Broncolast®

Montelukast Sodium

FORMS AND PRESENTATION
Broncolast® 4: Chewable tablets: Box of 30.
Broncolast® 5: Chewable tablets: Box of 30.

COMPOSITION
Broncolast® 4: Each chewable tablet contains Montelukast sodium eq. to Montelukast 4mg
Broncolast® 5: Each chewable tablet contains Montelukast sodium eq. to Montelukast 5mg
Excipients: Mannitol, Croscarmellose sodium, Hydroxyl propyl cellulose, Ferric oxide, Cellulose microcrystalline, Aspartame, ART Cherry Flavor, Magnesium Stearate

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: Leukotriene receptor antagonist.
ATC-Code: R03D C03.
Pharmacodynamic effects
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 two 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.
Pharmacokinetic properties
Absorption
Montelukast is rapidly absorbed following oral administration. For the 5 mg chewable tablet, the C_{max} is achieved in two 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 radiolabeled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabelled material at 24 hours post-dose were minimal in all other tissues.
Biotransformation
Montelukast is extensively metabolised. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and children.
Cytochrome P450 2C8 is the major enzyme in the metabolism of montelukast. Additionally CYP 3A4, and 2C9 may have a minor contribution, although itraconazole, an inhibitor of CYP 3A4, was shown not to change pharmacokinetic variables of montelukast in healthy subjects that received 10 mg montelukast daily. Based on in vitro results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6. The contribution of metabolites to the therapeutic effect of montelukast is minimal.
Elimination
The plasma clearance of montelukast averages 45 ml/min in healthy adults. Following an oral dose of radiolabelled montelukast, 86% of the radioactivity was recovered in 5-day faecal collections and <0.2% was recovered in urine. Coupled with estimates of montelukast oral bioavailability, this indicates that montelukast and its metabolites are excreted almost exclusively via the bile.
Characteristics in Patients
No dosage adjustment is necessary for the elderly or mild to moderate hepatic insufficiency. Studies in patients with renal impairment have not been undertaken. Because montelukast and its metabolites are eliminated by the biliary route, no dose adjustment is anticipated to be necessary in patients with renal impairment. There are no data on the pharmacokinetics of montelukast in patients with severe hepatic insufficiency (Child-Pugh score >9).
With high doses of montelukast (20- and 60-fold the recommended adult dose), a 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.
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
Hypersensitivity to the active substance or to any of the excipients.

PRECAUTIONS
Patients should be advised never to use oral montelukast to treat acute asthma attacks and to keep their usual appropriate rescue medication for this purpose readily available. If an acute attack occurs, a short-acting inhaled β-agonist should be used. Patients should seek their doctors' advice as soon as possible if they need more inhalations of short-acting β-agonists than usual.
Montelukast should not be 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 have been sometimes associated with the reduction or withdrawal of oral corticosteroid therapy. Although a causal relationship with leukotriene receptor antagonism has not been established, physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. Patients who develop these symptoms should be reassessed and their treatment regimens evaluated.
Treatment with montelukast does not alter the need for patients with aspirin-sensitive asthma to avoid taking aspirin and other non-steroidal anti-inflammatory drugs.
Broncolast® contains aspartame, a source of phenylalanine. Patients with phenylketonuria should take into account that each 5 mg chewable tablet contains phenylalanine in an amount equivalent to 0.842 mg phenylalanine per dose.
Ability to drive and use machines
Broncolast® has no or negligible influence on the ability to drive and use machines. However, individuals have reported drowsiness or dizziness.

PREGNANCY AND LACTATION
Pregnancy
Limited data from available pregnancy databases do not suggest a causal relationship between Broncolast® and malformations (i.e. limb defects) that have been rarely reported in worldwide post-marketing experience.
Broncolast® may be used during pregnancy only if it is considered to be clearly essential.
Breast-feeding
Studies in rats have shown that montelukast is excreted in milk. It is unknown whether montelukast/metabolites are excreted in human milk.
Broncolast® may be used in breast-feeding mothers 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 oestradiol/norethindrone 35/1), terfenadine, digoxin and warfarin.
The area under the plasma concentration curve (AUC) for montelukast was decreased approximately 40% in subjects with co-administration of phenobarbital. Since montelukast is metabolised by CYP 3A4, 2C8, and 2C9, caution should be exercised, particularly in children, when montelukast is co-administered with inducers of CYP 3A4, 2C8, and 2C9, such as phenytoin, phenobarbital and rifampicin.
In vitro studies have shown that montelukast is a potent inhibitor of CYP 2C8. However, data from a clinical drug-drug interaction study involving montelukast and rosiglitazone (a probe substrate representative of medicinal products primarily metabolised by CYP 2C8) demonstrated that montelukast does not inhibit CYP 2C8 *in vivo*. Therefore, montelukast is not anticipated to markedly alter the metabolism of medicinal products metabolised by this enzyme (e.g., paclitaxel, rosiglitazone, and repaglinide).
In vitro studies have shown that montelukast is a substrate of CYP 2C8, and to a less significant extent, of 2C9, and 3A4. In a clinical drug-drug interaction study involving montelukast and gemfibrozil (an inhibitor of both CYP 2C8 and 2C9) gemfibrozil increased the systemic exposure of montelukast by 4.4-fold. No routine dosage adjustment of montelukast is required upon co-administration with gemfibrozil or other potent inhibitors of CYP 2C8, but the physician should be aware of the potential for an increase in adverse reactions.
Based on *in vitro* data, clinically important drug interactions with less potent inhibitors of CYP 2C8 (e.g., trimethoprim) are not anticipated. Co-administration of montelukast with itraconazole, a strong inhibitor of CYP 3A4, resulted

in no significant increase in the systemic exposure of montelukast.

ADVERSE EFFECTS
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 and Adolescent Patients 15 years and older	Pediatric Patients 6 to 14 years old
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: 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, somnambulism, anxiety, agitation including aggressive behavior or hostility, depression, psychomotor hyperactivity (including irritability, restlessness, tremor) Rare disturbance in attention, memory impairment Very Rare: hallucinations, disorientation, suicidal thinking and behaviour (suicidality)
Nervous system disorders: Uncommon: Dizziness, drowsiness, paraesthesia/hypoesthesia, seizure
Cardiac disorders: Rare: palpitations.
Respiratory, thoracic and mediastinal disorders: Uncommon: Epistaxis Very Rare: Hurg-Strauss Syndrome (CSS), pulmonary eosinophilia
Gastro-intestinal disorders: Common: diarrhea, 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: angiooedema. Very Rrae: 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, edema

DOSAGE AND ADMINISTRATION
Posology
The recommended dose for pediatric patients 6-14 years of age is one 5 mg chewable tablet daily to be taken in the evening. If taken in connection with food, Broncolast® 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.
No dosage adjustment is necessary 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.
Broncolast® as an alternative treatment option to low-dose inhaled corticosteroids for mild persistent asthma
~~Montelukast is not recommend~~ed as monotherapy in patients with moderate persistent asthma. The use of montelukast 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.
Therapy with Broncolast® in relation to other treatments for asthma
When treatment with Broncolast® is used as add-on therapy to inhaled corticosteroids, Broncolast® should not be abruptly substituted for inhaled corticosteroids.
10 mg tablets are available for adults and adolescents 15 years of age and older.
Pediatric population
Do not give Broncolast® 5 to children less than 6 years of age. The safety and efficacy of Broncolast® 5 in children less than 6 years of age has not been established.
Broncolast® 4 chewable tablets are available for pediatric patients 2 to 5 years of age.
Method of administration
Oral use.
The tablets are to be chewed before swallowing.

OVERDOSAGE
There were no side effects reported in the majority of overdose reports. The most frequently occurring symptoms reported with overdose in adults and children included abdominal pain, sleepiness, thirst, headache, vomiting, and hyperactivity.

STORAGE CONDITIONS
Store below 25°C.
Keep in original pack in intact conditions.

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Manufactured by:
Benta S.A.L. - Lebanon
BPI

Tardemark Owner
Abbott Healthcare Products B.V. Netherlands
Abbott

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

Council of Arab Health Ministers
Union of Arab Pharmacists