

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BRONCHOREST® 10 mg/5 mg capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substances:

Each capsule contains:

Montelukast (equivalent to 10.40 mg of Montelukast sodium)	10.00 mg
Levocetirizine dihydrochloride	5 mg

Excipients:

Lactose DCL 14(bovine) 148,38 mg

See warning in section 4.4. For a full list of

excipients, see section 6.1

3. PHARMACEUTICAL FORM

Capsule.

White coloured, round film tablet and blue-green coloured hard gelatin capsule containing white-yellowish granular powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Bronchorest is indicated for;

- ✓ the treatment and the relief of symptoms of allergic rhinitis and asthma accompanied by allergic rhinitis
- ✓ BRONCHOREST® is also indicated for the treatment of an antihistamine-resistant skin disease caused by allergy (chronic idiopathic urticaria) in patients 15 years of age and over.

4.2. Posology and method of administration

Posology/frequency and duration of administration:

The recommended dose for adults from 15 years of age is one capsule (5 mg levocetirizine dihydrochloride and 10 mg montelukast) daily.

Patients already taking levocetirizine and montelukast capsules separately for compliance may start to take BRONCHOREST® containing the same components at the same doses.

Therapeutic effect of BRONCHOREST® on allergic rhinitis and allergy-induced asthma starts within one day. Patients should be advised to continue taking BRONCHOREST® even during the periods of allergic contact.

Duration of use depends on the type, duration and course of complaints. 3-6 weeks for hay fever and in case of short term exposure to pollens, one week treatment is generally sufficient.

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

In case of persistent allergic rhinitis (symptoms >4 days/week and during more than 4 weeks), continuous therapy can be proposed to the patient during the period of exposure to allergens.

Method of administration:

BRONCHOREST[®] must be taken orally, swallowed whole with some water. BRONCHOREST[®] may be taken with or without food. Capsules should not be chewed or crushed.

Additional information on special populations:

Renal/Hepatic impairment:

The dosing intervals must be adjusted individually according to renal function. Refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in ml/min is needed. The CLcr (ml/min) may be estimated from serum creatinine (mg/dl) determination using the following formula:

$$\text{CLcr} = \frac{[140 - \text{age (year)}] \times \text{body weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} \quad (\times 0,85 \text{ for women})$$

Dose adjustment in patients with renal impairment

Group	Creatinine clearance (ml/minute)	Dose and dosing frequency
Normal	≥80	5 mg daily
Mild	50-79	5 mg once daily
Moderate	30-49	5 mg every other day
Severe	< 30	5 mg every three days
In patients with end-stage renal impairment and patients undergoing dialysis Dialysis patients	< 10	Contraindicated

Dose adjustment is recommended in patients with hepatic impairment and renal impairment. No dose adjustment is required in patients with mild to moderate hepatic impairment. However, there is no data available on patients with severe hepatic impairment.

Paediatric population:

Efficacy and safety in children below age 15 have not been determined.

Geriatric population:

Dose adjustment is recommended in elderly patients with moderate and severe renal impairment (see section “Renal/Hepatic Impairment”).

Therapy with BRONCHOREST® in relation to other treatments for asthma
BRONCHOREST® can be added to the patient's existing treatment regimen.

Dose reduction in concomitant treatments

Treatment with bronchodilators:

BRONCHOREST® can be added to the treatment regimen of patients who are not adequately controlled with a single bronchodilator. Following clinical response (usually after the first dose) bronchodilator therapy may be reduced as tolerated.

Inhaled corticosteroids:

BRONCHOREST® treatment provides additional clinical benefit in patients treated with inhaled corticosteroids. The dose of corticosteroids may be reduced as tolerated. Dose should be gradually reduced under medical supervision. In some patients, the dose of inhaled corticosteroid may be gradually discontinued. In some patients BRONCHOREST® treatment should not be abruptly substituted for inhaled corticosteroids.

4.3. Contraindications

It is contraindicated in patients with hypersensitivity to any of the ingredients or to any piperazine derivatives;

- ✓ Patients with severe renal impairment (creatinine clearance less than 10 ml/min.).

4.4. Special warnings and precautions for use

General recommendations

BRONCHOREST® is not recommended in children aged less than 15 years since the pharmaceutical form of currently available capsules do not allow dose adjustment.

Precaution is recommended if alcohol is taken concomitantly (See Section 4.5 Interaction with other medicinal products and other forms of interaction).

Caution should be taken in patients with predisposing factors of urinary retention (e.g. spinal cord lesion, prostatic hyperplasia) as levocetirizine may increase the risk of urinary retention.

Patients should be advised never to use BRONCHOREST® 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.

BRONCHOREST® should not be substituted abruptly for inhaled or oral corticosteroids.

There are no data demonstrating that oral corticosteroids can be discontinued when BRONCHOREST® is given concomitantly.

Neuropsychiatric cases

Neuropsychiatric cases have been reported in adult, adolescents and paediatric patients using montelukast/levocetirizine combination. Post-marketing reports with montelukast/levocetirizine combination use include agitation, aggressive behaviours or hostility, anxiousness, depression, disorientation, dream abnormalities, hallucinations, insomnia, irritability, memory impairment, restlessness, somnambulism, suicidal thinking and behaviour (including suicide) and tremor. The clinical details of some post-marketing reports involving montelukast/levocetirizine combination appear consistent with a drug-induced effect.

Patients and prescribers should be alert for neuropsychiatric events. Patients should be instructed to notify their prescriber if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with BRONCHOREST[®] if such events occur (see Section 4.8).

Eosinophilic Conditions

Patients with asthma on therapy with BRONCHOREST[®] 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 events have been sometimes associated with the reduction of oral corticosteroid therapy. The possibility that leukotriene receptor antagonists may be associated with emergence of Churg-Strauss syndrome can neither be excluded nor established. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. Patients who develop these symptoms should be reassessed and their treatment regimens evaluated.. Treatment with BRONCHOREST[®] does not alter the need for patients with aspirin-sensitive asthma to avoid taking aspirin and other non-steroidal anti-inflammatory drugs.

Excipients:

Lactose warning

Each capsule of BRONCHOREST[®] 10 mg/5 mg contains 148.38 mg of lactose.

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

Levocetirizine-related interactions

No interaction studies have been performed with levocetirizine (including no studies with CYP3A4 inducers). Studies with the racemate compound cetirizine demonstrated that there were no clinically relevant adverse interactions with pseudoephedrine, cimetidine, ketoconazole, erythromycin, azithromycin, glipizide and diazepam. A small decrease in the clearance of cetirizine (16%) was observed in a multiple dose study with theophylline (400 mg once a day); while the disposition of theophylline was not altered by concomitant cetirizine administration.

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 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 simultaneous administration of cetirizine or levocetirizine and alcohol or other CNS depressants may have effects on the central nervous system, although it has been shown that the racemate cetirizine does not potentiate the effect of alcohol.

Montelukast-related interactions

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 metabolized 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 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 metabolized by this enzyme (e.g. Paclitaxel, rosiglitazone and repaglinide).

In vitro studies have shown that montelukast is a substrate of CYP 2C8, 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. Co-administration of montelukast and gemfibrozil with itraconazole, a strong inhibitor of CYP 3A4 resulted in no significant increase in the systemic exposure of montelukast. Based on the absence of clinically important adverse events in adults when montelukast has been administered at doses higher than the recommended dose of 10 mg (e.g. Doses up to 200 mg/day to adult patients for 22 weeks and up to 900 mg for approximately one week), it has been suggested that the effect of gemfibrozil on systemic exposure of montelukast is not clinically significant. Therefore, no dosage adjustment of montelukast is required upon co-administration with gemfibrozil. Based on *in vitro* data, clinically important drug interactions with other known inhibitors of CYP 2C8 (e.g., trimethoprim) are not anticipated. Furthermore, when montelukast is co-administered only with itraconazole, no significant increase in the systemic exposure of montelukast has occurred.

4.6. Pregnancy and lactation

General recommendation

Pregnancy category is C.

Women with childbearing potential / Contraception

There are no adequate data on the effects on the fertility of women with childbearing potential.

Pregnancy

There are no adequate data on the use of BRONCHOREST® in pregnant women. Animal studies showed reproductive toxicity (see section 5.3). Potential risk in humans is unknown.

Breastfeeding

It is unknown whether montelukast is excreted in human milk. Cetirizine is excreted in human milk.

BRONCHOREST® is not recommended in breastfeeding women.

Fertility

In fertility studies in female rats, montelukast produced reductions in fertility and fecundity indices at an oral dose of 200 mg/kg (estimated exposure was approximately 70 times the AUC for adults at the maximum recommended daily oral dose). No effects on female fertility or fecundity were observed at an oral dose of 100 mg/kg (estimated exposure was approximately 20 times the AUC for adults at the maximum recommended daily oral dose). Montelukast had no effects on fertility in male rats at oral doses up to 800 mg/kg (estimated exposure was approximately 160 times the AUC for adults at the maximum recommended daily oral dose).

Animal studies showed that levocetirizine has no effect on fertility.

There are no adequate data on the effect of BRONCHOREST® on human reproductive ability.

4.7. Effects on ability to drive and use machines

Montelukast has no influence on the ability to drive and use machines. However, drowsiness and dizziness have been reported rarely.

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

Levocetirizine

In therapeutic studies in women and men aged 12 to 71 years, 15.1% of the patients in the levocetirizine 5mg group had at least one adverse drug reaction compared to 11.3% in the placebo group

In therapeutic trials, the drop out rate due to adverse events was 1.0% (9/935) with levocetirizine 5mg and 1.8% (14/771) with placebo.

Clinical therapeutic trials with levocetirizine included 935 subjects exposed to the drug at the recommended dose of 5mg daily. From this pooling, following incidence of common adverse drug reactions were reported at rates of 1 % or greater (common: $\geq 1/100$, $\leq 1/10$) under levocetirizine 5mg or placebo:

Advers Event	Placebo (n=771)	Levocetirizine 5 mg (n=995)
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 $\geq 1/1000$, $\leq 1/100$) such as 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 5mg 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 Organ Class and Preferred Term	Placebo (n=83)	Levocetirizine (n=159)
Gastrointestinal Disorders		
Diarrhoea	0	3 (1.9%)
Vomiting	2 (1.2%)	1 (0.6%)
Constipation	0	2 (1.3%)
Nervous System Disorders		
Somnolence	2 (2.4%)	3 (1.9%)
Psychiatric Disorders		
Sleep disorders	0	2 (1.3%)

In children aged 6-15 years double blind placebo controlled studies were performed where 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 5 mg (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: Very common ($\geq 1/10$); common ($\geq 1/100$ to $\leq 1/10$); uncommon ($\geq 1/1,000$ to

$\leq 1/100$); rare ($\geq 1/10,000$ to $\leq 1/1,000$); very rare ($\leq 1/10,000$), not known (cannot be estimated from the available data).

Immune system disorders

Very rare: Hypersensitivity including anaphylactic shock

Not known: Hypersensitivity reaction including anaphylaxis

Metabolism and nutrition disorders

Not known: Increased appetite

Psychiatric disorders

Not known: Aggression, agitation, hallucination, depression, insomnia, suicidal ideation

Nervous system disorders

Common: Somnolence, headache

Not known: Convulsion, paraesthesia, dizziness, syncope, tremor, dysgeusia

Eye disorders

Not known: Visual disturbances, blurred vision, oculogyration

Ear and labyrinth disorders

Not known: Vertigo

Cardiac disorders

Very rare: Palpitations, tachycardia

Respiratory, thoracic, and mediastinal disorders

Not known: Dispnea

Gastrointestinal disorders

Common: Mouth dry

Uncommon: Abdominal pain

Not known: Nausea, vomiting

Hepatobiliary disorders

Not known: Hepatitis

Skin and subcutaneous tissue disorders

Unknown: Angioneurotic edema, fixed drug eruption, pruritus, rash, urticaria

Musculoskeletal, connective tissues, and bone disorders

Not known: Myalgia

Renal and urinary disorders

Not known: Dysuria, urinary retention

General disorders and administration site conditions

Common: Fatigue

Uncommon: Asthenia

Not known: Edema

Investigations

Not known: Weight increased, abnormal liver function tests

Montelukast

Montelukast has been evaluated in clinical studies as follows:

- ✓ 10 mg film-coated tablets in approximately 4,000 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.

The following drug-related adverse reactions in clinical studies were reported commonly ($\geq 1/100$ to $< 1/10$) in asthmatic patients 15 years of age and older treated with montelukast and at a greater incidence than in patients treated with placebo:

Nervous system disorders

Common: Headache

Gastrointestinal disorders

Common: Abdominal pain

Post-marketing experience

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. 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 ($< 1/10,000$).

Infections and infestations

Very common: Upper respiratory infection*

Blood and lymphatic system disorders

Rare: Increased bleeding tendency

Immune system disorders

Uncommon: Hypersensitivity reactions including anaphylaxis

Very rare: Hepatic eosinophilic infiltration

Psychiatric disorders

Uncommon: Dream abnormalities including nightmares, insomnia, irritability, anxiety, restlessness, agitation including aggressive behaviour or hostility, depression, somnambulism

Rare: Tremor, lack of attention, forgetfulness

Very rare: Hallucinations, suicidal thinking and behaviour (suicidality), disorientation

Nervous system disorders

Uncommon: Dizziness, drowsiness, paraesthesia/hypoesthesia, seizure

Cardiac disorders

Rare: Palpitations

Respiratory, thoracic, and mediastinal disorders

Uncommon: Epistaxis

Very rare: Churg-Strauss Syndrome (CSS) (see section 4.4), Pulmonary eosinophilia

Gastrointestinal disorders

Common: Diarrhoea**, nausea**, vomiting**

Uncommon: Dry mouth, dyspepsia

Hepatobiliary disorders

Common: Elevated levels of serum transaminases (ALT, AST)

Very rare: Hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury).

Skin and subcutaneous tissue disorders

Common: Rash**

Uncommon: Bruising, urticaria, pruritus

Rare: Angioedema

Very rare: Erythema nodosum, erythema multiforme

Musculoskeletal and connective tissue disorders

Uncommon: Arthralgia, myalgia including muscle cramps

General disorders and administration site conditions

Common: Pyrexia**

Uncommon: Asthenia/fatigue, malaise, oedema

*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.

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. Healthcare professionals are asked to report any suspected adverse reactions to Turkish Pharmacovigilance Center (TÜFAM) at www.tick.gov.tr; e-mail: tufam@titck.gov.tr; tel: 0 800 314 00 08; fax: 0 312 218 35 99)

4.9. Overdose

There have been no reports of overdose with BRONCHOREST®.

Levocetirizine

Symptoms:

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

Treatment:

There is no known specific antidote to levocetirizine.

In case of overdose, 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

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

It is not known whether montelukast is dialyzable by peritoneal- or haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Combination of systemic antihistamine, piperazine derivative and leukotriene receptor antagonist

ATCcode:R03DC53

Levocetirizine

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

Binding studies revealed that levocetirizine has high affinity for human H₁-receptors ($K_i = 3.2$ nmol/l). Levocetirizine has an affinity 2-fold higher than that of cetirizine ($K_i = 6.3$ nmol/l). Levocetirizine dissociates from H₁-receptors with a half-life of 115 ± 38 min. After single administration, levocetirizine shows a receptor occupancy of 90% at 4 hours and 57% at 24 hours.

Pharmacodynamic studies in healthy volunteers demonstrate that, at half the dose, levocetirizine has comparable activity to cetirizine, both in the skin and in the nose.

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

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

The onset of action of levocetirizine 5mg 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 5mg in the first 6 hours of pollen-induced reaction, compared with placebo in 14 adult patients. Inhibition of VCAM-1 release, modulation of vascular permeability and a decrease in eosinophil recruitment.

The efficacy and safety of levocetirizine has been demonstrated in several double-blind, placebo controlled, clinical trials performed in adult patients suffering from seasonal allergic rhinitis, perennial allergic rhinitis, or persistent allergic rhinitis. Levocetirizine has been shown to significantly improve symptoms of allergic rhinitis, including nasal obstruction in some studies.

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

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

Montelukast

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.

Levocetirizine / Montelukast

In a 32-week randomized, double-blind, placebo-controlled, crossover study in 20 patients with persistent allergic rhinitis, patients received montelukast 10 mg/day and/or levocetirizine 5 mg/day or placebo. In addition to sleep problems, quality of life was assessed on the day before starting treatment and on the last day of each treatment period using the Rhinoconjunctivitis Quality of Life Questionnaire. In the study, the mean quality of life score before treatment was 2.58 (0.49) and after placebo it was 1.78 (0.46), after levocetirizine 1.38 (0.42), after montelukast 1.36 (0.37), and after montelukast plus levocetirizine it was 1.26 (0.39). For persistent AR, the combination treatment was found to be more effective than monotherapy.

A randomized, double-blind, placebo-controlled crossover study was performed in patients with persistent allergic rhinitis, who received levocetirizine (5 mg/day), montelukast (10 mg/day), placebo, or a combination of levocetirizine and montelukast. The treatment periods were separated by 2-week washout periods. Symptom scoring, skin prick tests, spirometry, rhinometry, and nasal lavage were performed the day before and the last days of the treatment

periods. Eosinophil cationic protein levels were evaluated by means of nasal lavage. The mean SD total baseline nasal symptom score was 7.95 +/- 0.68 before treatment, 3.02 +/- 0.64 after levocetirizine use, 3.44 +/- 0.55 after montelukast use, and 2.14 +/- 0.39 after montelukast-levocetirizine use. The greatest improvement in nasal symptoms occurred after combination treatment. Decreases in the level of eosinophil cationic protein were greater after the combined use of montelukast and levocetirizine.

5.2. Pharmacokinetic properties

General properties

Following oral administration of BRONCHOREST[®], levocetirizine and montelukast reach peak plasma concentrations after 3 hours. Rate and extent of absorption of BRONCHOREST[®] is equivalent to the bioavailability of levocetirizine and montelukast given as single tablet.

Levocetirizine

The pharmacokinetics of levocetirizine are linear, dose- and time-independent, with low 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.

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 o.d. dose, respectively. The extent of absorption is dose-independent and is not altered by food, but the peak concentration is reduced and delayed.

Distribution:

No tissue distribution data are available in humans, neither concerning the passage of levocetirizine through the blood-brain-barrier. In rats and dogs, the highest tissue levels are found in liver and kidneys, the lowest in the CNS compartment.

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

Biotransformation:

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

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

Elimination:

The plasma half-life in adults is 7.9 ± 1.9 hours. In children, the half-life is shorter. In adults, the mean apparent total body clearance is 0.63ml/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.

Linearity/Non Linearity

Levocetirizine exhibits linear pharmacokinetics.

Montelukast

Absorption:

Montelukast is rapidly absorbed from the gastrointestinal tract 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 *in vitro* studies using human liver microsomes indicate that CYP3A4, 2C8, and 2C9 are involved in the metabolism of montelukast. 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 radiolabeled montelukast, 86% of the radioactivity was recovered in 5-day fecal 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.

Linearity/Non Linearity

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%).

Patients characteristics

Race:

Based on the absorption and biotransformation properties of the drug, ethnical origin of the patient is not expected to have any effect on the pharmacokinetic characteristics of levocetirizine.

Gender:

Peak plasma concentrations and total absorption of levocetirizine are respectively 20% and 15% higher in women than in men. The half-life was slightly shorter in women (7.1 hours) than in men (8.6 hours). However, the body weight-adjusted oral clearance in women (0.67 ml/min/kg) appears to be comparable to that in men (0.59 ml/min/kg). The same daily doses and dosing intervals are applicable for men and women with normal renal function.

Renal/Hepatic impairment:

The apparent body clearance of levocetirizine is correlated to the creatinine clearance. It is therefore recommended to adjust the dosing intervals of levocetirizine, based on creatinine clearance in patients with moderate and severe renal impairment. In anuric end stage renal disease subjects, the total body clearance is decreased by approximately 80% when compared to normal subjects. The amount of levocetirizine removed during a standard 4-hour hemodialysis procedure was < 10%.

Dose adjustment is not required in patients with mild to moderate hepatic impairment. There are no data on the pharmacokinetics of montelukast in patients with severe hepatic impairment (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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction, genotoxicity or carcinogenicity.

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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Microcrystalline cellulose
Hydroxy propyl cellulose
Lactose DCL14(bovine)
Croscarmellose sodium
Magnesium stearate
Crospovidone

Talc
Sodium Stearyl Fumarate
HPMC 15 cP-Methocel
Titanium Dioxide
PEG 6000

Capsule:
Patent Blue V
Quinoline Yellow
Titanium Dioxide
Water
Gelatin(bovine)

6.2. Incompatibilities

There is no known incompatibility.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at room temperature below 25°C.

6.5. Nature and contents of container

30 and 90 capsules packaged in Alu-Alu-Aluminum folio blisters, in a cardboard box also containing the package leaflet.

6.6. Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Any unused medicinal product or waste material should be disposed of in accordance with the “Regulation on Medical Waste” and “Regulation on the Control of Packaging and Packaging Waste”.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

2015/866

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11.11.2015

Date of last renewal: ---

10. DATE OF REVISION OF THE TEXT

17.05.2019