Broncolast®

Montelukast Sodium

FORMS AND PRESENTATION

Broncolast® 4: Chewable tablets: Box of 30.
Broncolast® 5: Chewable tablets: Box of 30.
Broncolast® 10: Film coated tablets: Box of 30.

COMPOSITION:

Broncolast® 4: Each chewable tablet contains Montelukast Sodium equivalent to Montelukast 4 mg.
Excipients: Mannitol, croscarmellose sodium, hydroxypropylcellulose, ferric oxide, microcrystalline cellulose, aspartame, ART cherry flavor, magnesium stearate.
Broncolast® 5: Each chewable tablet contains Montelukast Sodium equivalent to Montelukast 5 mg.
Excipients: Mannitol, croscarmellose sodium, hydroxypropylcellulose, ferric oxide, microcrystalline cellulose, aspartame, ART cherry flavor, magnesium stearate.
Broncolast® 10: Each film coated tablet contains Montelukast Sodium equivalent to Montelukast 10 mg.
Excipients: Lactose monohydrate, mannitol, croscarmellose sodium, hydroxypropylcellulose, microcrystalline cellulose, magnesium stearate, red iron oxide, yellow iron oxide, carnauba wax, hydroxypropyl methylcellulose, titanium dioxide.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Therapeutic class: Drugs for obstructive airway diseases.
ATC code: R03DC03
The cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4), 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 ($CysLT_1$) 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.
Montelukast is an orally active compound which binds with high affinity and selectivity to the $CysLT_1$ receptor. In clinical studies, Montelukast inhibits bronchoconstriction due to inhaled LTD_4 at doses as low as 5 mg. Bronchodilation was observed within 2 hours of oral administration. The bronchodilation effect caused by a β-agonist was additive to that caused by Montelukast. Treatment with Montelukast inhibited both early- and late-phase bronchoconstriction due to antigen challenge. Montelukast, compared with placebo, decreased peripheral blood eosinophils in adult and paediatric patients. In a separate study, treatment with Montelukast significantly decreased eosinophils in the airways (as measured in sputum) and in peripheral blood while improving clinical asthma control.

Preclinical Safety Data

In animal toxicity studies, minor serum biochemical alterations in ALT, glucose, phosphorus and triglycerides were observed which were transient in nature. The signs of toxicity in animals were increased excretion of saliva, gastrointestinal symptoms, loose stools and ion imbalance. These occurred at dosages which provided > 17-fold the systemic exposure seen at the clinical dosage. In monkeys, the adverse effects appeared at doses from 150 mg/kg/day (>232-fold the systemic exposure seen at the clinical dose). In animal studies, Montelukast did not affect fertility or reproductive performance at systemic exposure exceeding the clinical systemic exposure by greater than 24-fold. A slight decrease in pup body weight was noted in the female fertility study in rats at 200 mg/kg/day (>69-fold the clinical systemic exposure). In studies in rabbits, a higher incidence of incomplete ossification, compared with concurrent control animals, was seen at systemic exposure > 24-fold the clinical systemic exposure seen at the clinical dose. No abnormalities were seen in rats. Montelukast has been shown to cross the placental barrier and is excreted in breast milk of animals.
No deaths occurred following a single oral administration of Montelukast sodium at doses up to 5000 mg/kg in mice and rats (15,000 mg/m^2 and 30,000 mg/m^2 in mice and rats, respectively), the maximum dose tested. This dose is equivalent to 25,000 times the recommended daily adult human dose (based on an adult patient weight of 50 kg).
Montelukast was determined not to be phototoxic in mice for UVA, UVB or visible light spectra at doses up to 500 mg/kg/day (approximately > 200-fold based on systemic exposure).
Montelukast was neither mutagenic in *in vitro* and *in vivo* tests nor tumorigenic in rodent species.

Pharmacokinetic Properties

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 hrs (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.
For the 5 mg chewable tablet, the C_{max} is achieved in 2 hrs 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 to 11 liters. Studies in rats with radiolabelled Montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabelled material at 24 hrs post-dose were minimal in all other tissues.
Metabolism: Montelukast is extensively metabolized. In studies with therapeutic doses, plasma concentrations of metabolites of Montelukast are undetectable at steady state in adults and children. In vitro studies using human liver microsomes indicate that cytochrome P450 3A4, 2A6 and 2C9 are involved in the metabolism of Montelukast. Based on further 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 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.
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.

INDICATIONS

Broncolast® is indicated in the treatment of asthma as add-on therapy in those patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom “as-needed” short acting β-agonists provide inadequate clinical control of asthma. In those asthmatic patients in whom Broncolast® is indicated in asthma, Broncolast® can also provide symptomatic relief of seasonal allergic rhinitis.
Broncolast® may also be an alternative treatment option to low-dose inhaled corticosteroids for patients with mild persistent asthma who do not have a recent history of serious asthma attacks that required oral corticosteroid use, and who have demonstrated that they are not capable of using inhaled corticosteroids.
Broncolast® is also indicated in the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

CONTRAINDICATIONS

Patients who are hypersensitive to the active substance or to any ingredient in the formulation.

PRECAUTIONS

Montelukast should not be used to treat acute asthma attacks. Patients should be advised to have appropriate rescue medication available. If an acute attack occurs, a short-acting inhaled β-agonist should be used. Patients should seek their physician's advice as soon as possible if they need more inhalations of short-acting β-agonists than usual.
Montelukast should not be abruptly substituted 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 usually, but not always, have been associated with the reduction or withdrawal 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 Montelukast does not alter the need for patients with acetylsalicylic acid (ASA)-sensitive asthma to avoid taking ASA and other non-steroidal anti-inflammatory drugs.

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

Broncolast® 5 contains aspartame, a source of phenylalanine. Patients with phenylketonuria should take into account that each 5 mg chewable tablet contains phenylalanine.

PREGNANCY AND LACTATION

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

Limited data from available pregnancy databases do not suggest a causal relationship between Montelukast and malformations (i.e. limb defects) that have been rarely reported in worldwide post marketing experience.

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

Studies in rats have shown that Montelukast is excreted in milk. It is not known if Montelukast is excreted in human milk.

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

DRUG 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 metabolised by CYP 3A4, caution should be exercised, particularly in children, when Montelukast is co-administered with inducers of CYP 3A4, such as phenytoin, phenobarbital and rifampicin.

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

ADVERSE EFFECTS

Montelukast has been evaluated in clinical studies as follows:

- 10 mg film-coated tablets in approximately 4000 adult asthmatic patients 15 years of age and older.
- 10 mg film-coated tablets in approximately 400 adult asthmatic patients with seasonal allergic rhinitis 15 years of age and older.
- 5 mg chewable tablets in approximately 1750 pediatric asthmatic patients 6 to 14 years of age.

The following drug-related adverse effects in clinical studies were reported commonly (≥ 1/100 to <1/10) in asthmatic patients treated with Montelukast and at a greater incidence than in patients treated with placebo:

Body System Class	Adult Patients 15 years and older (two 12-week studies; n=795)	Pediatric 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 pediatric patients 6 to 14 years of age, the safety profile did not change.

The following adverse effects have been reported in post-marketing use:

Infections and infestations: upper respiratory infection.

Blood and lymphatic system disorders: increased bleeding tendency.

Immune system disorders: hypersensitivity reactions including anaphylaxis, hepatic eosinophilic infiltration.

Psychiatric disorders: dream abnormalities including nightmares, hallucinations, insomnia, somnambulism, irritability, anxiety, restlessness, agitation including aggressive behavior or hostility, tremor, depression, suicidal thinking and behavior (suicidality) in very rare cases.

Nervous system disorders: dizziness, drowsiness, paraesthesia/hypoesthesia, seizure.

Cardiac disorders: palpitations.

Respiratory, thoracic and mediastinal disorders: epistaxis

Gastro-intestinal disorders: diarrhoea, dry mouth, dyspepsia, nausea, vomiting.

Hepatobiliary disorders: elevated levels of serum transaminases (ALT, AST), hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury).

Skin and subcutaneous tissue disorders: angiooedema, bruising, urticaria, pruritus, rash, erythema nodosum.

Musculoskeletal and connective tissue disorders: arthralgia, myalgia including muscle cramps.

General disorders and administration site conditions: asthenia/fatigue, malaise, oedema, pyrexia.

Very rare cases of Churg-Strauss Syndrome (CSS) have been reported during Montelukast treatment in asthmatic patients.

DOSAGE AND ADMINISTRATION

The dosage for adults 15 years of age and older with asthma, or with asthma and concomitant seasonal allergic rhinitis, is one Broncolast® 10 tablet daily to be taken in the evening. Broncolast® 10 may be taken with or without food.

The dosage for pediatric patients 6-14 years of age is one Broncolast® 5 chewable tablet daily to be taken in the evening. If taken in connection with food, Broncolast® 5 should be taken 1 hour before or 2 hours after food. No dosage adjustment within this age group is necessary.

General recommendations

The therapeutic effect of Broncolast® on parameters of asthma control occurs within one day. Patients should be advised to continue taking Broncolast® even if their asthma is under control, as well as during periods of worsening asthma. Broncolast® should not be used concomitantly with other products containing the same active ingredient, Montelukast.

No dosage adjustment is necessary for the elderly, or for patients with renal insufficiency, or mild to moderate hepatic impairment. There are no data on patients with severe hepatic impairment. The dosage is the same for both male and female patients.

Therapy with Broncolast® in relation to other treatments for asthma

Broncolast® can be added to a patient's existing treatment regimen.

Inhaled corticosteroids: Treatment with Broncolast® can be used as add-on therapy in patients when inhaled corticosteroids plus "as needed" short acting β-agonists provide inadequate clinical control. Broncolast® should not be abruptly substituted for inhaled corticosteroids.

Broncolast® as an alternative treatment option to low-dose inhaled corticosteroids for mild persistent asthma

Broncolast® is not recommended as monotherapy in patients with moderate persistent asthma. The use of Broncolast® as an alternative treatment option to low-dose inhaled corticosteroids for children with mild persistent asthma should only be considered for patients who do not have a recent history of serious asthma attacks that required oral corticosteroid use and who have demonstrated that they are not capable of using inhaled corticosteroids. Mild persistent asthma is defined as asthma symptoms more than once a week but less than once a day, nocturnal symptoms more than twice a month but less than once a week, normal lung function between episodes. If satisfactory control of asthma is not achieved at follow-up (usually within one month), the need for an additional or different anti-inflammatory therapy based on the step system for asthma therapy should be evaluated. Patients should be periodically evaluated for their asthma control.

OVERDOSAGE

No specific information is available on the treatment of overdosage with Montelukast. In chronic asthma studies, Montelukast has been administered at doses up to 200 mg/day to patients for 22 weeks and in short-term studies, up to 900 mg/day to patients for approximately one week without clinically important adverse experiences. There have been reports of acute overdose in post-marketing experience and clinical studies with Montelukast. These include reports in adults and children with a dose as high as 1000 mg (approximately 61mg/kg in a 42 month old child). The clinical and laboratory findings observed were consistent with the safety profile in adults and pediatric 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 hemo- dialysis.

STORAGE CONDITIONS

Store below 30°C.

Keep in original pack in intact conditions.

Date of revision: February 2014.

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

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