

Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Montelukast Sodium & Levocetirizine Hydrochloride Tablets –
LEVOLUKAST 5-12

2. Qualitative and quantitative composition

Each film-coated tablet contains:

Montelukast Sodium

Eq. to Montelukast 5 mg

Levocetirizine Hydrochloride 2.5 mg

Excipients with known effects

Colour: Titanium Dioxide BP

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Film-coated tablets.

A white-coloured, round-shaped, biconvex, film-coated tablet with a break-line on one side and a plain other side.

4. Clinical particulars

4.1 Therapeutic indications

LEVOLUKAST 5-12 tablets are indicated for the relief and/or prevention of symptoms of allergic rhinitis (seasonal or perennial).

4.2 Posology and method of administration

Posology

Children 5-12years old

One LEVOLUKAST 5-12 tablet once daily.

Method of administration

For oral use only.

Tablets may be taken with or without food.

4.3 Contraindications

-LEVOLUKAST 5-12 is contraindicated in patients hypersensitive to montelukast sodium, levocetirizine, cetirizine, or any excipients listed in section 6.1.

-LEVOLUKAST 5-12 is also contraindicated in patients with severe renal impairment at less than 10ml/min creatinine clearance.

-It is also contraindicated in patients with end-stage renal disease with estimated Glomerular Filtration Rate (eGFR) below 15 ml/min (requiring dialysis treatment).

4.4 Special warnings and precautions for use

LEVOLUKAST 5-12 should not be prescribed for the treatment of asthma. However, it may be prescribed with other medications used to manage asthma.

Levocetirizine Hydrochloride

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 convulsions, as levocetirizine may cause seizure aggravation. Response to allergy skin tests is inhibited by antihistamines, and a wash-out period (of 3 days) is required before performing them.

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

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.

Pediatric 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 pediatric formulation of levocetirizine

Montelukast Sodium

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 beta-agonist should be used. Patients should seek their doctor's advice as soon as possible if they need more inhalations of short-acting beta-agonists than usual.

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

No data demonstrates that oral corticosteroids can be reduced when montelukast is given concomitantly.

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 (see section 4.8). 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.

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 sometimes

been 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.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions common to the combination

No drug-drug interaction studies have been performed with levocetirizine/montelukast fixed-dose combination and other medicinal products.

Levocetirizine Hydrochloride

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.

No interaction studies have been performed with levocetirizine (including no studies with CYP3A4 inducers); studies with the racemate compound cetirizine demonstrated that there were no clinically relevant adverse interactions (with antipyrine, azithromycin, cimetidine, diazepam, erythromycin, glipizide, ketoconazole, and pseudoephedrine). A small decrease in the clearance of cetirizine (16%) was observed in a multiple-dose study with theophylline (400 mg once a day), while the disposition of theophylline was not altered by concomitant cetirizine administration. In a multiple-dose study of ritonavir (600 mg twice daily) and cetirizine (10 mg daily), the extent of exposure to cetirizine was increased by about 40% while the disposition of ritonavir was slightly altered (-11%) further to concomitant cetirizine administration.

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

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

Montelukast Sodium

Montelukast may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma. In drug-interaction 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 by 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.

4.6 Pregnancy and Lactation

Pregnancy

As a precautionary measure, it is preferable to avoid the use of levocetirizine and/or montelukast during pregnancy.

Levocetirizine: There is no to 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 indicates no malformative or fetoneonatal toxicity. Animal studies do not indicate direct or indirect harmful effects concerning pregnancy, embryo/fetal development, parturition, or postnatal development (see section 5.3). The use of levocetirizine may be considered during pregnancy, if necessary.

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 essential.

Lactation

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from levocetirizine/montelukast therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Levocetirizine: Cetirizine, the racemate of levocetirizine, is excreted in humans. Therefore, the excretion of levocetirizine in human milk is likely. Adverse reactions associated with levocetirizine may be observed in breastfed infants. Caution should thus be exercised when prescribing levocetirizine to lactating women.

Montelukast: Studies in rats have shown that montelukast is excreted in milk (see section 5.3). It is unknown whether montelukast or its metabolites are excreted in human milk.

Montelukast may be used in breastfeeding only if it is considered to be essential.

Fertility

There is no data available on male and female fertility for both levocetirizine and montelukast.

4.7 Effects on the ability to drive and use machines

Some patients could experience somnolence, fatigue, and asthenia under therapy with levocetirizine. As there is individual variation in response to all medicinal products, it is recommended that patients be advised not to engage in activities requiring mental alertness, such as driving a car or using machines, until they have established their response to the medicinal product.

4.8 Undesirable effects

Levocetirizine Hydrochloride

In therapeutic studies in women and men aged 12 to 71, 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, the following incidence of adverse drug reactions were reported at rates of 1% or greater (common: $\geq 1/100$ 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 $\geq 1/1,000$ to $< 1/100$), like asthenia or abdominal pain, were observed. The incidence of sedating adverse drug reactions such as somnolence, fatigue, and asthenia was altogether more common (8.1%) under levocetirizine 5 mg than under placebo (3.1%).

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 1.25 mg daily for 2 weeks and 1.25 mg twice daily, respectively. The following incidence of adverse drug reactions was reported at rates of 1% or greater under levocetirizine or placebo.

System order class and preferred term	Placebo (n=83)	Levocetirizine
Gastrointestinal disorders		
Diarrhea	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 controlled studies were performed where 243 children were exposed to 5 mg 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%)

Montelukast Sodium

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 and older.
- 5 mg chewable tablets in approximately 1,750 pediatric asthmatic patients 6 to 14 years of age.

The following drug-related adverse reactions in clinical studies were reported commonly ($\geq 1/100$ 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 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
Gastrointestinal 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 pediatric patients 6 to 14 years of age, the safety profile did not change.

Common side effects include dyspepsia, abdominal pain, rash, dizziness, headache, fatigue, fever, trauma, cough, and nasal congestion.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via the pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>

4.9 Overdose

There is no data reported on the overdose of this combination. However, overdose has been reported with individual molecules.

Levocetirizine Hydrochloride

Symptoms of overdose:

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

Management of overdoses:

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

Montelukast Sodium

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.

Symptoms of overdose:

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.

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 haemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Cetirizine Hydrochloride

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

Mechanism of Action

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

Binding studies revealed that levocetirizine has high affinity for human H₁-receptors ($K_i = 3.2$ nmol/l). Levocetirizine has an affinity 2-fold higher than cetirizine ($K_i = 6.3$ nmol/l). Levocetirizine dissociates from H₁-receptors with a half-life of 115 ± 38 min.

After a 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 5 mg, desloratadine 5 mg, and placebo on histamine-induced wheal and flare, levocetirizine treatment resulted in significantly decreased wheal and flare formation, which was highest in the first 12 hours and lasted for 24 hours ($p < 0.001$) compared with placebo and desloratadine.

The onset of action of levocetirizine 5 mg in controlling pollen-induced symptoms has been observed at one-hour post-drug intake in placebo-controlled trials in the model of the allergen challenge chamber.

In vitro studies (Boyden chambers and cell layers' techniques) show that levocetirizine inhibits eotaxin-induced eosinophil transendothelial migration through both dermal and lung cells. A pharmacodynamic

experimental study in vivo (skin chamber technique) showed three main inhibitory effects of levocetirizine 5 mg in the first 6 hours of pollen-induced reaction, compared with placebo in 14 adult patients: inhibition of VCAM-1 release, modulation of vascular permeability and a decrease in eosinophil recruitment.

Clinical efficacy and safety

The efficacy and safety of levocetirizine have 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 a placebo and 81 patients with levocetirizine 5 mg once daily over six weeks. Treatment with levocetirizine resulted in a 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 the QT interval.

Paediatric population

The paediatric safety and efficacy of levocetirizine tablets have 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 aged 1 to 5.

Montelukast sodium

Pharmacotherapeutic group: Leukotriene receptor antagonist

ATC-code: R03D C03

Mechanism of Action

The cysteinyl leukotrienes (LTC₄, LTD₄, LTE₄) are potent inflammatory eicosanoids released from various cells, including mast cells and eosinophils. These important pro-asthmatic mediators bind to cysteinyl leukotriene (CysLT) receptors. The CysLT type-1 (CysLT₁) 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.

Doses as low as 5 mg cause substantial blockage of LTD₄-induced bronchoconstriction.

Pharmacodynamic effects

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

Clinical efficacy and safety

In studies in adults, montelukast, 10 mg once daily, compared with placebo, demonstrated significant improvements in morning FEV1 (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 night-time 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 FEV1: 5.43% vs 1.04%; β -agonist use: -8.70% vs 2.64%). Compared with inhaled beclomethasone (200 μ g 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 FEV1: 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 FEV1 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 Nighttime 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 (FEV1 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 FEV1 22.33% for montelukast vs 32.40% for placebo; time to recovery to within 5% of baseline FEV1 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 FEV1 18.27% vs 26.11%; time to recovery to within 5% of baseline

FEV1 17.76 min vs 27.98 min). Both studies demonstrated the effect 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 (FEV1 8.55% vs -1.74% change from baseline and decrease in total β -agonist use -27.78% vs 2.09% change from baseline).

5.2 Pharmacokinetic properties

Levocetirizine Hydrochloride

The pharmacokinetics of levocetirizine are linear, dose—and time-independent, and low inter-subject variability. The pharmacokinetic profile is the same when given as the single enantiomer or as cetirizine. No chiral inversion occurs during absorption and elimination.

Absorption

Levocetirizine is rapidly and extensively absorbed following oral administration. In adults, peak plasma concentrations are achieved 0.9 h after dosing. Steady state is achieved after two days. Peak concentrations are typically 270 ng/ml and 308 ng/ml following a single and a repeated 5 mg once daily 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, nor concerning the passage of levocetirizine through the blood-brain-barrier. In rats and dogs, the highest tissue levels are found in the liver and kidneys, the lowest in the CNS compartment.

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

Biotransformation

The extent of metabolism of levocetirizine in humans is less than 14% of the dose, and therefore, differences resulting from genetic polymorphism or concomitant intake of enzyme inhibitors are expected to be negligible. Metabolic pathways include aromatic oxidation, N- and O-dealkylation, and taurine conjugation. Dealkylation pathways are primarily mediated by CYP 3A4, while aromatic oxidation involves multiple and/or unidentified CYP isoforms. Levocetirizine did not affect the activities of CYP iso-enzymes 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 half-life is shorter in small children.

The mean apparent total body clearance in adults is 0.63 ml/min/kg. The major route of excretion of levocetirizine and metabolites is via urine, accounting for a mean of 85.4% of the dose. Excretion via faeces accounts for only 12.9% of the dose. Levocetirizine is excreted both by glomerular filtration and active tubular secretion.

Special population

Renal impairment

The apparent body clearance of levocetirizine is correlated with the creatinine clearance. It is therefore recommended to adjust the dosing intervals of levocetirizine 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 aged 6 to 11 with body weight ranging between 20 and 40 kg show that C_{max} and AUC values are about 2-fold greater than those 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 323 subjects (181 children, 1 to 5 years of age, 18 children 6 to 11 years of age, and 124 adults 18 to 55 years of age) who received single or multiple doses of levocetirizine ranging from 1.25 mg to 30 mg. Data generated from this analysis indicated that administration of 1.25 mg once daily to children 6 months to 5 years of age is expected to result in plasma concentrations similar to those of adults receiving 5 mg once daily.

Elderly

Limited pharmacokinetic data are available in elderly subjects. Following once daily repeat oral administration of 30 mg levocetirizine for 6 days in 9 elderly subjects (65– 74 years of age), the total body clearance was approximately 33% lower compared to that in younger adults. The disposition of racemic cetirizine is 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 per renal function in elderly patients.

Gender

Pharmacokinetic results for 77 patients (40 men, 37 women) were evaluated for the 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, the 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.

Pharmacokinetic/pharmacodynamic relationship

The action on histamine-induced skin reactions is out of phase with the plasma concentrations.

Montelukast Sodium

Absorption

After administration of a 10-mg tablet to fasted adults, the mean peak montelukast plasma concentration (C_{max}) is achieved in 3 to 4 hours (T_{max}). 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.

Distribution

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

Biotransformation

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

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

Elimination

The plasma clearance of montelukast averages 45 ml/min in healthy adults. Following an oral dose of radiolabelled montelukast, 86% of the radioactivity was recovered in 5-day faecal collections and <0.2% was recovered in urine. Coupled with estimates of montelukast oral bioavailability, this indicates that montelukast and its metabolites are excreted almost exclusively via the bile.

In several studies, the mean plasma half-life of montelukast ranged from 2.7 to 5.5 hours in healthy young adults. The pharmacokinetics of montelukast are nearly linear for oral doses up to 50 mg. During once daily dosing with 10-mg montelukast, there is little accumulation of the parent drug in plasma (~14%).

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

5.3 Preclinical safety data

Levocetirizine Hydrochloride

Non-clinical data do not reveal any special hazards for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, reproductive toxicity and development.

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, 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 the breast milk of animals.

No deaths occurred following a single oral administration of montelukast sodium at doses up to 5,000 mg/kg in mice and rats (15,000 mg/m² and 30,000 mg/m² in mice and rats, respectively), the maximum dose tested. This dose is equivalent to 25,000 times the recommended daily adult human dose (based on an adult patient weight of 50 kg).

Montelukast was 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.

6. Pharmaceutical Particulars

6.1 List of Excipients

Microcrystalline Cellulose
Magnesium Stearate
Crospovidone
Purified Talc
Colloidal Silicon Dioxide
Croscarmellose Sodium
Sodium Starch Glycolate
Hydroxy Propyl Methyl Cellulose
Titanium Dioxide
Polyethylene glycol-6000

6.2 Incompatibilities

None known

6.3 Shelf-Life

36 months

6.4 Special Precautions for Storage

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

6.5 Nature and Content of Container

Alu/Alu blister pack of 10 tablets.

Pack Size: 3x10 Tablets.

6.6 Special precautions for disposal and other handling

This medicinal product should not be disposed of via wastewater or household waste. Any unused medicinal product or waste material should be disposed of per local requirements.

7. Marketing Authorization Holder

Conical Pharmaceuticals

13 FF, Raghuvir, Bapasitaram chowk,

Nava Naroda, Ahmedabad- 382346,

Gujarat, India.

info@conicalpharmaceuticals.com

8. Marketing Authorization Number

CTD9085

9. Date of first authorization/renewal of the authorization

27/07/2023

10. Date of revision of the text

10/05/2025