Billerg-M

Bilastine & Montelukast Oral Suspension

Quantitative composition : Each 5 ml contains : Bilastine 10mg and Montelukast (as sodium) BP 4mg.
Pharmaceutical form: Oral Suspension
Pharmacology: Bilastine is a non-sedating second generation H1-antihistamine, long-acting histamine antagonist with selective peripheral H1 receptor antagonist affinity and no affinity for muscarinic receptors. Bilastine inhibited histamine-induced wheal and flare skin reactions for 24 hours following single doses. Montelukast is a potent and selective antagonist of leukotriene D4 (LTD4) at the cysteinyl leukotriene receptor, CysLT1, found in the human airway. The cysteinyl leukotrienes (LTC4, LTD4, and LTE4) are important intermediaries of allergic airway disease. It improves the signs and symptoms of asthma and allergic rhinitis by inhibiting the physiologic actions of LTD4 at the CysLT1 receptor.
Pharmacokinetics: Bilastine is rapidly absorbed after oral administration with a time to maximum plasma concentration of around 1.3 hours. No accumulation was observed. The mean value of bilastine oral bioavailability is 61%. *In vitro and in vivo* studies have shown that bilastine is a substrate of P-gp and OATP. At therapeutic doses bilastine is 84-90% bound to plasma proteins. Bilastine did not induce or inhibit activity of CYP450 isoenzymes in vitro studies. In a mass balance study performed in healthy adult volunteers, after administration of a single dose of 20 mg 14C-bilastine, almost 95% of the administered dose was recovered in urine (28.3%) and faeces (66.5%) as unchanged bilastine, confirming that bilastine is not significantly metabolized in humans. The mean elimination half-life calculated in healthy volunteers was 14.5 h. Bilastine presents linear pharmacokinetics in the dose range studied (5 to 220 mg), with a low interindividual variability.
Renal impairment: In a study in subjects with renal impairment the mean (SD) AUC0-∞ increased from 737.4 (± 260.8) ng x hr/mL in subjects without impairment (GFR: > 80 mL/min/1.73 m2) to: 967.4 (± 140.2) ng x hr/mL in subjects with mild impairment (GFR: 50-80 mL/min/1.73 m2), 1384.2 (± 263.23) ng x hr/mL in subjects with moderate impairment (GFR: 30 - <50 mL/min/1.73 m2), and 1708.5 (± 699.0) ng x hr/mL in subjects with severe impairment (GFR: < 30 mL/min/1.73 m2). Mean (SD) half-life of bilastine was 9.3 h (± 2.8) in subjects without impairment, 15.1 h (± 7.7) in subjects with mild impairment, 10.5 h (± 2.3) in subjects with moderate impairment and 18.4 h (± 11.4) in subjects with severe impairment. Urinary excretion of bilastine was essentially complete after 48 -72 h in all subjects. These pharmacokinetic changes are not expected to have a clinically relevant influence on the safety of bilastine, since bilastine plasma levels in patients with renal impairment are still within the safety range of bilastine.
Hepatic impairment: There is no pharmacokinetic data in subjects with hepatic impairment. Bilastine is not metabolized in humans. Since the results of the renal impairment study indicate renal elimination to be a major contributor in the elimination, biliary excretion is expected to be only marginally involved in the elimination of bilastine. Changes in liver function are not expected to have a clinically relevant influence on bilastine pharmacokinetics.
Elderly: Only limited pharmacokinetic data are available in subjects older than 65 years. No statistically significant differences have been observed with regard to PK of bilastine in elderly aged over 65 years compared to adult population aged between 18 and 35 years.
Paediatric population: Children aged 4 to 11 years with allergic rhinoconjunctivitis or chronic urticaria, administered once daily with bilastine 10 mg Orodispersible tablet. Pharmacokinetic analysis of plasma concentration data showed that the pediatric dose of bilastine 10 mg once daily results in systemic exposure equivalent to that seen after a 20 mg dose in adults and adolescents, being the mean AUC value 1014 ng* x hr/mL for children 6 to 11 years.
Montelukast is rapidly absorbed following oral administration. For the 10 mg film-coated tablet, the mean peak plasma concentration (Cmax) is achieved 3 hours (Tmax) after administration in adults in the fasted state. The mean oral bioavailability is 64%. The oral bioavailability and Cmax are not influenced by a standard meal. Montelukast is more than 99% bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8-11 litres. 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. 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 faecal collections and <0.2% was recovered in urine.
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.
Therapeutic indication: For treatment of allergic rhinitis in children aged 6 to 11 years (both inclusive) with a body weight of at least 20 kg.
Posology and method of administration: For children 6 to 11 years of age, body weight ≥ 20kg: 5 ml once daily or as directed by the Physician.
Method of administration: For oral use only
The suspension should be taken 1 hour before or 2 hours after intake of food or fruit juice. Shake well before use.
Contraindications: Known hypersensitivity to Bilastine or Montelukast or any component of the formulation.
History of QT prolongation and/or torsade de pointes, including congenital long QT syndromes
Special warnings and precautions for use:
Cardiovascular: Particular care should be exercised when administering antihistamines, including Bilastine, to patients who are suspected to be at an increased risk of experiencing torsade de pointes during treatment with a QTc-prolonging drug. This includes patients who have a history of cardiac arrhythmias; hypokalemia; hypomagnesaemia; significant bradycardia; family history of sudden cardiac death; concomitant use of other QT/QTc-prolonging drugs. When drugs that prolong the QTc interval are prescribed, healthcare professionals should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug.
Hepatic: It has not been studied in subjects with hepatic impairment. Since Bilastine is not metabolized and renal clearance is the major route of elimination, hepatic impairment is not expected to increase systemic exposure above the safety margin.
Renal: In subjects with moderate or severe renal impairment co-administration of Bilastine with P glycoprotein inhibitors, such as ketoconazole, erythromycin, cyclosporine, ritonavir or diltiazem, may increase plasma levels of Bilastine and therefore increase the risk of adverse effects. Co administration of Bilastine and P-glycoprotein inhibitors should be avoided in subjects with moderate or severe renal impairment.
Acute asthma: Montelukast is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus. Patients should be advised to have appropriate rescue medication available. Therapy with Montelukast can be continued during acute exacerbations of asthma. There are no data demonstrating that oral corticosteroids can be reduced when Montelukast is given concomitantly. Patients who have exacerbations of asthma after exercise should have available for rescue a short-acting inhaled beta2-agonist.
Concomitant corticosteroid use: While the dose of inhaled corticosteroid may be reduced gradually under medical supervision, Montelukast should not be abruptly substituted for inhaled or oral corticosteroids.
Aspirin sensitivity: Patients with known aspirin sensitivity should continue avoidance of Aspirin or non-steroidal antiinflammatory agents while taking Montelukast. Although Montelukast is effective in improving airway function in asthmatics with documented aspirin sensitivity, it has not been shown to truncate bronchoconstrictor response to Aspirin and other non-steroidal anti-inflammatory drugs in Aspirin sensitive asthmatic patients.
Eosinophilic conditions: Patients with asthma on therapy with 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 events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between Montelukast and these underlying conditions has not been established. Patients who develop these symptoms should be reassessed and their treatment regimens evaluated.
Neuropsychiatric events: Neuropsychiatric events have been reported in adult, adolescent, and paediatric patients taking Montelukast. Post-marketing reports with Montelukast use include agitation, aggressive behaviour or hostility, anxiousness, depression, disorientation, dream abnormalities, hallucinations, insomnia, irritability, memory impairment, restlessness, somnambulism, suicidal thinking and behaviour (including suicide), tic, and tremor.
Interaction with other medicinal products and other forms of interaction:
Concomitant intake of Bilastine and Ketoconazole or Erythromycin increased Bilastine AUC 2-fold and Cmax 2-3 fold. These changes can be explained by interaction with intestinal efflux transporters, since Bilastine is substrate for P-gp and not metabolized. These changes do not appear to affect the safety profile of Bilastine and Ketoconazole or Erythromycin, respectively. Other medicinal products that are substrates or inhibitors of P-gp, such as Cyclosporine, may likewise have the potential to increase plasma concentrations of Bilastine.
Concomitant intake of Bilastine 20 mg and Diltiazem 60 mg increased Cmax of Bilastine by 50%. This effect can be explained by interaction with intestinal efflux transporters, and does not appear to affect the safety profile of Bilastine
Concomitant intake of Bilastine 20 mg and Lorazepam 3 mg for 8 days did not potentiate the depressant CNS effects of Lorazepam.
The psychomotor performance after concomitant intake of Alcohol and 20 mg Bilastine was similar to that observed after intake of Alcohol and placebo.
Concomitant intake of Bilastine and Grapefruit juice decreased Bilastine bioavailability by 30%. This effect may also apply to other fruit juices. The degree of bioavailability decrease may vary between producers and fruits. The mechanism for this interaction is an inhibition of OATP1A2, an uptake transporter for which Bilastine is a substrate. Medicinal products that are substrates or inhibitors of OATP1A2, such as ritonavir or rifampicin, may likewise have the potential to decrease plasma concentrations of Bilastine.
Food significantly reduces the oral bioavailability of Bilastine by 30%.
No interaction studies have been performed in children with Bilastine Orodispersible suspension. As there is no clinical experience regarding the interaction of Bilastine with other medicinal products, food or fruit juices in children, the results obtained in adult interactions studies should be at present taken into consideration when prescribing Bilastine to children. There are no clinical data in children to state whether changes to the AUC or Cmax due to interactions affect the safety profile of Bilastine.
Montelukast may be administered with other therapies routinely used in prophylaxis and chronic treatment of asthma. In drug-interaction studies, the recommended clinical dose of Montelukast did not have clinically important effects on the pharmacokinetics of the following drugs : Theophylline, Prednisone, Prednisolone, Oral contraceptives (Norethindrone 1 mg / Ethinyl Estradiol 35 mcg), Terfenadine, Digoxin, Warfarin, Gemfibrozil, Itraconazole, Thyroid hormones, Sedative hypnotics, Non-steroidal anti-inflammatory agents, Benzodiazepines, Decongestants and Cytochrome P450 (CYP) enzyme inducers.
Pregnancy, Lactation and fertility:
As a precautionary measure, it is preferable to avoid the use of Billerg- M during pregnancy. It may be used during pregnancy only if it is considered to be clearly essential. Pharmacokinetic data in animals has shown the excretion of Bilastine and Montelukast in milk. A decision on whether to continue/discontinue breast-feeding or to discontinue/abstain from therapy must be made taking into account the benefit of breast-feeding for the child and the benefit of Billerg-M therapy for the mother. A study in rats did not indicate any negative effect on fertility.
Effects on the ability to drive and use machines: Patients should be advised not to drive or use machines until they have established their own response to Billerg-M oral suspension.
Adverse reactions: Common adverse reactions: headache, somnolence, dizziness, fatigue, abdominal pain, upper respiratory infection, dry mouth dyspepsia, elevated levels of serum transaminases (ALT, AST)
Uncommon: Increased appetite, abdominal discomfort, Oral herpes, Anxiety, Insomnia, Tinnitus ,Vertigo, Sinus arrhythmia, Electrocardiogram QT prolonged, Other ECG abnormalities, Dyspnoea, Nasal discomfort, Pruritus, Pyrexia, Asthenia, bruising, urticaria, pruritus ,arthralgia, myalgia including muscle cramps, Churg-Strauss Syndrome (CSS), rash, diarrhoea, nausea, vomiting, hepatitis , angioedema, erythema nodosum, erythema multiforme, asthenia, malaise, oedema, palpitations, epistaxis, hallucinations, disorientation, Psychiatric disorders
Overdose and Treatment:
The most frequently occurring adverse experiences were consistent with the safety profile and included abdominal pain, somnolence, thirst, headache, vomiting, and psychomotor hyperactivity. The clinical and laboratory findings observed were consistent with the safety profile in adults and paediatric patients. In the event of overdose symptomatic and supportive treatment is recommended
Presentation: 60 ml (about 2.03 oz) Amber PET Bottle, packed in unit carton along with literature insert.
Shelf life: 2 years from the date of manufacture.
Storage: Do not store above 30°C. Protect from direct sunlight. Keep all medicines out of reach of children.
Distribution category: Prescription only medicine (POM).

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