

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE HUMAN MEDICAL PRODUCT

BRONCHOREST 4 mg/2.5 mg chewable tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each chewable tablet;

Active ingredient:

Levocetirizine dihydrochloride	2.5 mg
Montelukast sodium	4,157 mg
(Equivalent to 4 mg montelukast)	

Excipients:

Maltitol (E965)	122.2 mg
Lactose monohydrate	32mg
Croscarmellose sodium	7.2 mg

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Chewable tablet.

Flat, round tablet with pink or pinkish surface on one side and white or whitish surface on the other.

4. CLINICAL FEATURES

4.1. Therapeutic indications

It is indicated for the treatment and relief of symptoms of allergic rhinitis (intermittent/persistent or seasonal/perennial) and asthma accompanied by allergic rhinitis.

4.2. Posology and method of application Posology/frequency and duration of application:

Children aged 15 years and over and adults: Two BRONCHOREST 4/2.5 mg chewable tablets are used once a day.

Children aged 2-14 years: One BRONCHOREST 4/2.5 mg chewable tablet is used once a day.

For compliance, patients taking levocetirizine and montelukast as separate tablets may be switched to BRONCHOREST, which contains the same component doses.

The therapeutic effect of BRONCHOREST on allergic rhinitis and allergic asthma begins within one day. Patients should be advised to continue taking BRONCHOREST during periods of allergic contact.

Intermittent allergic rhinitis (symptoms lasting less than 4 days per week or less than 4 weeks) is treated according to the disease and history; treatment can be stopped when symptoms resolve and restarted when symptoms reappear.

In persistent allergic rhinitis (symptoms lasting more than 4 days per week and more than 4 weeks), it is recommended that treatment be continued throughout the period the patient is exposed to allergens.

Application method:

BRONCHOREST is taken orally by chewing.

BRONCHOREST can be taken on an empty or full stomach.

Additional information regarding special populations:

Kidney failure:

Levocetirizine dosing intervals in patients with renal impairment should be adjusted based on renal function and using the table below. To use this dosage table, the patient's creatinine clearance (Clcr) in ml/min is required. Clcr (ml/min) can be calculated from serum creatinine (mg/dl) values using the following formula:

$$\text{Clcr} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine value (mg/dl)}} (\times 0.85 \text{ [for women]})$$

Dosage Adjustment for Patients with Impaired Renal Function

Group	Creatinine clearance (ml/min)	Dosage and frequency
Normal	≥ 80	Levocetirizine 5 mg per day
Light	50-79	Levocetirizine 5 mg per day
Middle	30-49	Levocetirizine 5 mg every 2 days
Serious	< 30	Levocetirizine 5 mg every 3 days
In patients with end-stage renal disease and those on dialysis	< 10	Contraindicated

In pediatric patients with renal impairment, the dose should be adjusted individually based on the patient's renal clearance and body weight. No specific data are available for children with renal impairment.

Liver failure:

No dose adjustment is required in patients with mild to moderate hepatic impairment. However, there are no data available for patients with severe hepatic impairment.

Dosage adjustment is recommended in patients with combined hepatic and renal failure.

Pediatric population:

BRONCHOREST is not recommended for use in children and infants under 2 years of age due to lack of data.

Geriatric population:

In geriatric populations, dose adjustment is recommended in elderly patients with moderate to severe renal impairment (see "Renal/Liver impairment" section).

In combination with other asthma treatments Treatment with BRONCHOREST

Inhaled corticosteroids: BRONCHOREST may be used as an adjunctive treatment if necessary in patients inadequately controlled with inhaled corticosteroids and/or short-acting β_2 -agonists. If necessary, the dose of inhaled corticosteroids may be gradually reduced. However, inhaled corticosteroids should not be stopped abruptly and treatment with BRONCHOREST should be initiated.

4.3. Contraindications

- People with hypersensitivity to BRONCHOREST, levocetirizine, montelukast or any of the excipients contained in the tablet composition or piperazine derivatives,
- Contraindicated in patients with severe renal impairment (creatinine clearance below 10 ml/min).

4.4. Special use warnings and precautions

General

Caution is advised when taken with alcohol (see section 4.5 Interactions with other medicinal products and other forms of interaction).

Levocetirizine should be used with caution in patients with predisposing factors for urinary retention (e.g., spinal cord lesion, prostatic hyperplasia) as it may increase the risk of urinary retention.

Patients should be advised never to use BRONCHOREST for the treatment of acute asthma attacks and to keep their usual rescue medication readily available for this purpose.

A short-acting inhaled beta-agonist should be used during an acute attack. Patients should contact their doctor as soon as possible if they require more inhalations of a short-acting beta-agonist than usual.

BRONCHOREST should not be stopped and replaced with inhaled or oral corticosteroids abruptly.

There are no data to suggest that oral corticosteroids can be discontinued when montelukast is given concomitantly.

Neuropsychiatric events

Neuropsychiatric events, including behavioural changes, depression and suicidality, have been reported in all age groups using montelukast (see section 4.8).

Symptoms may be severe and persist if treatment is not discontinued.

Therefore, if neuropsychiatric symptoms occur during treatment, treatment with montelukast should be discontinued.

Advise patients and/or caregivers to be alert for neuropsychiatric events and instruct patients to notify their physicians if such changes in behavior occur.

Eosinophilic conditions

In rare cases, patients treated with antiasthmatic agents such as BRONCHOREST may present with systemic eosinophilia, which may occasionally be accompanied by clinical features of vasculitis consistent with Churg-Strauss syndrome, a disorder usually treated with systemic corticosteroid medications. These events have generally, but not invariably, been associated with the reduction or discontinuation of oral corticosteroid therapy. The possibility that leukotriene receptor antagonists are associated with the onset of Churg-Strauss syndrome cannot be excluded or proven. Physicians should be alert for eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac

complications, and/or neuropathy in their patients. Patients who develop these symptoms should be re-evaluated, and their treatment regimens should be reviewed. Treatment with BRONCHOREST does not alter the need for aspirin-sensitive patients to avoid aspirin and other nonsteroidal anti-inflammatory drugs.

Excipient warning

Contains maltitol. Patients with rare hereditary fructose intolerance problems should not use this medicine.

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

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, i.e. it is essentially “sodium-free”.

4.5. Interactions with other medical products and other forms of interaction

Interactions associated with levocetirizine

There are no interaction studies with levocetirizine (nor are there studies with CYP3A4 inducers). Studies with cetirizine, the racemate of levocetirizine, have shown no clinically significant adverse interactions (with pseudoephedrine, cimetidine, ketoconazole, erythromycin, azithromycin, glipizide, and diazepam). In a multiple-dose study with theophylline (400 mg once daily), a small decrease in cetirizine clearance (16%) was observed; however, the disposition of theophylline was not altered when co-administered with cetirizine.

Although the rate of absorption decreases when BRONCHOREST is taken with food, the amount of absorption does not change.

Although racemate cetirizine has not been shown to potentiate the effects of alcohol, in susceptible patients, concomitant use of alcohol or other CNS depressants with cetirizine or levocetirizine may have CNS effects.

In a multiple dose study with ritonavir (600 mg twice daily) and cetirizine (10 mg daily), exposure to cetirizine was increased by approximately 40%, while the disposition of ritonavir was slightly decreased when co-administered with cetirizine.

Interactions associated with Montelukast

Montelukast has been administered with other treatments routinely used for asthma prophylaxis and chronic treatment. In drug interaction studies, montelukast at the recommended clinical dose did not have clinically important effects on the pharmacokinetics of the following drugs:

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

The area under the plasma concentration curve (AUC) of montelukast decreased by approximately 40% in patients concomitantly administered phenobarbital. Because montelukast is metabolized by CYP 3A4, 2C8, and 2C9, caution should be exercised when administering montelukast, especially to children, with inducers of CYP 3A4, 2C8, and 2C9, such as phenytoin, phenobarbital, and rifampin.

In vitro Studies have shown that montelukast is a potent inhibitor of CYP 2C8. However, data from a clinical 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 expected to significantly

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. Data from a clinical drug interaction study involving montelukast and gemfibrozil (an inhibitor of both CYP 2C8 and 2C9) showed that gemfibrozil increased the systemic exposure of montelukast by 4.4-fold. Co-administration of itraconazole, a strong CYP 3A4 inhibitor, with gemfibrozil and montelukast did not further increase the systemic exposure of montelukast. Based on the absence of clinically important adverse events at doses higher than the approved 10 mg dose in adults (e.g., 200 mg daily for 22 weeks and up to 900 mg daily for approximately one week in adult patients), the effect of gemfibrozil on the systemic exposure of montelukast is not considered to be clinically significant. Therefore, no dose adjustment of montelukast is necessary when co-administered with gemfibrozil. Based on *in vitro* data, clinically significant drug interactions are not expected with other known inhibitors of CYP 2C8 (e.g., trimethoprim). Additionally, co-administration of montelukast with itraconazole alone did not result in a significant increase in montelukast systemic exposure.

4.6. Pregnancy and lactation

General advice

Pregnancy category: C

Women of childbearing potential/Birth control (Contraception)

There are insufficient data on the effects on reproductive capacity in women of childbearing potential.

Pregnancy period

There is insufficient data on the use of BRONCHOREST in pregnant women.

Animal studies with levocetirizine have not reported any direct or indirect harmful effects on pregnancy, embryonal/fetal development, parturition or postnatal development.

Animal studies with montelukast do not indicate harmful effects with respect to pregnancy or embryonal/fetal development.

Limited data from available pregnancy databases do not suggest a causal relationship between montelukast and malformations (e.g., longitudinal defects) rarely reported during worldwide post-marketing use.

BRONCHOREST can be used during pregnancy only if it is decided that it is absolutely necessary.

Lactation period

It is unknown whether montelukast is excreted in human milk. Cetirizine, the racemate of levocetirizine, is excreted in human milk; therefore, it is likely that levocetirizine is also excreted in human milk.

BRONCHOREST is not recommended for use by breastfeeding women.

Reproductive ability/Fertility

Animal studies with levocetirizine have shown no effect on fertility.

In fertility studies in female rats, montelukast caused decreases in fertility and fecundity indicators at an oral dose of 200 mg/kg (estimated exposure was approximately 70 times the AUC in adults at the maximum recommended daily oral dose). No effects on fertility or fecundity were observed in females at an oral dose of 100 mg/kg (estimated exposure was approximately 20 times the AUC in

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 in adults at the maximum recommended daily oral dose).

There are insufficient data on the reproductive potential of BRONCHOREST in humans.

4.7. Effects on ability to drive and use machines

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

Comparative clinical studies have shown that levocetirizine, at recommended doses, does not impair mental alertness, driving responsiveness, or ability to drive. However, some patients may experience somnolence, fatigue, and asthenia while on levocetirizine therapy. Montelukast is not expected to have any adverse effects on the ability to drive or operate machinery. However, drowsiness has been reported in very rare cases.

Therefore, patients who must drive, engage in potentially hazardous activities, or operate machinery should consider their response to the medication.

4.8. Undesirable effects

Like all medicines, BRONCHOREST may cause side effects in people who are sensitive to the ingredients it contains.

Additional information about each component

Levocetirizine

In therapeutic studies in males and females aged 12-71 years, 15.1% of patients in the levocetirizine 5 mg group and 11.3% of patients in the placebo group experienced at least one adverse drug reaction.

In therapeutic studies, the proportion discontinuing treatment due to adverse events was 1.0% (9/935) with levocetirizine 5 mg and 1.8% (14/771) with placebo.

In clinical studies with levocetirizine, 935 subjects received the recommended daily dose of 5 mg. In these data from patients receiving levocetirizine 5 mg or placebo, the following adverse drug reactions were reported at an incidence of 1% or greater (common: $\geq 1/100$, $< 1/10$):

Adverse effects	Placebo (n=771)	Levocetirizine 5 mg (n=935)
Headache	25 (3.2%)	24 (2.6%)
Somnolence	11 (1.4%)	49 (5.2%)
Dry mouth	12 (1.6%)	24 (2.6%)
Fatigue	9 (1.2%)	23 (2.5%)

Additionally, uncommon ($\geq 1/1,000$ to $< 1/100$) adverse reactions such as asthenia or abdominal pain were observed.

All sedative adverse drug reactions, such as somnolence, fatigue, and asthenia, were more frequent with levocetirizine 5 mg (8.1%) than with placebo (3.1%).

Pediatric Population

In two placebo-controlled studies in pediatric patients aged 6 to 11 months and 1 year to less than 6 years, 159 volunteers received levocetirizine 1.25 mg daily and 1.25 mg twice daily for 2 weeks,

respectively. The following adverse reactions were reported at rates of 1% or greater in those treated with levocetirizine or placebo:

System Organ Class and Preferred Name	Placebo (n=83)	Levocetirizine (n=159)
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 disorders	0	2 (1.3%)

Double-blind, placebo-controlled studies were conducted in children aged 6 to 15 years who were exposed to 5 mg levocetirizine for various periods ranging from less than 1 week to 13 weeks. The following adverse reactions were reported at rates of 1% or greater in those treated with levocetirizine or placebo:

Preferred name	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 presented by system organ class and frequency: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$) and very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Immune system diseases

Very rare: Hypersensitivity, including anaphylactic shock Not known: Hypersensitivity reaction, including anaphylaxis

Metabolism and nutritional diseases

Unknown: Increased appetite

Psychiatric illnesses

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

Nervous system diseases

Common: Somnolence, headache

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

Eye diseases

Not known: Visual disturbance, blurred vision, oculogyration

Ear and inner ear diseases

Unknown: Vertigo

Cardiac diseases

Very rare: Palpitations, tachycardia

Respiratory, thoracic and mediastinal diseases

Unknown: Dyspnea

Gastrointestinal diseases

Common: Dry mouth

Uncommon: Abdominal pain

Not known: Nausea, vomiting

Hepatobiliary diseases

Unknown: Hepatitis

Skin and subcutaneous tissue disorders

Not known: Angioneurotic edema, fixed drug eruption, pruritus, rash, urticaria

Musculoskeletal disorders, connective tissue and bone diseases

Not known: Muscle pain (myalgia)

Kidney and urinary diseases

Not known: Dysuria, urinary retention

General disorders and diseases related to the application area

Common: Weakness

Uncommon: Asthenia

Unknown: Edema

Research

Not known: Weight gain, liver function test abnormalities

Montelukast

Montelukast has been evaluated in clinical studies in patients with persistent asthma as follows:

- 10 mg film-coated tablets in approximately 4000 adolescent and adult patients aged 15 years and over
- 5 mg chewable tablets in 1750 pediatric patients aged 6-14 years
- 4 mg chewable tablets in 851 pediatric patients aged 2-5 years

Montelukast has been evaluated in clinical studies in patients with intermittent asthma as follows.

4 mg granules and chewable tablets In clinical trials in pediatric asthmatic patients 2 to 5 years of age treated with Montelukast (one 12-week study, n=461) (one 48-week study, n=278) in 1038 pediatric patients 6 months to 5 years of age, the following drug-related adverse reactions were reported at a higher rate than placebo:

Gastrointestinal diseases:

Common: Abdominal pain

General disorders and diseases related to the application area:

Common: Thirst

In clinical studies in adolescent and adult asthmatic patients aged 15 years and older (two 12-week studies n=795) treated with montelukast, common drug-related adverse reactions ($\geq 1/100$, $< 1/10$) reported at a higher rate than placebo were as follows:

Nervous system diseases:

Common: Headache

Gastrointestinal diseases:

Common: Abdominal pain

In clinical studies in pediatric asthmatic patients aged 6 to 14 years treated with montelukast (one 8-week study, n=201) (two 56-week studies, n=615) and with a higher rate than placebo, the following drug-related adverse reactions were reported commonly ($\geq 1/100$, $< 1/10$):

Nervous system diseases:

Common: Headache

In long-term asthma treatment in adults in a limited number of patients in clinical trials

The safety profile was unchanged for up to 2 years in pediatric patients and for up to 12 months in patients aged 6 to 14 years.

Cumulatively, 502 pediatric patients aged 2 to 5 years were treated with montelukast for at least 3 months, 338 patients were treated for 6 months or longer, and 534 patients were treated for 12 months or longer. The safety profile did not change with long-term treatment in these patients.

Post-marketing experience

Adverse reactions reported from post-marketing use are listed by System Organ Class and the specific Adverse Event Term. Frequency Categories are calculated based on relevant clinical studies. Frequency Category: For each Adverse Event Term, defined as the incidence reported in the clinical studies database: 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 tract infection†

Blood and lymphatic system diseases:

Rare: Increased tendency to bleed

Immune system diseases:

Uncommon: Hypersensitivity reactions including anaphylaxis

Very rare: Eosinophilic infiltration of the liver

Psychiatric diseases:

Uncommon: Dream abnormalities including nightmares, insomnia, anxiety, agitation including aggressive behaviour or hostility, depression, sleepwalking, psychomotor hyperactivity (including irritability, restlessness, tremor§)

Rare: Attention deficit, forgetfulness

Very rare: Hallucinations, suicidal ideation and behavior (suicidality), behavioral changes

Nervous system diseases:

Uncommon: Dizziness, drowsiness, paraesthesia/hypoesthesia, seizure

Cardiac diseases:

Rare: Palpitations

Respiratory, thoracic and mediastinal disorders:

Uncommon: Epistaxis

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

Gastrointestinal diseases

Common: Diarrhea‡, nausea‡, vomiting‡

Uncommon: Dry mouth, dyspepsia

Hepatobiliary diseases:

Common: Increased serum transaminase (ALT, AST) levels.

Very rare: Hepatitis (cholestatic hepatitis including hepatocellular and mixed regular liver scarring)

Skin and subcutaneous tissue diseases

Common: Rash‡

Uncommon: Bruising, urticaria, pruritus

Rare: Angioedema

Very rare: Erythema nodosum, erythema multiforme

Musculoskeletal disorders and connective tissue and bone diseases:

Uncommon: Arthralgia, myalgia including muscle cramps

General disorders and diseases related to the application area:

Common: Pyrexia‡

Uncommon: Fatigue/weakness, restlessness, edema

† This adverse event, reported as Very Common in patients receiving montelukast, was also reported as Very Common in patients receiving placebo in clinical trials.

‡ This adverse event, reported Commonly in patients receiving montelukast, was also reported Commonly in patients receiving placebo in clinical trials.

§ Frequency category: Rare

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorization is crucial. Reporting allows for continuous monitoring of the drug's benefit/risk balance. Healthcare professionals are required to report any suspected adverse reactions to the Turkish Pharmacovigilance Center (TÜFAM). www.titck.gov.tr; email: tufam@titck.gov.tr; Tel: 0 800 314 00 08; Fax: 0 312 218 35 99)

4.9. Overdose and treatment

There is no experience yet with overdose with BRONCHOREST.

Levocetirizine

Symptoms of overdose include drowsiness in adults and agitation and restlessness, followed by drowsiness, in children. There is no known specific antidote. If overdose occurs, symptomatic or supportive treatment is recommended. If ingestion has occurred recently, gastric lavage should be considered. Levocetirizine is not effectively removed by hemodialysis.

Montelukast

There is no specific information regarding the treatment of montelukast overdose. Montelukast has been administered to adult patients at doses up to 200 mg per day for 22 weeks in chronic asthma studies and up to 900 mg per day for approximately 1 week in short-term studies without clinically important adverse events.

Acute overdose has been reported in post-marketing experience and clinical studies with montelukast. These include reports of doses as high as 1000 mg in adults and children (approximately 61 mg/kg in a 42-month-old child). The observed clinical and laboratory findings are consistent with the safety profile in adult and pediatric patients. The majority of overdose reports have no adverse events. The most common adverse events, consistent with the safety profile of montelukast, include abdominal pain, somnolence, thirst, headache, vomiting, and psychomotor hyperactivity.

There is no information on whether montelukast is removed by peritoneal dialysis or hemodialysis.

5. PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Combination of systemic antihistamines, piperazine derivatives and leukotriene receptor antagonists

ATC Code: R03DC53

Levocetirizine

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

Binding studies have shown that levocetirizine interacts with human H₁ receptors (K_i = 3.2 nmol/l). Levocetirizine has twice the affinity of cetirizine (K_i = 6.3 nmol/l). Levocetirizine dissociates from H₁-receptors with a half-life of 115 ± 38 minutes.

After a single administration, the receptor retention rate of levocetirizine was 90% at 4 hours and 57% at 24 hours.

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

The pharmacodynamic activity of levocetirizine has been studied in randomized, 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 significantly ($p < 0.001$) reduced wheal and flare formation, with an effect that was highest in the first 12 hours and lasted for 24 hours, compared with placebo and desloratadine.

In placebo-controlled studies in the allergen challenge chamber model, the onset of action of levocetirizine 5 mg in controlling pollen-induced symptoms was observed 1 hour after drug intake.

In vitro studies ("Boyden Chamber" and cell layering techniques), levocetirizine has been shown to inhibit eotaxin-induced eosinophil transendothelial migration across skin and lung cells. An *in vivo* ("skin chamber" technique) pharmacodynamic experimental study in 14 adult patients identified three main inhibitory effects of levocetirizine 5 mg compared to placebo during the first 6 hours of the pollen-induced reaction: inhibition of Vascular Cell Adhesion Molecule-1 (VCAM-1) release, modulation of vascular permeability, and reduction in eosinophil recruitment.

The efficacy and safety of levocetirizine have been demonstrated in numerous double-blind, placebo-controlled clinical studies in adult patients with seasonal allergic rhinitis, perennial allergic rhinitis, or persistent allergic rhinitis. In some studies, levocetirizine has been shown to significantly improve all symptoms of allergic rhinitis, including nasal obstruction.

In a 6-month clinical study in 551 adult patients (including 276 patients receiving levocetirizine) with persistent allergic rhinitis (symptoms persisting for 4 days per week for at least 4 consecutive weeks) and sensitization to house dust mites and grass pollen, 5 mg levocetirizine was shown to be clinically and statistically significantly more effective than placebo in reducing the total symptom score of allergic rhinitis without tachyphylaxis throughout the study period. Levocetirizine significantly improved patients' quality of life throughout the study. Its effect on histamine-induced skin reactions was not dependent on plasma concentrations.

Levocetirizine had no effect on the QT interval on ECGs.

Montelukast

Cysteinyl leukotrienes (LTC₄, LTD₄, LTE₄) are potent inflammatory eicosanoids released from a variety of 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 (respiratory smooth muscle cells and respiratory macrophages) and on other pro-inflammatory cells (eosinophils and certain myeloid stem cells). CysLTs have been implicated in the pathophysiology of asthma and allergic rhinitis. Leukotriene-mediated effects in asthma include bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment. In allergic rhinitis, CysLTs are released from the nasal mucosa during both early- and late-phase reactions after allergen exposure and are associated with allergic rhinitis symptoms. CysLTs administered intranasally have been shown to increase nasal airway resistance and symptoms of nasal congestion.

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. Quality of life, as well as sleep problems, was assessed before starting treatment and on the last day of treatment using the Rhinoconjunctivitis Quality of Life Scale. The mean pre-treatment quality of life score was 2.58 (0.49), 1.78 (0.46) after placebo treatment, 1.38 (0.42) after

levocetirizine treatment, 1.36 (0.37) after montelukast treatment, and 1.26 (0.39) after montelukast plus levocetirizine treatment. Combination therapy was more effective than monotherapy in the treatment of persistent allergic rhinitis.

In a randomized, double-blind, placebo-controlled, crossover study, patients with persistent allergic rhinitis received levocetirizine (5 mg/day), montelukast (10 mg/day), placebo, or a combination of levocetirizine and montelukast. The treatment period was divided into a 2-week washout period. Symptom scoring, skin prick tests, spirometry, rhinometry, and nasal lavage were performed before treatment and on the last day of treatment. Eosinophil cationic protein levels were assessed by nasal lavage means. The mean SD total baseline nasal symptom score was 7.95 $\pm$ 0.68 before treatment, 3.02 $\pm$ 0.64 with levocetirizine, 3.44 $\pm$ 0.55 with montelukast, and 2.14 $\pm$ 0.39 with the montelukast/levocetirizine combination. The greatest improvement in nasal symptoms occurred after combination therapy. The greatest reduction in eosinophil cationic protein levels was achieved with the combined use of montelukast and levocetirizine.

5.2. Pharmacokinetic properties

General features

Following oral administration of BRONCHOREST, levocetirizine, and montelukast reach peak plasma concentrations after 3 hours. The rate and extent of absorption of BRONCHOREST are equivalent to the bioavailability of levocetirizine and montelukast administered as a single tablet.

Levocetirizine

Absorption:

Levocetirizine is rapidly and extensively absorbed after oral administration. Peak concentrations are reached 0.9 hours after dosing. Steady-state levels are reached after 2 hours. Food does not affect the absorption of levocetirizine.

Distribution:

There is no information on the tissue distribution and blood-brain barrier clearance of levocetirizine in humans. In rats and dogs, the highest tissue concentrations were found in the liver and kidneys, and the lowest in the central nervous system compartment.

Levocetirizine is 90% bound to plasma proteins. Its distribution is limited because its volume of distribution is 0.4 l/kg.

Biotransformation:

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

Due to its low metabolism and lack of metabolic inhibition potential, levocetirizine is not expected to interact with other substances, nor are other substances expected to interact with levocetirizine.

Elimination:

The plasma half-life in adults is 7.9 ± 1.9 hours. The half-life is shorter in young children. The mean apparent total body clearance in adults is 0.63 ml/min/kg. The primary route of elimination for levocetirizine and its metabolites is urine, with an average of 85.4% of the dose being excreted in the urine. Only 12.9% of the dose is excreted in the feces. Levocetirizine is eliminated by both glomerular filtration and active tubular secretion.

Linearity/Nonlinearity:

The pharmacokinetics of levocetirizine are linear, with low inter-subject variability, independent of dose and time. No chiral inversion occurs during absorption and excretion.

Montelukast

Absorption:

Montelukast is rapidly absorbed following oral administration. Following administration of a 10 mg film-coated tablet in adults, mean peak plasma concentration (C_{max}) is reached within 3–4 hours. Mean oral bioavailability is 64%. Oral bioavailability or C_{max} is not affected by a standard breakfast.

Average C for 4 mg chewable tabletThe mean C_{max} is reached within 2 hours after administration to pediatric patients 2–5 years of age in the fasted state. The mean C_{max} is 66% higher and the mean C_{min} is lower than in adults receiving 10 mg film-coated tablets.

Distribution:

Montelukast is more than 99% bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8–11 L. Animal studies have shown minimal cross-sectional area across the blood-brain barrier. Concentrations in other tissues were also minimal 24 hours after the last dose.

Biotransformation:

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

In vitro studies using human liver microsomes indicate that cytochromes P450 3A4 and 2C9 play a role in the metabolism of montelukast. Additional in vitro results from human liver microsomes indicate that 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 mean plasma clearance of montelukast in healthy adults is 45 mL/min. Following oral administration, 86% of radiolabeled montelukast was recovered in feces and <0.2% in urine within 5 days. Montelukast and its metabolites are almost entirely excreted via the bile.

Linearity/Nonlinearity:

The plasma elimination half-life is 2.7–5.5 hours. Montelukast pharmacokinetics are nearly linear with oral doses up to 50 mg. There is a small (14%) accumulation of parent drug at a daily dose of 10 mg once daily.

Characteristic features of patients

Race:

Based on the absorption and biotransformation properties of the drug, it is expected that the patient's ethnic origin will not have an effect on the pharmacokinetic parameters of levocetirizine.

Gender:

Levocetirizine peak plasma concentrations and total absorption are approximately 20% and 15% higher in women than in men. In general, the half-life tends to be slightly shorter in women (7.1 hours) than in men (8.6 hours). However, weight-adjusted clearances are similar in women (0.67 ml/min/kg) and men (0.59 ml/min/kg). These differences are not clinically significant, and therefore, similar daily doses and dosing intervals can be applied to men and women.

Kidney / Liver failure:

The apparent clearance of levocetirizine is correlated with creatinine clearance. Therefore, it is recommended that levocetirizine dosing intervals be adjusted according to creatinine clearance in patients with moderate and severe renal impairment. In anuric subjects with end-stage renal disease, total body clearance is decreased by approximately 80% compared to normal subjects. The amount of levocetirizine removed during a standard 4-hour hemodialysis session is <10%.

No montelukast dose adjustment is required in patients with mild to moderate hepatic impairment. There are no pharmacokinetic data on the pharmacokinetics of montelukast in patients with severe hepatic impairment (Child-Pugh score >9).

Decreased plasma theophylline concentrations have been observed with the use of high doses of montelukast (20 to 60 times the recommended adult dose). This effect was not seen at the recommended dose of 10 mg once daily.

5.3. Preclinical safety data

Levocetirizine

Preclinical data for levocetirizine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and reproductive toxicology.

Montelukast

Animal toxicity studies with montelukast have shown small, transient changes in serum biochemistry including ALT, glucose, phosphorus, and triglycerides. Signs of toxicity in animals included increased salivation, gastrointestinal symptoms, loose stools, and ionic imbalance. These events occurred at dosages resulting in systemic exposures >17 times those seen at the clinical dosage.

In monkeys, adverse effects were seen at doses greater than 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 exposures greater than 24-fold the clinical systemic exposure. A small decrease in offspring body weights was noted in a female fertility study in rats receiving 200 mg/kg/day (>69-fold the clinical systemic exposure). Studies in rabbits showed a higher incidence of deficient bone development than in concurrent control animals at systemic exposures greater than 24-fold the clinical systemic exposure seen at the clinical dose. No abnormalities were seen in rats. Montelukast has been shown to cross the placenta in animals and is excreted in breast milk.

No mortality was observed in mice and rats following single oral administration of montelukast sodium doses up to 5,000 mg/kg (15,000 mg/m² in mice and 30,000 mg/m² in rats) (maximum dose

tested). This dose is equivalent to 25,000 times the recommended daily adult human dose (based on a 50 kg patient).

Montelukast was not determined to be phototoxic in mice for UVA, UVB, or visible light spectra at doses up to 500 mg/kg/day (approximately >200-fold the systemic exposure).

Montelukast did not demonstrate mutagenicity or tumorigenicity in in vitro and in vivo tests in rodent species.

6. PHARMACEUTICAL PROPERTIES

6.1 List of excipients

Microcrystalline Cellulose pH 112

Maltitol (E965)

Low Substituted Hydroxypropyl Cellulose

Croscarmellose Sodium

Red Iron Oxide

Sucralose

Gum Flavor

Magnesium Stearate

Lactose monohydrate

Colloidal Anhydrous Silica

Tutti Frutti Flavor

6.2 Incompatibilities

There are no known incompatibilities.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at room temperature below 25°C. Protect from moisture and light.

6.5 Nature and content of packaging

Containing 30 and 90 chewable tablets, Al/Al blister and cardboard box packaging

6.6. Disposal of residual materials from human medicinal products and other special precautions

Unused products or waste materials must be disposed of in accordance with the “Medical Waste Control Regulation” and “Packaging Waste Control Regulation”.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORISATION NUMBER (S)

2023/274

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07.07.2023

Date of last renewal:-

10. DATE OF REVISION OF THE TEXT

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