocetirizine Dihydrochloride 5mg monotherapy.

Clinical efficacy and safety of Montelukast 10mg film-coated tablets

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 patient-reported 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 beclomethasone plus montelukast vs beclomethasone, respectively for FEV_1: 5.43% vs 1.04%; β-agonist use: -8.70% vs 2.64%). Compared with inhaled beclomethasone (200 µg twice daily with a spacer device), montelukast demonstrated a more rapid initial response, although over the 12-week study, beclomethasone provided a greater average treatment effect (% change from baseline for montelukast vs beclomethasone, respectively for FEV_1: 7.49% vs 13.3%; β-agonist use: -28.28% vs -43.89%). However, compared with beclomethasone, a high percentage of patients treated with montelukast achieved similar clinical responses (e.g., 50% of patients treated with beclomethasone 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).

A clinical study was conducted to evaluate montelukast for the symptomatic treatment of seasonal allergic rhinitis in adult and adolescent asthmatic patients 15 years of age and older with concomitant seasonal allergic rhinitis. In this study, montelukast 10 mg tablets administered once daily demonstrated a statistically significant improvement in the Daily Rhinitis Symptoms score, compared with placebo. The Daily Rhinitis Symptoms score is the average of the Daytime Nasal Symptoms score (mean of nasal congestion, rhinorrhea, sneezing, nasal itching) and the Night time Symptoms score (mean of nasal congestion upon awakening, difficulty going to sleep, and nighttime awakenings scores). Global evaluations of allergic rhinitis by patients and physicians were significantly improved, compared with placebo. The evaluation of asthma efficacy was not a primary objective in this study.

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 "as-needed" β-agonist use (-11.7% vs +8.2% change from baseline).

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).

<u>Clinical efficacy and safety of Levocetirizine 5mg film-coated tablets</u>
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.

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 5 mg 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.

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.

5.2 Pharmacokinetic properties

No separate pharmacokinetic study was performed with the FDC of Montelukast and Levocetirizine to characterize its pharmacokinetics.

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.

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.

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
Montelukast: Montelukast is more than 99% bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8-11 liters. Studies in rats with radio-labeled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radio-labeled 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 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
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 radio-labeled 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 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.

Special Population

Studies in patients with renal and hepatic impairment have not been undertaken for FDC of Montelukast and Levocetirizine.

Renal impairment:
Montelukast: 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.

Levocetirizine: 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%.

Hepatic impairment:
Montelukast: No dosage adjustment is necessary for mild to moderate hepatic insufficiency. There are no data on the pharmacokinetics of montelukast in patients with severe hepatic insufficiency (Child-Pugh score >9).

Levocetirizine:
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.

Paediatric population:
Levocetirizine:
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:
Montelukast: 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. No dosage adjustment is necessary for the elderly.

Levocetirizine:
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:
Levocetirizine:
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:
Levocetirizine:
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.

Pharmacokinetic / pharmacodynamic relationship
Levocetirizine:
The action on histamine-induced skin reactions is out of phase with the plasma concentrations.

5.3 Preclinical safety data
Acute toxicity studies on rats and mice and repeated dose toxicity studies on rats were conducted of FDC of Montelukast and Levocetirizine.

Montelukast Sodium + Levocetirizine Dihydrochloride				
Study Type	**Animals**	**Route**	**NOAEL Dose (mg/kg)**	**Treatment Related Toxicity**
Acute	Rats	Oral	>2000 (1335 + 665)	None
Acute	Mice	Oral	>2000 (1335 + 665)	None
Repeated dose Toxicity	Rats	Oral (14 day)	270 (180 + 90)	None

The combination of montelukast and levocetirizine did not show any target organs of toxicity in 14-day oral (gavage) toxicity study in rats and the NOAEL established was 270 (180+90) mg/kg which is approximately 175 times (based on body surface area and considering human body weight as 60 kg) to the maximum recommended human daily dose [15 (10+5) mg/kg].

Carcinogenesis, Mutagenesis, Impairment of Fertility
No separate Carcinogenesis, Mutagenesis, Impairment of Fertility studies were performed with the FDC of Montelukast and Levocetirizine.

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, gastrointestinal 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
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
Microcrystalline Cellulose, Lactose Monohydrate, Anhydrous dibasic calcium phosphate, Croscarmellose Sodium, Hydroxypropyl Cellulose, Magnesium stearate, Opadry yellow 13B52204, Purified water

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store below 30°C. Protect from light and humidity.

6.5 Nature and contents of container
Pack size 7's- A printed carton with a leaflet containing labeled HDPE container containing 7 yellow, round, biconvex, film coated tablets plain on both sides with a “1 G silica gel” canister, container is closed with child resistant cap and subject for induction sealing.

Pack size 28's- A printed carton with a leaflet containing labeled HDPE container containing 28 yellow, round, biconvex, film coated tablets plain on both sides with a “1 G silica gel” canister, container is closed with child resistant cap and subject for induction sealing.

6.6 Special precautions for disposal and other handling

No special requirements.

7. APPLICANT

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8. MANUFACTURER

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