1.NAME OF THE MEDICINAL PRODUCT

Bilas M Suspension

2.QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml contains: bilastine10mg and montelukast sodium BP 4mg

For the full list of excipients, see section 6.1.

3.PHARMACEUTICAL FORM

Oral Suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Bilas M suspension is indicated for the treatment of Allergic Rhinitis in children.

4.2 Posology and method of administration

Posology

Children

5ml once daily or as prescribed by the physician.

Method of administration

Oral use.

To be taken orally. The Oral Suspension should be taken one hour before or two hours after intake of food or fruit juice.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Bilastine

Paediatric Population

In patients with moderate or severe renal impairment co-administration 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, co-administration of bilastine and P-glycoprotein inhibitors should be avoided in patients with moderate or severe renal impairment.

Montelukast

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 substituted abruptly 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, vasculitis 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.

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

Neuropsychiatric events have been reported in adults, adolescents, and children taking montelukast. Patients and physicians should be alert for neuropsychiatric events. Patients and/or caregivers should be instructed to notify their physician if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with montelukast if such events occur.

4.5 Interaction with other medicinal products and other forms of interaction

Bilastine

Interaction studies have only been performed in adults and are summarised below.

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. 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.

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 ePux 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 Cmax of bilastine by 50%. This effect can be explained by

interaction with intestinal ePux 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.

Paediatric population: Interaction studies have only been performed in adults. 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

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, 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 metabolized 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.

4.6 Fertility, pregnancy and lactation

Pregnant Women

Bilastine

There are no or limited amount of data from the use of bilastine in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity, parturition or postnatal development.

Montelukast

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

Available data from published prospective and retrospective cohort studies with montelukast use in pregnant women evaluating major birth defects have not established a drug-associated risk. Available studies have methodologic limitations, including small sample size, retrospective data collection (in some cases), and inconsistent comparator groups.

As a precautionary measure, it is preferable to avoid the use of the bilastine plus montelukast combination suspension during pregnancy.

Lactating Women

Bilastine

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 breastfeeding or to discontinue/abstain from bilastine therapy must be made taking into account the benefit of breastfeeding for the child and the benefit of bilastine therapy for the mother.

Montelukast

Studies in rats have shown that montelukast is excreted in milk. It is unknown whether montelukast and/or metabolites are excreted in human milk.

A decision on whether to continue/discontinue breastfeeding or to discontinue/abstain from the bilastine plus montelukast combination therapy must be made taking into account the benefit of breastfeeding for the child and the benefit of the therapy for the mother.

Fertility

There are no or limited amount of clinical data regarding effect on fertility. A study in rats did not indicate any negative effect on fertility with bilastine.

Paediatric Patients

Bilastine

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

Montelukast

The effectiveness of montelukast for the treatment of seasonal allergic rhinitis in paediatric patients 2 to 14 years of age and for the treatment of perennial allergic rhinitis in paediatric patients 6 months to 14 years of age have been established and is supported by extrapolation from the demonstrated effectiveness in patients 15 years of

age and older with allergic rhinitis as well as the assumption that the disease course, pathophysiology and the drug's effect are substantially similar among these populations.
The safety of montelukast 4 mg and 5 mg chewable tablets in paediatric patients 2 to 14 years of age with allergic rhinitis is supported by data from studies conducted in paediatric patients 2 to 14 years of age with asthma. A safety study in paediatric patients 2 to 14 years of age with seasonal allergic rhinitis demonstrated a similar safety profile.
The safety of montelukast 4 mg oral granules in paediatric patients as young as 6 months of age with perennial allergic rhinitis is supported by extrapolation from safety data obtained from studies conducted in paediatric patients 6 months to 23 months of age with asthma and from pharmacokinetic data comparing systemic exposures in patients 6 months to 23 months of age to systemic exposures in adults.
The safety and effectiveness in paediatric patients below the age of 12 months with asthma, 6 months with perennial allergic rhinitis, and 6 years with exercise-induced bronchoconstriction have not been established.
FDC of Bilastine 10mg + Montelukast 4 mg per 5 ml suspension for the treatment of allergic rhinitis in Children aged 6 to 11 years (both inclusive) with a body weight of at least 20 kg the safety and efficacy in children has been established.

4.7 Effects on ability to drive and use machines
A study performed in adults to assess the effects of bilastine on the ability to drive demonstrated that:
Bilastine
A study performed in adults to assess the effects of bilastine on the ability to drive demonstrated that treatment with 20 mg did not affect the driving performance. However, as the individual response to the medicinal product may vary, patients should be advised not to drive or use machines until they have established their own response to bilastine.
Montelukast
Montelukast has no or negligible influence on the ability to drive and use machines. However, individuals have reported drowsiness or dizziness

4.8 Undesirable effects
Bilastine
Summary of safety profile in adults and adolescent patients
The incidence of adverse events in patients suffering from allergic rhino conjunctivitis or chronic idiopathic urticaria treated with 20 mg bilastine in clinical trials was comparable with the incidence in patients receiving placebo (12.7% versus 12.8%).
The phase II and III clinical trials performed during the clinical development included 2525 patients treated with different doses of bilastine, of which 1697 received bilastine 20 mg. In these trials 1362 patients received placebo. The ADRs most commonly reported by patients receiving 20 mg bilastine for the indication of allergic rhino conjunctivitis 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 AEs in Paedriatic Patients

AEs, at least possibly related to bilastine and reported in more than 0.1% of children (2 to 11 years of age) receiving bilastine during the clinical development, are tabulated below.

Frequencies were assigned as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); and, 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 10 mg (N=291)[#]	Placebo (N=249)
Frequency	AE		
Infections and infestations			
Common	Rhinitis	3 (1.0%)	3 (1.2%)
Nervous system disorders			
Common	Headache	6 (2.1%)	3 (1.2%)
Uncommon	Dizziness	1 (0.3%)	0 (0.0%)
	Loss of consciousness	1 (0.3%)	0 (0.0%)
Eye disorders			
Common	Allergic conjunctivitis	4 (1.4%)	5 (2.0%)
Uncommon	Eye irritation	1 (0.3%)	0 (0.0%)
Gastrointestinal disorders			
Common	Abdominal pain/upper abdominal pain	3 (1.0%)	3 (1.2%)
Uncommon	Diarrhoea	2 (0.7%)	0 (0.0%)
	Nausea	1 (0.3%)	0 (0.0%)
	Lip swelling	1 (0.3%)	0 (0.0%)
Skin and subcutaneous tissue disorders			
Uncommon	Eczema	1 (0.3%)	0 (0.0%)
	Urticaria	2 (0.7%)	2 (0.8%)
General disorders and administration site conditions			
Uncommon	Fatigue	2 (0.7%)	0 (0.0%)

[#] 260 children exposed in the clinical safety study; 31 children exposed in the

pharmacokinetic study

Description of Selected AEs in Paediatric Patients
Headache, abdominal pain, allergic conjunctivitis and rhinitis were observed in children treated with either bilastine 10 mg or with placebo. The frequency reported was 2.1% vs 1.2% for headache; 1.0% vs 1.2% for abdominal pain; 1.4% vs 2.0% for allergic conjunctivitis; and, 1.0% vs 1.2% for rhinitis.

Summary of Safety Profile in Adult and Adolescent Patients
The incidence of adverse events in patients suffering from allergic rhinoconjunctivitis or chronic idiopathic urticaria treated with 20 mg bilastine in clinical trials was comparable with the incidence in patients receiving placebo (12.7% vs 12.8%).
The Phase II and III clinical trials performed during the clinical development included 2,525 patients treated with different doses of bilastine, of whom 1,697 received bilastine 20 mg. In these trials, 1,362 patients received placebo. The AEs 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 AEs 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%)	10 (0.59%)	10 (0.59%)
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.

Montelukast
Montelukast has been evaluated in clinical studies as follows:
10-mg film-coated tablets in approximately 4,000 adult and adolescent asthmatic patients 15 years of age and older.
10-mg film-coated tablets in approximately 400 adult and adolescent asthmatic patients with seasonal allergic rhinitis 15 years of age and older.
5-mg chewable tablets in approximately 1,750 paediatric asthmatic patients 6 to 14 years of age.
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

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 paediatric patients 6 to 14 years of age, the safety profile did not change.
Tabulated list of Adverse Reactions

Adverse reactions reported in post-marketing use and clinical experience are listed, by MedDRA System Organ Class and ranked by frequency as follows:
Very Common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1000 to <1/100), Rare (≥1/10,000 to <1/1000), Very Rare (≥1/10,000) and Not known (cannot be estimated from the available data)

System Organ Class	**Adverse Experience Term**	**Frequency Category***
Infections and infestations	upper respiratory infection†	Very Common
Blood and lymphatic system disorders	increased bleeding tendency	Rare
Immune system disorder	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	Rare
	hallucinations, disorientation, suicidal thinking and behaviour (suicidality), dysphemia	Very Rare
Nervous system disorder	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
Gastrointestinal 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, connective tissue and bone disorders	arthralgia, myalgia including muscle cramps	Uncommon
General disorders and administration site conditions	pyrexia‡	Common
	asthenia/fatigue, malaise, oedema,	Uncommon

‡ This adverse experience, reported as Common in the patients who received montelukast, was also reported as Common in the patients who received placebo in clinical trials.
§ Frequency Category: Rare

Reporting of suspected adverse reactions

Healthcare professionals are requested to report any suspected adverse reactions via national Pharmacovigilance Electronic Reporting Systems to the respective national regulatory authorities

4.9 Overdose

Bilastine

Information regarding acute overdose of bilastine is retrieved from the experience of clinical trials conducted during the development and the post-marketing surveillance. In clinical trials, 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 healthy volunteer's 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. The information collected in the post-marketing surveillance is consistent with that reported in clinical trials.
Critical evaluation of bilastine's multiple dose (100 mg x4 days) effect on ventricular repolarization by a "thorough QT/QTc cross-over study" involving 30 healthy volunteers 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.

Montelukast

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 adult 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 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.

Symptoms of overdose

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

5.Pharmacological properties

5.1Pharmacodynamic properties

Mechanism of Action

Bilastine

Bilastine is a non-sedating, 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

Montelukast is an orally active compound which binds with high afinity and selectivity to the CysLT1 receptor. Cysteinyl leukotriene (CysLT) receptors have been correlated with the pathophysiology of asthma and allergic rhinitis. In allergic rhinitis, CysLTs receptors 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.

Pharmacodynamic Properties

Bilastine

Pharmacotherapeutic group: Antihistamines for systemic use, other antihistamines for systemic use. ATC code R06AX29.

Bilastine is a non-sedating, long-acting histamine antagonist with selective peripheral H1 receptor antagonist affinity.

In clinical trials performed in adult and adolescent patients with allergic rhino conjunctivitis (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 co-administered with P-gp inhibitors, such as ketoconazole (24 subjects) and erythromycin (24 subjects). Additionally, a thorough QT study including 30 volunteers has been performed.

In controlled clinical trials at the recommended dose of 20 mg once daily, the CNS safety profile of bilastine was similar to placebo and the incidence of somnolence was not statistically different from placebo. Bilastine at doses of up to 40 mg q.d. did not affect psychomotor performance in clinical trials and did not affect driving performance in a standard driving test.

Elderly patients (≥ 65 years) included in phase II and III studies showed no difference in efficacy or safety with respect to younger patients. A post- authorisation study in 146 elderly patients showed no differences in the safety profile with respect to the adult population.

Montelukast

Pharmacotherapeutic group: Leukotriene receptor antagonist. ATC-code: R03D C03.

Montelukast is an orally active compound which binds with high afinity and selectivity to

the CysLT1 receptor. In clinical studies, montelukast inhibits bronchoconstriction due to inhaled LTD4 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.
In studies in adults, montelukast, 10 mg once daily, compared with placebo, demonstrated significant improvements in morning FEV1 (10.4% vs 2.7% change from baseline), AM peak expiratory flow rate (PEFR) (24.5 L/min vs 3.3 L/min change from baseline), and significant decrease in total β-agonist use (-26.1% vs -4.6% change from baseline).
Improvement in patient-reported daytime and nighttime asthma symptoms scores was significantly better than placebo.
Studies in adults demonstrated the ability of montelukast to add to the clinical effect of inhaled corticosteroid (% change from baseline for inhaled beclometasone plus montelukast vs beclometasone, respectively for FEV1: 5.43% vs 1.04%; β- agonist use:
-8.70% vs 2.64%). Compared with inhaled beclometasone (200 µg twice daily with a spacer device), montelukast demonstrated a more rapid initial response, although over the 12-week study, beclometasone provided a greater average treatment effect (% change from baseline for montelukast vs beclometasone, respectively for FEV1: 7.49% vs 13.3%; β--agonist use: -28.28% vs -43.89%). However, compared with beclometasone, a high percentage of patients treated with montelukast achieved similar clinical responses (e.g. 50% of patients treated with beclomethasone achieved an improvement in FEV1 of approximately 11% or more over baseline while approximately 42% of patients treated with montelukast achieved the same response).
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 Night-time Symptoms score (mean of nasal congestion upon awakening, dificulty going to sleep, and night-time awakenings scores). Global evaluations of allergic rhinitis by patients and physicians were significantly improved, compared with placebo. The evaluation of asthma eficacy was not a primary objective in this study.
In an 8-week study in paediatric patients 6 to 14 years of age, montelukast 5 mg once daily, compared with placebo, significantly improved respiratory function (FEV1 8.71% vs 4.16% change from baseline; AM PEFR 27.9 L/min vs 17.8 L/min change from baseline) and decreased "as-needed"β-agonist use (-11.7% vs +8.2% change from baseline).
Significant reduction of exercise-induced bronchoconstriction (EIB) was demonstrated in a 12-week study in adults (maximal fall in FEV1 22.33% for montelukast vs 32.40% for placebo; time to recovery to within 5% of baseline FEV1 44.22 min vs 60.64 min). This effect was consistent throughout the 12-week study period. Reduction in EIB was also

demonstrated in a short-term study in paediatric patients (maximal fall in FEV1 18.27% vs 26.11%; time to recovery to within 5% of baseline FEV1 17.76 min vs 27.98 min). The effect in both studies was demonstrated at the end of the once-daily dosing interval.
In aspirin-sensitive asthmatic patients receiving concomitant inhaled and/or oral corticosteroids, treatment with montelukast, compared with placebo, resulted in significant improvement in asthma control (FEV1 8.55% vs -1.74% change from baseline and decrease in total β-agonist use -27.78% vs 2.09% change from baseline).

5.2 Pharmacokinetic properties

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 (see section 4.5 "Interaction with ketoconazole, erythromycin and diltiazem") and OATP (see section 4.5 "Interaction with grapefruit juice"). 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 IC50 ≥ 300 μM, much higher than the calculated clinical plasma Cmax 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.

Metabolism

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

Excretion

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.

Linearity

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 are no pharmacokinetic data in subjects with hepatic impairment. Bilastine is not metabolized in human. 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.

Montelukast

Absorption

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. 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 Cmax 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 radio-labelled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radio-labelled material at 24 hours' post-dose were minimal in all other tissues.

Metabolism

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.

Excretion

The plasma clearance of montelukast averages 45 ml/min in healthy adults. Following an oral dose of radio-labelled 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

5.3 Preclinical safety data

Animal toxicology or pharmacology

Bilastine

Non-clinical data with bilastine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

In reproduction toxicity studies effects of bilastine on the foetus (pre-and post-implantation loss in rats and incomplete ossification of cranial bones, sternebrae and limbs in rabbits) were only observed at maternal toxic doses. The exposure levels at the NOAELs are sufficiently in excess (> 30 fold) to the human exposure at the recommended therapeutic dose.

In a lactation study, bilastine was identified in the milk of nursing rats administered a single oral dose (20 mg/kg). Concentrations of bilastine in milk were about half of those in maternal plasma. The relevance of those results for humans is unknown.

In a fertility study in rats, bilastine administered orally up to 1000 mg/kg/day did not induce any effect on female and male reproductive organs. Mating, fertility and pregnancy indices were not affected.

As seen in a distribution study in rats with determination of drug concentrations by autoradiography, bilastine does not accumulate in the CNS.

Montelukast

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/m2 and 30,000 mg/m2 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.

Description
Bilastine is a second generation H1-antihistamine, indicated for the treatment of allergic rhinitis. Bilastine is known chemically as 2- piperidin-1-yl} ethyl) phenyl]-2-methylpropanoic acid; 2- piperidin-1-yl] ethyl] phenyl]-2-methylpropanoic acid. Its empirical formula is $C_{28}H_{37}N_3O_3$ and the molecular weight is 463.61168 g/mol.
Montelukast is a leukotriene receptor antagonist which inhibits physiologic actions of LTD4 at the CysLT1 receptor without any agonist activity. Montelukast is chemically known as -1- phenyl]-3- propyl] thio] methyl] cyclopropane acetic acid. Its empirical formula is $C_{35}H_{35}ClNO_3S$ and the molecular weight is 586.183.

6. Pharmaceutical particulars

6.1 List of excipients
Xanthan Gum, Hydroxypropyl Beta Cyclodextrin, Propylene Glycol, Refined sugar, Sodium Methyl Hydroxybenzoate, Sodium Propyl Hydroxybenzoate, Sodium Benzoate, Disodium Edetate, Sucralose, Potassium Dihydrogen Phosphate, Butylated Hydroxy Toluene (BHT), Ponceau 4R supra colour, Mango Liquid Flavour, Pineapple Liquid Flavour, Sodium Hydroxide Pallets, Concentrated Hydrochloric Acid, Purified water.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Dot not store above 30° C. Protect from direct sunlight. Keep all medicines out of reach of children

6.5 Nature and contents of container
60 ml PET Bottle, packed in printed unit carton with literature insert.

6.6 Special precautions for disposal and other handling
This medicinal product does not require any special storage conditions.

7. Marketing authorization holder
Dawa Limited,
Plot No. 7879/8, Baba Dogo Road, Ruaraka,
P.O Box 16633-00620
Nairobi, Kenya

Manufacturing site

Ravenbhel Healthcare Pvt. Ltd.
16-17, EPIP, SIDCO, Kartholi,
Bari Brahmana- 181133, Jammu, India

8. Marketing authorization number
H2025/CTD11991/25062

9. Date of First Authorization/renewal of the authorization
November 2023

10. Date of revision of the text
November 2023