

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lorclast 5 mg /10 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains desloratadine 5 mg and 10.4 mg montelukast sodium which is equivalent to 10 mg montelukast.

Excipient with known effect: This medicine contains 30 mg croscarmellose sodium and 117.10 mg mannitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pink colored, oval, biconvex, one face notched film coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

It is indicated for the treatment and relief of symptoms related to allergic rhinitis with or without concomitant asthma in adults and adolescents aged 15 years and older.

4.2 Posology and method of administration

Posology

The recommended dose for adults and adolescents 15 years of age and older with allergic rhinitis, or with asthma and concomitant allergic rhinitis, is one tablet (5 mg desloratadine / 10 mg montelukast) daily to be taken in the evening.

For compliance, patients taking desloratadine and montelukast in separate tablets may switch to LORCLAST containing the same component doses.

Intermittent allergic rhinitis (presence of symptoms less than 4 days per week or less than 4 weeks per week) should be managed in accordance with the evaluation of patient's disease history and the treatment could be discontinued after symptoms are resolved and reinitiated upon their reappearance.

In persistent allergic rhinitis (presence of symptoms for 4 days or more per week and for more than 4 weeks), continued treatment may be proposed to the patients during the allergen exposure periods.

Method of administration

Oral use.

4.3 Contraindications

Hypersensitivity to the active substances montelukast and/or desloratadine or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Montelukast:

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

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

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

In rare cases, patients on therapy with anti-asthma agents including montelukast may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These cases have been sometimes associated with the reduction or withdrawal of oral corticosteroid therapy. Although a causal relationship with leukotriene receptor antagonism has not been established, physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. Patients who develop these symptoms should be reassessed and their treatment regimens evaluated.

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

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.

Desloratadine:

Renal function impairment

In the case of severe renal insufficiency, desloratadine should be used with caution (see section 5.2).

Seizures

Desloratadine should be administered with caution in patients with medical or familial history of seizures, and mainly young children, being more susceptible to develop new

seizures under desloratadine treatment. Healthcare providers may consider discontinuing desloratadine in patients who experience a seizure while on treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Montelukast:

Montelukast may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma. In drug-interactions studies, the recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following medicinal products:

Theophylline, prednisone, prednisolone, oral contraceptives (ethinyl estradiol/norethindrone 35/1), terfenadine, digoxin and warfarin.

The area under the plasma concentration curve (AUC) for montelukast was decreased approximately 40% in subjects with co-administration of phenobarbital. Since montelukast is metabolised by CYP 3A4, 2C8, and 2C9, caution should be exercised, particularly in children, when montelukast is co-administered with inducers of CYP 3A4, 2C8, and 2C9, such as phenytoin, phenobarbital and rifampicin.

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

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

Based on *in vitro* data, clinically important drug interactions with less potent inhibitors of CYP 2C8 (e.g., trimethoprim) are not anticipated. Co-administration of montelukast with itraconazole, a strong inhibitor of CYP 3A4, resulted in no significant increase in the systemic exposure of montelukast.

Desloratadine:

No clinically relevant interactions were observed in clinical trials with desloratadine in which erythromycin or ketoconazole were co-administered (see section 5.1).

Paediatric population

Interaction studies have only been performed in adults.

In a clinical pharmacology trial, desloratadine tablets taken concomitantly with alcohol did not potentiate the performance impairing effects of alcohol (see section 5.1). However, cases of alcohol intolerance and intoxication have been reported during

post-marketing use. Therefore, caution is recommended if alcohol is taken concomitantly.

4.6 Fertility, pregnancy and lactation

Montelukast:

Pregnancy

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.

Breast-feeding

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

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

Desloratadine:

Pregnancy

A large amount of data on pregnant women (more than 1,000 pregnancy outcomes) indicate no malformative nor foeto/ neonatal toxicity of desloratadine. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of desloratadine during pregnancy.

Breast-feeding

Desloratadine has been identified in breastfed new-borns/infants of treated women. The effect of desloratadine on new-borns/infants is unknown. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from desloratadine therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data available on male and female fertility.

4.7 Effects on ability to drive and use machines

Montelukast:

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

Desloratadine:

Desloratadine has no or negligible influence on the ability to drive and use machines based on clinical trials. Patients should be informed that most people do not experience drowsiness. Nevertheless, as there is individual variation in response to all medicinal products, it is recommended that patients are advised not to engage in activities requiring mental alertness, such as driving a car or using machines, until they have established their own response to the medicinal product.

4.8 Undesirable effects

Montelukast:

Montelukast has been evaluated in clinical studies as follows:

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

The following drug-related adverse reactions in clinical studies were reported commonly ($\geq 1/100$ 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
Gastro-intestinal disorders	abdominal pain	

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

Tabulated list of Adverse Reactions

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

System Organ Class	Adverse Reactions	Frequency Category*
Infections and infestations	upper respiratory infection [†]	Very Common
Blood and lymphatic system disorders	increased bleeding tendency	Rare
	thrombocytopenia	Very Rare
Immune system disorders	hypersensitivity reactions including anaphylaxis	Uncommon
	hepatic eosinophilic infiltration	Very Rare
Psychiatric disorders	dream abnormalities including nightmares, insomnia, somnambulism, anxiety, agitation including aggressive behaviour or hostility, depression, psychomotor hyperactivity (including irritability, restlessness, tremor [§])	Uncommon
	disturbance in attention, memory impairment, tic	Rare
	hallucinations, disorientation, suicidal thinking and behaviour (suicidality), obsessive-compulsive symptoms, dysphemia	Very Rare
Nervous system disorders	dizziness, drowsiness, paraesthesia/hypoesthesia, seizure	Uncommon
Cardiac disorders	palpitations	Rare
Respiratory, thoracic and mediastinal disorders	epistaxis	Uncommon
	Churg-Strauss Syndrome (CSS) (see section 4.4)	Very Rare
	pulmonary eosinophilia	Very Rare
Gastro-intestinal disorders	diarrhoea [‡] , nausea [‡] , vomiting [‡]	Common
	dry mouth, dyspepsia	Uncommon
Hepatobiliary disorders	elevated levels of serum transaminases (ALT, AST)	Common
	hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury).	Very Rare
Skin and subcutaneous tissue disorders	rash [‡]	Common
	bruising, urticaria, pruritus	Uncommon
	angiooedema	Rare
	erythema nodosum, erythema multiforme	Very Rare

Musculoskeletal and connective tissue disorders	arthralgia, myalgia including muscle cramps	Uncommon
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 Reaction by the incidence reported in the clinical trials data base: Very Common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1,000$ to $< 1/100$), Rare ($\geq 1/10,000$ to $< 1/1,000$), Very Rare ($< 1/10,000$). [†]This adverse experience, reported as Very Common in the patients who received montelukast, was also reported as Very Common in the patients who received placebo in clinical trials. [‡]This adverse experience, reported as Common in the patients who received montelukast, was also reported as Common in the patients who received placebo in clinical trials. [§] Frequency Category: Rare		

Desloratadine:

Summary of the safety profile

In clinical trials in a range of indications including allergic rhinitis and chronic idiopathic urticaria, at the recommended dose of 5 mg daily, undesirable effects with desloratadine were reported in 3 % of patients in excess of those treated with placebo. The most frequent of adverse reactions reported in excess of placebo were fatigue (1.2 %), dry mouth (0.8 %) and headache (0.6 %).

Paediatric population

In a clinical trial with 578 adolescent patients, 12 through 17 years of age, the most common adverse event was headache; this occurred in 5.9 % of patients treated with desloratadine and 6.9 % of patients receiving placebo.

Tabulated list of adverse reactions

The frequency of the clinical trial adverse reactions reported in excess of placebo and other undesirable effects reported during the post-marketing period are listed in the following table. Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse reactions seen with desloratadine
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Metabolism and nutrition disorders	Not known	Increased appetite
Psychiatric disorders	Very rare Not known	Hallucinations Abnormal behaviour, aggression
Nervous system disorders	Common Very rare	Headache Dizziness, somnolence, insomnia, psychomotor hyperactivity, seizures
Cardiac disorders	Very rare Not known	Tachycardia, palpitations QT prolongation
Gastrointestinal disorders	Common Very rare	Dry mouth Abdominal pain, nausea, vomiting, dyspepsia, diarrhoea
Hepatobiliary disorders	Very rare Not known	Elevations of liver enzymes, increased bilirubin, hepatitis Jaundice
Skin and subcutaneous tissue disorders	Not known	Photosensitivity
Musculoskeletal and connective tissue disorders	Very rare	Myalgia
General disorders and administration site conditions	Common Very rare Not known	Fatigue Hypersensitivity reactions (such as anaphylaxis, angioedema, dyspnoea, pruritus, rash, and urticaria) Asthenia
Investigations	Not Known	Weight increased

Paediatric population

Other undesirable effects reported during the post-marketing period in paediatric patients with an unknown frequency included QT prolongation, arrhythmia, bradycardia, abnormal behaviour, and aggression.

A retrospective observational safety study indicated an increased incidence of new-onset seizure in patients 0 to 19 years of age when receiving desloratadine compared with periods not receiving desloratadine. Among children 0-4 years old, the adjusted absolute increase was 37.5 (95% Confidence Interval (CI) 10.5-64.5) per 100,000 person years (PY) with a background rate of new onset seizure of 80.3 per 100,000 PY. Among patients 5-19 years of age, the adjusted absolute increase was 11.3 (95% CI 2.3-20.2) per 100,000 PY with a background rate of 36.4 per 100,000 PY. (See section 4.4.)

4.9 Overdose

Montelukast:

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

There have been reports of acute overdose in post-marketing experience and clinical studies with montelukast. These include reports in adults and children with a dose as high as 1,000 mg (approximately 61 mg/kg in a 42 month old child). The clinical and laboratory findings observed were consistent with the safety profile in adults and paediatric patients. There were no adverse experiences in the majority of overdose reports.

Symptoms of overdose

The most frequently occurring adverse experiences were consistent with the safety profile of montelukast and included abdominal pain, somnolence, thirst, headache, vomiting, and psychomotor hyperactivity.

Management of overdose

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

Desloratadine:

The adverse event profile associated with overdosage, as seen during post-marketing use, is similar to that seen with therapeutic doses, but the magnitude of the effects can be higher.

Symptoms

Based on a multiple dose clinical trial, in which up to 45 mg of desloratadine was administered (nine times the clinical dose), no clinically relevant effects were observed.

Treatment

In the event of overdose, consider standard measures to remove unabsorbed active substance. Symptomatic and supportive treatment is recommended.

Desloratadine is not eliminated by haemodialysis; it is not known if it is eliminated by peritoneal dialysis.

Paediatric population

The adverse event profile associated with overdosage, as seen during post-marketing use, is similar to that seen with therapeutic doses, but the magnitude of the effects can be higher.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Leukotriene receptor antagonist/antihistamine combination

ATC-code: R03D C53

Montelukast:

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.

Pharmacodynamic effects

Montelukast is an orally active compound which binds with high affinity and selectivity to the CysLT₁ receptor. In clinical studies, montelukast inhibits bronchoconstriction due to inhaled LTD₄ at doses as low as 5 mg. Bronchodilation was observed within 2 hours of oral administration. The bronchodilation effect caused by a β -agonist was additive to that caused by montelukast. Treatment with montelukast inhibited both early- and late-phase bronchoconstriction due to antigen challenge. Montelukast, compared with placebo, 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, rhinorrhoea, 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 PEF 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). 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 (FEV₁ 8.55% vs -1.74% change from baseline and decrease in total β -agonist use -27.78% vs 2.09% change from baseline).

Desloratadine:

Mechanism of action

Desloratadine is a non-sedating, long-acting histamine antagonist with selective peripheral H₁-receptor antagonist activity. After oral administration, desloratadine selectively blocks peripheral histamine H₁-receptors because the substance is excluded from entry to the central nervous system.

Desloratadine has demonstrated antiallergic properties from *in vitro* studies. These include inhibiting the release of proinflammatory cytokines such as IL-4, IL-6, IL-8, and IL-13 from human mast cells/basophils, as well as inhibition of the expression of the adhesion molecule P-selectin on endothelial cells. The clinical relevance of these observations remains to be confirmed.

Clinical efficacy and safety

In a multiple dose clinical trial, in which up to 20 mg of desloratadine was administered daily for 14 days, no statistically or clinically relevant cardiovascular effect was observed. In a clinical pharmacology trial, in which desloratadine was administered at a dose of 45 mg daily (nine times the clinical dose) for ten days, no prolongation of QTc interval was seen.

No clinically relevant changes in desloratadine plasma concentrations were observed in multiple-dose ketoconazole and erythromycin interaction trials.

Pharmacodynamic effects

Desloratadine does not readily penetrate the central nervous system. In controlled clinical trials, at the recommended dose of 5 mg daily, there was no excess incidence of somnolence as compared to placebo. Desloratadine given at a single daily dose of 7.5 mg did not affect psychomotor performance in clinical trials. In a single dose study performed in adults, desloratadine 5 mg did not affect standard measures of flight performance including exacerbation of subjective sleepiness or tasks related to flying.

In clinical pharmacology trials, co-administration with alcohol did not increase the alcohol-induced impairment in performance or increase in sleepiness. No significant differences were found in the psychomotor test results between desloratadine and placebo groups, whether administered alone or with alcohol.

In patients with allergic rhinitis, desloratadine was effective in relieving symptoms such as sneezing, nasal discharge and itching, as well as ocular itching, tearing and redness, and itching of palate. Desloratadine effectively controlled symptoms for 24 hours.

Paediatric population

The efficacy of desloratadine tablets has not been clearly demonstrated in trials with adolescent patients 12 through 17 years of age.

In addition to the established classifications of seasonal and perennial, allergic rhinitis can alternatively be classified as intermittent allergic rhinitis and persistent allergic rhinitis according to the duration of symptoms. Intermittent allergic rhinitis is defined as the presence of symptoms for less than 4 days per week or for less than 4 weeks. Persistent allergic rhinitis is defined as the presence of symptoms for 4 days or more per week and for more than 4 weeks.

Desloratadine was effective in alleviating the burden of seasonal allergic rhinitis as shown by the total score of the rhino-conjunctivitis quality of life questionnaire. The

greatest amelioration was seen in the domains of practical problems and daily activities limited by symptoms.

Chronic idiopathic urticaria was studied as a clinical model for urticarial conditions, since the underlying pathophysiology is similar, regardless of ethology, and because chronic patients can be more easily recruited prospectively. Since histamine release is a causal factor in all urticarial diseases, desloratadine is expected to be effective in providing symptomatic relief for other urticarial conditions, in addition to chronic idiopathic urticaria, as advised in clinical guidelines.

In two placebo-controlled six-week trials in patients with chronic idiopathic urticaria, desloratadine was effective in relieving pruritus and decreasing the size and number of hives by the end of the first dosing interval. In each trial, the effects were sustained over the 24 hour dosing interval. As with other antihistamine trials in chronic idiopathic urticaria, the minority of patients who were identified as non-responsive to antihistamines was excluded. An improvement in pruritus of more than 50 % was observed in 55 % of patients treated with desloratadine compared with 19 % of patients treated with placebo. Treatment with desloratadine also significantly reduced interference with sleep and daytime function, as measured by a four-point scale used to assess these variables.

5.2 Pharmacokinetic properties

Montelukast:

Absorption

Montelukast is rapidly absorbed following oral administration. For the 10 mg film-coated tablet, the mean peak plasma concentration (C_{max}) is achieved 3 hours (T_{max}) after administration in adults in the fasted state. The mean oral bioavailability is 64 %. The oral bioavailability and C_{max} are not influenced by a standard meal. Safety and efficacy were demonstrated in clinical trials where the 10 mg film-coated tablet was administered without regard to the timing of food ingestion.

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

Distribution

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

Biotransformation

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

Cytochrome P450 2C8 is the major enzyme in the metabolism of montelukast. Additionally CYP 3A4 and 2C9 may have a minor contribution, although itraconazole, an inhibitor of CYP 3A4, was shown not to change pharmacokinetic variables of montelukast in healthy subjects that received 10 mg montelukast daily. Based on *in*

vitro results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6. The contribution of metabolites to the therapeutic effect of montelukast is minimal.

Elimination

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

Characteristics in Patients

No dosage adjustment is necessary for the elderly or mild to moderate hepatic insufficiency. Studies in patients with renal impairment have not been undertaken. Because montelukast and its metabolites are eliminated by the biliary route, no dose adjustment is anticipated to be necessary in patients with renal impairment. There are no data on the pharmacokinetics of montelukast in patients with severe hepatic insufficiency (Child-Pugh score >9).

With high doses of montelukast (20- and 60-fold the recommended adult dose), decrease in plasma theophylline concentration was observed. This effect was not seen at the recommended dose of 10 mg once daily.

Desloratadine:

Absorption

Desloratadine plasma concentrations can be detected within 30 minutes of administration. Desloratadine is well absorbed with maximum concentration achieved after approximately 3 hours; the terminal phase half-life is approximately 27 hours. The degree of accumulation of desloratadine was consistent with its half-life (approximately 27 hours) and a once daily dosing frequency. The bioavailability of desloratadine was dose proportional over the range of 5 mg to 20 mg.

In a pharmacokinetic trial in which patient demographics were comparable to those of the general seasonal allergic rhinitis population, 4 % of the subjects achieved a higher concentration of desloratadine. This percentage may vary according to ethnic background. Maximum desloratadine concentration was about 3-fold higher at approximately 7 hours with a terminal phase half-life of approximately 89 hours. The safety profile of these subjects was not different from that of the general population.

Distribution

Desloratadine is moderately bound (83 % - 87 %) to plasma proteins. There is no evidence of clinically relevant medicine accumulation following once daily dosing of desloratadine (5 mg to 20 mg) for 14 days.

Biotransformation

The enzyme responsible for the metabolism of desloratadine has not been identified yet, and therefore, some interactions with other medicinal products cannot be fully excluded. Desloratadine does not inhibit CYP3A4 *in vivo*, and *in vitro* studies have shown that the medicinal product does not inhibit CYP2D6 and is neither a substrate nor an inhibitor of P-glycoprotein.

Elimination

In a single dose trial using a 7.5 mg dose of desloratadine, there was no effect of food (high-fat, high caloric breakfast) on the disposition of desloratadine. In another study, grapefruit juice had no effect on the disposition of desloratadine.

Renally impaired patients

The pharmacokinetics of desloratadine in patients with chronic renal insufficiency (CRI) was compared with that of healthy subjects in one single-dose study and one multiple dose study. In the single-dose study, the exposure to desloratadine was approximately 2 and 2.5-fold greater in subjects with mild to moderate and severe CRI, respectively, than in healthy subjects. In the multiple-dose study, steady state was reached after Day 11, and compared to healthy subjects the exposure to desloratadine was ~1.5-fold greater in subjects with mild to moderate CRI and ~2.5-fold greater in subjects with severe CRI. In both studies, changes in exposure (AUC and C_{max}) of desloratadine and 3-hydroxydesloratadine were not clinically relevant.

5.3 Preclinical safety data

Montelukast:

In animal toxicity studies, minor serum biochemical alterations in ALT, glucose, phosphorus and triglycerides were observed which were transient in nature. The signs of toxicity in animals were increased excretion of saliva, 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 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.

Desloratadine:

Desloratadine is the primary active metabolite of loratadine. Non-clinical studies conducted with desloratadine and loratadine demonstrated that there are no qualitative or quantitative differences in the toxicity profile of desloratadine and loratadine at comparable levels of exposure to desloratadine.

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 and development. The lack of carcinogenic potential was demonstrated in studies conducted with desloratadine and loratadine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Mannitol (Delta M)

Croscarmellose sodium

Hydroxypropyl cellulose 11(L-HPC LH 11)

Colloidal silicon dioxide (Aerosil 200)

Microcrystalline cellulose PH 102

Microcrystalline cellulose PH 200

Magnesium stearate

Dibasic calcium phosphate dihydrate coarse powder

Pregelatinized maize starch

L-Leucine

Talc

Tablet coating:

Film coating material No:3 (Opadry Pink OY 34948): Hypromellose, titanium dioxide (E 171), polyethylene glycol / Macrogol, red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 30°C in its own pack.

6.5 Nature and contents of container

PE aluminium foil-PE aluminium formatura is packed in blister carton box.

Boxes of 30 film coated tablets: 10 tablets/3 blisters/1 box.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

8/10/2025

10. Date of revision of the text

10/2025