For the use of a Registered Medical Practitioner only

NILHIST®-M

℞ Bilastine and Montelukast Tablets

COMPOSITION

Each film coated bilayered tablet contains:
Bilastine.....20 mg
Montelukast Sodium IP
Equivalent to Montelukast.....10 mg
Excipients ..... q.s.
Colours: Erythrosine Lake (In Montelukast Layer)

PHARMACEUTICAL FORM

Film coated bilayered tablet

THERAPEUTIC INDICATION

The FDC of Montelukast 10 mg & Bilastine 20mg Tablet is indicated for the treatment of allergic rhinitis in adults.

POSOLOGY AND METHOD OF ADMINISTRATION

To be taken orally once a day or as directed by physician.

Special Population-

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.

Bilastine

Elderly

No dosage adjustments are required in elderly patients.

Renal impairment

Studies conducted in adults in special risk groups (renally impaired patients) indicate that it is not necessary to adjust the dose of Bilastine in adults.

Hepatic impairment

There is no clinical experience in adult patients with hepatic impairment. However, since Bilastine is not metabolized and is eliminated as unchanged in urine and faeces, hepatic impairment is not expected to increase systemic exposure above the safety margin in adult patients. Therefore, no dosage adjustment is required in adult patients with hepatic impairment.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Montelukast

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. Patients who have exacerbations of asthma after exercise should have available for rescue a short-acting inhaled β-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 anti-inflammatory 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 have been sometimes 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.

Bilastine

In patients with moderate or severe renal impairment coadministration of Bilastine with P-glycoprotein inhibitors, such as e.g, ketoconazole, erythromycin, cyclosporine, ritonavir or diltiazem, may increase plasmatic levels of Bilastine and therefore increase the risk of adverse effects of Bilastine. Therefore, coadministration of Bilastine and P-glycoprotein inhibitors should be avoided in patients with moderate or severe renal impairment.

DRUG INTERACTIONS

Montelukast

No dose adjustment is needed when Montelukast is co-administered with theophylline, prednisone, prednisolone, oral contraceptives, terfenadine, digoxin, warfarin, gemfibrozil, itraconazole, thyroid hormones, sedative hypnotics, non-steroidal anti-inflammatory agents, benzodiazepines, decongestants, and Cytochrome P450 (CYP) enzyme inducers.

Bilastine

Interaction with food: Food significantly reduces the oral bioavailability of Bilastine by 30%.

Interaction with grapefruit juice: concomitant intake of Bilastine 20 mg 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.

Interaction with ketoconazole or erythromycin: Concomitant intake of Bilastine 20 mg o.d. and ketoconazole 400 mg o.d. or erythromycin 500 mg t.i.d. 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 metabolised. 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.

Interaction with diltiazem: Concomitant intake of Bilastine 20 mg o.d. and diltiazem 60 mg o.d. increased C_{max} 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.

Interaction with alcohol: The psychomotor performance after concomitant intake of alcohol and 20 mg bilastine o.d. was similar to that observed after intake of alcohol and placebo.

Interaction with lorazepam: Concomitant intake of Bilastine 20 mg o.d. and lorazepam 3 mg o.d. for 8 days did not potentiate the depressant CNS effects of lorazepam.

USE IN SPECIFIC POPULATIONS

Pregnancy and Lactation

Montelukast

Pregnancy

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

Lactation

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

Bilastine

Pregnancy

There are no or limited amount of data from the use of Bilastine in pregnant women. As a precautionary measure, it is preferable to avoid the use of Bilastine during pregnancy.

Lactation

The excretion of Bilastine in milk has not been studied in humans. Available pharmacokinetic data in animals have shown excretion of Bilastine in milk. A decision on whether to continue/discontinue breast-feeding or to discontinue/abstain from Bilastine therapy must be made taking into account the benefit of breast-feeding for the child and the benefit of Bilastine therapy for the mother.

UNDESIRABLE EFFECTS

Montelukast

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.

System Organ Class	Adverse Reactions	Frequency Category*
Infections and infestations	upper respiratory infection	Very Common
Blood and lymphatic system disorders	increased bleeding tendency	Rare
	thrombocytopenia	Very Rare
Immune system disorders	hypersensitivity reactions including anaphylaxis	Uncommon
	hepatic eosinophilic infiltration	Very Rare
Psychiatric disorders	dream abnormalities including nightmares, insomnia, somnambulism, anxiety, agitation including aggressive behaviour or hostility, depression, psychomotor hyperactivity (including irritability, restlessness, tremor)	Uncommon
	disturbance in attention, memory impairment, tic	Rare
	hallucinations, disorientation, suicidal thinking and behaviour (suicidality), obsessive-compulsive symptoms, dysphemia	Very Rare
Nervous system disorders	dizziness, drowsiness, paraesthesia/hypoesthesia, seizure	Uncommon
Cardiac disorders	palpitations	Rare
Respiratory, thoracic and mediastinal disorders	epistaxis	Uncommon
	Churg-Strauss Syndrome (CSS)	Very Rare
	pulmonary eosinophilia	Very Rare
Gastro-intestinal disorders	diarrhoea, nausea, vomiting	Common
	dry mouth, dyspepsia	Uncommon
Hepatobiliary disorders	elevated levels of serum transaminases (ALT, AST)	Common
	hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury).	Very Rare
Skin and subcutaneous tissue disorders	rash	Common
	bruising, urticaria, pruritus	Uncommon
	angiooedema	Rare
	erythema nodosum, erythema multiforme	Very Rare
Musculoskeletal and connective tissue disorders	arthralgia, myalgia including muscle cramps	Uncommon

Renal and urinary disorders	enuresis in children	Uncommon
General disorders and administration site conditions	pyrexia	Common
	asthenia/fatigue, malaise, oedema	Uncommon

*Frequency Category: Defined for each Adverse Reaction by the incidence reported in the clinical trials data base: Very Common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very Rare (<1/10,000).

The following drug-related adverse reactions 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 (two 12-week studies; n=795)
Nervous system disorders	headache
Gastro-intestinal disorders	abdominal pain

Bilastine

The ADRs most commonly reported by patients receiving 20 mg Bilastine for the indication of allergic rhinoconjunctivitis or chronic idiopathic urticaria were headache, somnolence, dizziness, and fatigue. These adverse events occurred with a comparable frequency in patients receiving placebo.

Tabulated summary of adverse reactions in adult and adolescent patients

ADRs at least possibly related to Bilastine and reported in more than 0.1% of the patients receiving 20 mg Bilastine during the clinical development (N = 1697) are tabulated below.

Frequencies are assigned as follows: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), Not known (cannot be estimated from the available data)

Rare, very rare and reactions with unknown frequency have not been included in the table.

System Organ Class		Bilastine 20 mg N = 1697	All Bilastine Doses N = 2525	Placebo N = 1362
Frequency	**Adverse reaction**			
Infections and infestations				
Uncommon	Oral herpes	2 (0.12%)	2 (0.08%)	0 (0.0%)
Metabolism and nutrition disorders				
Uncommon	Increased appetite	10 (0.59%)	11 (0.44%)	7 (0.51%)
Psychiatric disorders				
Uncommon	Anxiety	6 (0.35%)	8 (0.32%)	0 (0.0%)
	Insomnia	2 (0.12%)	4 (0.16%)	0 (0.0%)
Nervous system disorders				
Common	Somnolence	52 (3.06%)	82 (3.25%)	39 (2.86%)
	Headache	68 (4.01%)	90 (3.56%)	46 (3.38%)
Uncommon	Dizziness	14 (0.83%)	23 (0.91%)	8 (0.59%)
Ear and labyrinth disorders				
Uncommon	Tinnitus	2 (0.12%)	2 (0.08%)	0 (0.0%)
	Vertigo	3 (0.18%)	3 (0.12%)	0 (0.0%)
Cardiac disorders				
Uncommon	Right bundle branch block	4 (0.24%)	5 (0.20%)	3 (0.22%)
	Sinus arrhythmia	5 (0.30%)	5 (0.20%)	1 (0.07%)
	Electrocardiogram QT prolonged	9 (0.53%)	10 (0.40%)	5 (0.37%)
	Other ECG abnormalities	7 (0.41%)	11 (0.44%)	2 (0.15%)
Respiratory, thoracic and mediastinal disorders				
Uncommon	Dyspnoea	2 (0.12%)	2 (0.08%)	0 (0.0%)
	Nasal discomfort	2 (0.12%)	2 (0.08%)	0 (0.0%)
	Nasal dryness	3 (0.18%)	6 (0.24%)	4 (0.29%)
Gastrointestinal disorders				
Uncommon	Upper abdominal pain	11 (0.65%)	14 (0.55%)	6 (0.44%)
	Abdominal pain	5 (0.30%)	5 (0.20%)	4 (0.29%)
	Nausea	7 (0.41%)	10 (0.40%)	14 (1.03%)
	Stomach discomfort	3 (0.18%)	4 (0.16%)	0 (0.0%)
	Diarrhoea	4 (0.24%)	6 (0.24%)	3 (0.22%)
	Dry mouth	2 (0.12%)	6 (0.24%)	5 (0.37%)
	Dyspepsia	2 (0.12%)	4 (0.16%)	4 (0.29%)
	Gastritis	4 (0.24%)	4 (0.16%)	0 (0.0%)
Skin and subcutaneous tissue disorders				
Uncommon	Pruritus	2 (0.12%)	4 (0.16%)	2 (0.15%)
General disorders and administration site conditions				
Uncommon	Fatigue	14 (0.83%)	19 (0.75%)	18 (1.32%)
	Thirst	3 (0.18%)	4 (0.16%)	1 (0.07%)
	Improved pre-existing condition	2 (0.12%)	2 (0.08%)	1 (0.07%)
	Pyrexia	2 (0.12%)	3 (0.12%)	1 (0.07%)
	Asthenia	3 (0.18%)	4 (0.16%)	5 (0.37%)
Investigations				
Uncommon	Increased gamma-glutamyltransferase	7 (0.41%)	8 (0.32%)	2 (0.15%)
	Alanine aminotransferase increased	5 (0.30%)	5 (0.20%)	3 (0.22%)
	Aspartate aminotransferase increased	3 (0.18%)	3 (0.12%)	3 (0.22%)
	Blood creatinine increased	2 (0.12%)	2 (0.08%)	0 (0.0%)
	Blood triglicerides increased	2 (0.12%)	2 (0.08%)	3 (0.22%)
	Increased weight	8 (0.47%)	12 (0.48%)	2 (0.15%)

Frequency not known (cannot be estimated from the available data): Palpitations, tachycardia, hypersensitivity reactions (such as anaphylaxis, angioedema, dyspnoea, rash, localised oedema/ local swelling, and erythema), and vomiting have been observed during the post-marketing period.

Description of selected adverse reactions in adult and adolescent patients

Somnolence, headache, dizziness and fatigue were observed either in patients treated with Bilastine 20 mg or with placebo. The frequency reported was 3.06% vs. 2.86% for somnolence; 4.01% vs. 3.38% for headache; 0.83% vs. 0.59% for dizziness, and 0.83% vs. 1.32% for fatigue.

The information collected during the post-marketing surveillance has confirmed the safety profile observed during the clinical development.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Kindly report any suspected adverse reactions to pharmavigil@jbcpl.com

OVERDOSE

Montelukast

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. No specific information is available on the treatment of overdose with Montelukast. It is not known whether Montelukast is dialysable by peritoneal- or haemodialysis.

Bilastine

After administration of Bilastine at doses 10 to 11 times the therapeutic dose (220 mg as single dose; or 200 mg/day for 7 days) to 26 adult healthy volunteers frequency of treatment emergent adverse events was two times higher than with placebo. The adverse reactions most frequently reported were dizziness, headache and nausea. No serious adverse events and no significant prolongation in the QTc interval were reported. Critical evaluation of Bilastine's multiple dose (100 mg x 4 days) effect on ventricular repolarization did not show significant QTc prolongation. In the event of overdose symptomatic and supportive treatment is recommended. There is no known specific antidote to Bilastine.

PHARMACOLOGICAL PROPERTIES

Mechanism of Action

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.

Bilastine

Bilastine inhibited histamine-induced wheal and flare skin reactions for 24 hours following single doses.

Pharmacodynamic properties

Pharmacotherapeutic group: Leukotriene receptor antagonist and Antihistamines for systemic use.

Montelukast

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.

A clinical study was conducted to evaluate Montelukast for the symptomatic treatment of seasonal allergic rhinitis in adult and adolescent asthmatic patients 15 years of age and older with concomitant seasonal allergic rhinitis. In this study, Montelukast 10 mg tablets administered once daily demonstrated a statistically significant improvement in the Daily Rhinitis Symptoms score, compared with placebo. The Daily Rhinitis Symptoms score is the average of the Daytime Nasal Symptoms score (mean of nasal congestion, rhinorrhea, sneezing, nasal itching) and the Nighttime Symptoms score (mean of nasal congestion upon awakening, difficulty going to sleep, and nighttime awakenings scores). Global evaluations of allergic rhinitis by patients and physicians were significantly improved, compared with placebo. The evaluation of asthma efficacy was not a primary objective in this study.

Bilastine

Bilastine is a non-sedating, long-acting histamine antagonist with selective peripheral H1 receptor antagonist affinity and no affinity for muscarinic receptors.

In clinical trials performed in adult and adolescent patients with allergic rhinoconjunctivitis (seasonal and perennial), Bilastine 20 mg, administered once daily for 14-28 days, was effective in relieving symptoms such as sneezing, nasal discharge, nasal itching, nasal congestion, ocular itching, tearing and ocular redness. Bilastine effectively controlled symptoms for 24 hours.

No clinically relevant prolongation of QTc interval or any other cardiovascular effect has been observed in the clinical trials performed with bilastine, even at doses of 200 mg daily (10 times the clinical dose) for 7 days in 9 subjects, or even when coadministered with P-gp inhibitors, such as ketoconazole (24 subjects) and erythromycin (24 subjects). Additionally, a thorough QT study including 30 volunteers has been performed.

Pharmacokinetic properties

Montelukast

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 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 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.

Bilastine

Absorption

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%.

Distribution

In vitro and *in vivo* studies have shown that Bilastine is a substrate of P-gp and OATP. Bilastine does not appear to be a substrate of the transporter BCRP or renal transporters OCT2, OAT1 and OAT3. Based on *in vitro* studies, Bilastine is not expected to inhibit the following transporters in the systemic circulation: P-gp, MRP2, BCRP, BSEP, OATP1B1, OATP1B3, OATP2B1, OAT1, OAT3, OCT1, OCT2, and NTCP, since only mild inhibition was detected for P-gp, OATP2B1 and OCT1, with an estimated $IC_{50} \geq 300$ µM, much higher than the calculated clinical plasma C_{max} and therefore these interactions will not be clinically relevant. However, based on these results inhibition by Bilastine of transporters present in the intestinal mucosa, e.g. P-gp, cannot be excluded.

At therapeutic doses Bilastine is 84-90% bound to plasma proteins.

Biotransformation

Bilastine did not induce or inhibit activity of CYP450 isoenzymes in in vitro studies.

Elimination

In a mass balance study performed in healthy adult volunteers, after administration of a single dose of 20 mg ^{14}C-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.

Incompatibilities

Not applicable.

Packaging information

Blister of 2 tablets and 10 tablets

Storage and handing instructions

Store at a temperature not exceeding 30°C. Protect from light and moisture.

Marketed by & ® Regd. Trade Mark of :
J. B. CHEMICALS & PHARMACEUTICALS LTD.
Neelam Centre, 'B' Wing, Hind Cycle Road,
Worli, Mumbai - 400 030. India.

DATE OF REVISION
November 2021

Note: This prescribing information is applicable for India Market only.