

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

**Pr APO-BILASTINE ORODISPERSIBLE TABLETS**

Bilastine Orodispersible Tablets

Tablet (orally disintegrating), 10 mg, Oral

**Pr APO-BILASTINE TABLETS**

Bilastine Tablets

Tablet, 20 mg, Oral

**Pr APO-BILASTINE ORAL SOLUTION**

Bilastine Oral Solution

Solution, 2.5 mg/mL, Oral

Histamine H1-Receptor Antagonist

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## PART I: HEALTH PROFESSIONAL INFORMATION

### 1 INDICATIONS

#### Seasonal Allergic Rhinitis

APO-BILASTINE ORODISPERSIBLE TABLETS (bilastine), APO-BILASTINE TABLETS (bilastine) and APO-BILASTINE ORAL SOLUTION (bilastine) are indicated for the symptomatic relief of nasal and non-nasal symptoms of seasonal allergic rhinitis (SAR) in patients 4 years of age and older with a body weight of at least 16 kg.

#### Chronic Spontaneous Urticaria

APO-BILASTINE ORODISPERSIBLE TABLETS (bilastine), APO-BILASTINE TABLETS (bilastine) and APO-BILASTINE ORAL SOLUTION (bilastine) are indicated for the relief of the symptoms associated with chronic spontaneous urticaria (CSU) (e.g. pruritus and hives), in patients 4 years of age and older with a body weight of at least 16 kg.

#### 1.1 Pediatrics

**Pediatrics (< 4 years of age):** APO-BILASTINE ORODISPERSIBLE TABLETS, APO-BILASTINE TABLETS and APO-BILASTINE ORAL SOLUTION should not be administered to children below 4 years of age and under 16 kg due to limited data in this population.

#### 1.2 Geriatrics

**Geriatrics (> 65 years of age):** No dosage adjustments are necessary in patients over 65 years (see [ACTION AND CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION](#)).

### 2 CONTRAINDICATIONS

APO-BILASTINE ORODISPERSIBLE TABLETS, APO-BILASTINE TABLETS and APO-BILASTINE ORAL SOLUTION are contraindicated in patients with:

- hypersensitivity to bilastine or to any ingredient in the formulation or component of the container. For a complete listing of ingredients and components (see [Dosage Forms, Composition and Packaging](#)).
- a history of QT prolongation and/or torsade de pointes, including congenital long QT syndromes (see [WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS, ACTION AND CLINICAL PHARMACOLOGY](#)).

### 4 DOSAGE AND ADMINISTRATION

#### 4.1 Dosing Considerations

##### Renal impairment

No dosage adjustments are required in subjects with renal impairment.

##### Hepatic impairment

There is no clinical experience 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. Therefore, no dosage adjustment is required in subjects with hepatic impairment.

#### **Pediatrics (<4 years of age)**

APO-BILASTINE ORODISPERSIBLE TABLETS, APO-BILASTINE TABLETS and APO-BILASTINE ORAL SOLUTION should not be administered to children below 4 years of age and under 16 kg due to limited data in this population.

#### **Geriatrics (> 65 years of age)**

No dosage adjustments are recommended in subjects > 65 years of age.

### **4.2 Recommended Dose and Dosage Adjustment**

#### **Recommended daily dose:**

<b>Seasonal Allergic Rhinitis</b>	4-11 years with a body weight of at least 16 kg	10 mg (1 orodispersible tablet or 4 mL oral solution) once daily
	≥12 years	20 mg (1 tablet) once daily
<b>Chronic Spontaneous Urticaria</b>	4-11 years with a body weight of at least 16 kg	10 mg (1 orodispersible tablet or 4 mL oral solution) once daily
	≥12 years	20 mg (1 tablet) once daily

#### **Maximum daily dose**

##### 4-11 years with a body weight of at least 16 kg

The maximum recommended daily dose is 10 mg (1 orodispersible tablet or 4 mL oral solution) and should not be exceeded.

##### ≥12 years

The maximum recommended daily dose is 20 mg (1 tablet) and should not be exceeded.

### **4.4 Administration**

#### **10 mg orodispersible tablet**

The APO-BILASTINE ORODISPERSIBLE TABLETS (orodispersible tablet) are to be placed in the mouth where it disperses rapidly in saliva, so it can be easily swallowed.

Alternatively, the orodispersible tablet may be dispersed in water before administration. Grapefruit juice or any other fruit juice should not be used for dispersion (See [Drug-Food Interactions, Grapefruit juice](#)).

The APO-BILASTINE ORODISPERSIBLE TABLETS should be taken without food or grapefruit juice or other fruit juices, as these dietary compounds may decrease the effect of bilastine. Patients should be instructed to take the orodispersible tablet and wait for one hour before taking food or fruit juice, or if food or fruit juice has been taken, to wait for two hours before

taking the tablet.

### **20 mg tablet**

One 20 mg tablet of APO-BILASTINE TABLETS, once daily, should be swallowed with water on an empty stomach to achieve optimal exposure to bilastine. The APO-BILASTINE TABLETS should be taken without food or grapefruit juice or other fruit juices, as these dietary compounds may decrease the effect of bilastine. Patients should be instructed to take the tablet and wait for one hour before taking food or fruit juice, or if food or fruit juice has been taken, to wait for two hours before taking the tablet.

### **2.5 mg/mL oral solution**

The oral solution is accompanied by a dosing cup with a mark of 4 mL equivalent to 10 mg bilastine per dose. Patients should be instructed to fill the cup with 4 mL of the oral solution and administer directly from the cup. The APO-BILASTINE ORAL SOLUTION (oral solution) should be taken without food or grapefruit juice or other fruit juices as these dietary compounds may decrease the effect of bilastine. Patients should be instructed to take the oral solution and wait for one hour before taking food or fruit juice, or if food or fruit juice has been taken, to wait for two hours before taking the solution.

### **4.5 Missed Dose**

If a dose is missed, the next scheduled dose should be taken. An extra dose should not be taken.

## **5 OVERDOSAGE**

Information regarding acute overdose is limited to experience from clinical trials conducted during the development of bilastine. After administration of bilastine at doses 10 to 11 times the therapeutic dose (220 mg (single dose); or 200 mg/day for 7 days) to 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. There are no data for overdose in children.

Electrocardiogram monitoring is recommended in the event of overdosage (see [WARNINGS AND PRECAUTIONS](#), [ACTION AND CLINICAL PHARMACOLOGY](#), [Pharmacodynamics](#)).

Overdose in the post-marketing setting has been reported rarely; any adverse events were consistent with those seen in clinical trials.

In the event of overdose, symptomatic and supportive treatment is recommended. There is no known specific antidote to bilastine.

For management of a suspected drug overdose, contact your regional poison control centre.

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Table 1 – Dosage Forms, Strengths, Composition and Packaging.**

<b>Route of Administration</b>	<b>Dosage Form / Strength/Composition</b>	<b>Non-medicinal Ingredients</b>
oral	orodispersible tablet, 10 mg	croscarmellose sodium, mannitol, red grape flavour, sodium stearyl fumarate, sucralose (E955)
oral	tablet, 20 mg	colloidal anhydrous silica, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.
oral	oral solution, 2.5 mg/mL	betadex, hydrochloric acid 37% (for pH-adjustment), hydroxyethylcellulose, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), purified water, raspberry flavor, sodium hydroxide (for pH-adjustment), sucralose (E 955)

### **Composition**

#### **10 mg orodispersible tablet**

APO-BILASTINE ORODISPERSIBLE TABLETS (orodispersible tablets) are round, slightly biconvex white tablets of 8 mm diameter. Each tablet contains 10 mg of active ingredient, bilastine.

#### **20 mg tablet**

APO-BILASTINE TABLETS (tablets) are oval (length 10 mm, width 5 mm), biconvex, white, scored and free of cracks or defects. Each tablet contains 20 mg of active ingredient, bilastine.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

#### **2.5 mg/mL oral solution**

APO-BILASTINE ORAL SOLUTION (oral solution) is a clear, colourless, slightly viscous aqueous solution without precipitate.

### **Packaging**

#### **10 mg orodispersible tablet**

APO-BILASTINE ORODISPERSIBLE TABLETS (orodispersible tablets) are available in blister packs containing 10 tablets. Cartons contain 30 tablets.

#### **20 mg tablet**

APO-BILASTINE TABLETS (20 mg tablets) are available in blister packs containing 10 tablets.

Cartons contains 30 tablets.

### **2.5 mg/mL oral solution**

APO-BILASTINE ORAL SOLUTION (2.5 mg/mL oral solution) is packaged in an amber glass bottle containing 120 mL oral solution. Each bottle is accompanied by a dosing cup.

## **7 WARNINGS AND PRECAUTIONS**

### **Cardiovascular**

Bilastine has been associated with QTc interval prolongation (see [ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology](#)). Drugs that cause QT/QTc prolongation are suspected of increasing the risk of torsade de pointes. Torsade de pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of torsade de pointes increases with the magnitude of QT/QTc prolongation produced by the drug. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

APO-BILASTINE ORODISPERSIBLE TABLETS, APO-BILASTINE TABLETS and APO-BILASTINE ORAL SOLUTION should not be used in patients with a history of QTc prolongation and/or torsade de pointes, including congenital long QT syndromes (see [CONTRAINDICATIONS](#)).

Particular care should be exercised when administering antihistamines, including APO-BILASTINE ORODISPERSIBLE TABLETS, APO-BILASTINE TABLETS and APO-BILASTINE ORAL SOLUTION 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.

### **Driving and Operating Machinery**

A study was performed to assess the effects of bilastine and bilastine 40 mg on real time driving performance compared to placebo and hydroxyzine 50 mg. Bilastine did not affect driving performance differently than placebo following day one or after one week of treatment. However, patients should be informed that very rarely some people experience drowsiness, which may affect their ability to drive or use machines.

### **Hepatic**

Bilastine 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.

## **7.1 Special Populations**

### **7.1.1 Pregnant Women**

There are no adequate and well-controlled studies in pregnant women. Until such data become available, APO-BILASTINE ORODISPERSIBLE TABLETS, APO-BILASTINE TABLETS and APO-BILASTINE ORAL SOLUTION should be avoided during pregnancy, unless advised otherwise by a physician.

Animal studies do not indicate major direct or indirect harmful effects with respect to reproductive toxicity, parturition or postnatal development (see [TOXICOLOGY](#)).

Twelve (12) pregnancies were reported during bilastine investigation. Follow-up was performed by the investigators through to the birth of newborns. Their observations indicated that there had been a normal outcome reported for every pregnancy, except one miscarriage due to an antiphospholipid syndrome (case history of repeated miscarriages) resulting in an induced abortion (voluntary).

### **7.1.2 Breast-feeding**

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 continue/discontinue therapy with APO-BILASTINE ORODISPERSIBLE TABLETS, APO-BILASTINE TABLETS and APO-BILASTINE ORAL SOLUTION should be made taking into account the benefit of breast-feeding to the child, the benefit of bilastine therapy to the mother, and these should be weighed against possible effects on the infant.

### **7.1.3 Pediatrics (<4 years of age)**

APO-BILASTINE ORODISPERSIBLE TABLETS, APO-BILASTINE TABLETS and APO-BILASTINE ORAL SOLUTION should not be administered to children below 4 years of age and under 16 kg due to limited data in this population.

### **7.1.4 Geriatrics (>65 years of age)**

No dosage adjustments are recommended in subjects over 65 years of age (see [ACTION AND CLINICAL PHARMACOLOGY](#) and [DOSAGE AND ADMINISTRATION](#)).

## **8 ADVERSE REACTIONS**

### **8.1 Adverse Reaction Overview**

The clinical safety of bilastine was evaluated in 10 Phase 2 and 3 studies performed in 2186 adult and adolescent subjects with allergic rhinitis, or chronic spontaneous urticaria (CSU),

where bilastine was used at doses ranging from 10 – 40 mg over treatment periods of 2 – 4 weeks.

The most common treatment-emergent adverse reactions reported in the double-blind Phase 3 studies involving 931 subjects treated with bilastine 20 mg were related to the central nervous system (headache, dizziness, and somnolence) and the gastrointestinal system (abdominal pain upper).

Treatment-emergent cardiovascular effects occurred infrequently or rarely (bundle branch block right sinus arrhythmia, sinus bradycardia and ventricular extrasystoles, abnormal ECG investigations) in clinical studies.

A one year open-label safety study in 513 allergic rhinitis patients was conducted with bilastine. The most common adverse events seen in this open-label study were headache, influenza, and nasopharyngitis.

## 8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

### Adolescents and Adults

At the recommended dose of 20 mg daily, treatment-emergent adverse reactions with bilastine were equal to those treated with placebo. The most commonly reported related AEs were dizziness, headache and somnolence.

The incidence of treatment-emergent adverse reactions reported by  $\geq 1\%$  of subjects treated with bilastine in Phase 2 and 3 trials is presented in Table 2.

**Table 2 Treatment-Emergent Adverse Reactions Reported in  $\geq 1\%$  of Subjects Treated with Bilastine in the Double-Blind Studies**

<b>Body System / AE</b>	<b>Bilastine N=931</b>	<b>Placebo N=950</b>
<b>Gastrointestinal disorders</b>	28 (3.01%)	28 (2.95%)
Abdominal pain upper	10 (1.07%)	4 (0.42%)
<b>Nervous system disorders</b>	81 (8.70%)	55 (5.79%)
Dizziness	10 (1.07%)	4 (0.42%)
Headache	40 (4.30%)	28 (2.95%)
Somnolence	38 (4.08%)	25 (2.63%)

The incidence of adverse events in adult and adolescent patients suffering from allergic rhinoconjunctivitis or chronic spontaneous urticaria treated with 20 mg bilastine in clinical trials was comparable with the incidence in patients receiving placebo (12.7% versus 12.8%).

### **Long term open-label study:**

The adverse event profile in the long term follow up study (1 year) in 513 patients

demonstrated a similar profile to that observed in the controlled 2-4 week Phase 2 and 3 clinical studies (see [Adverse Reactions Overview](#)).

### 8.2.1 Clinical trial adverse reactions – pediatrics

#### **Pediatrics (2- 11 years)**

The percentage of children (2-11 years) which reported adverse events (AEs) after treatment with bilastine 10 mg for allergic rhinoconjunctivitis or chronic spontaneous urticaria in a 12-week controlled clinical trial was comparable with patients receiving placebo (68.5% versus 67.5%).

The related AEs most commonly reported by 291 children (2-11 years) receiving bilastine (orodispersible tablet formulation) during clinical trials (260 children exposed in the clinical safety study, 31 children exposed in the pharmacokinetic study) were headache, allergic conjunctivitis, rhinitis and abdominal pain. These related adverse events occurred with a comparable frequency in 249 patients receiving placebo.

The incidence of treatment-emergent adverse reactions reported in  $\geq 0.1\%$  of children (2-11 years) receiving bilastine during the clinical development are tabulated in **Error! Reference source not found.**

**Table 3 Related Treatment-Emergent Adverse Reactions Reported in  $\geq 1\%$  of Subjects Treated with Bilastine in the Pediatric Studies**

<b>Body System / AE</b>	<b>Bilastine 10 mg N=291<sup>a</sup></b>	<b>Placebo N=249</b>
<b>Gastrointestinal disorders</b>		
Abdominal pain/Abdominal pain upper	3 (1.0%)	3 (1.2%)
<b>Infections and infestations</b>		
Rhinitis	3 (1.0%)	3 (1.2%)
<b>Nervous system disorders</b>		
Headache	6 (2.1%)	3 (1.2%)
<b>Eye disorders</b>		
Allergic conjunctivitis	4 (1.4%)	5 (2.0%)

<sup>a</sup> 260 children exposed in the clinical safety study and 31 children exposed in the pharmacokinetics study.

### 8.3 Less Common Clinical Trial Adverse Reactions

The following events were observed in  $< 1\%$  of 2186 patients treated with bilastine in Phase 2 and 3 clinical studies.

**Blood and lymphatic system disorders:** Anaemia

**Cardiovascular:** Bundle branch block right, sinus arrhythmia, sinus bradycardia, ventricular extrasystoles

- ECG investigations: electrocardiogram QT prolonged, electrocardiogram ST-T segment abnormal, electrocardiogram T wave abnormal, electrocardiogram T wave inversion, electrocardiogram abnormal, QRS axis abnormal

**Ear and labyrinth disorders:** Motion sickness, tinnitus, vertigo

**Eye disorders:** Eye pain

**Gastrointestinal disorders:** Abdominal pain, constipation, diarrhoea, dry mouth, dysgeusia, dyspepsia, eructation, gastritis, nausea, stomach discomfort, tongue dry, vomiting

**General disorders and administration site conditions:** Asthenia, chest discomfort, discomfort, fatigue, feeling jittery, pain, pyrexia, thirst

**Infections and infestations:** Oral herpes, pharyngitis

**Metabolism and nutrition disorders:** Increased appetite

**Musculoskeletal and connective tissue disorders:** Back pain, muscular weakness, myalgia

**Nervous system disorders:** Disturbance in attention, hypersomnia

**Psychiatric disorders:** Anxiety, insomnia, nightmare

**Reproductive system and breast disorders:** Menstruation delayed

**Respiratory, thoracic and mediastinal disorders:** Dyspnoea, epistaxis, nasal discomfort, nasal dryness, throat irritation

**Skin and subcutaneous tissue disorders:** Dermatitis acneiform, pruritus, rash popular, urticaria

### 8.3.1 Less Common Clinical Trial Adverse Reactions-Pediatrics

The following events were observed in < 1% of 291 patients treated with bilastine in the clinical safety and pharmacokinetics studies possibly related to bilastine.

**Eye disorders:** Eye irritation

**Gastrointestinal disorders:** Diarrhea, nausea and Lip swelling

**General disorders and administration site conditions:** Fatigue

**Nervous system disorders:** Syncope, Loss of Consciousness

**Skin and subcutaneous tissue disorders:** Eczema and urticaria.

### 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

**Investigations:** Alanine aminotransferase increased, aspartate aminotransferase increased,

blood bilirubin increased, blood cholesterol increased, blood triglycerides increased, gamma-glutamyltransferase increased, weight decreased, weight increased

## 8.5 Post-Market Adverse Reactions

Because adverse events are spontaneously reported in a voluntary manner from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions have been observed during the post-marketing period: palpitations, tachycardia, hypersensitivity reactions (such as anaphylaxis, angioedema, dyspnoea, rash, localized edema/local swelling, and erythema).

A case of torsade de pointes has been reported following the use of bilastine when administered with concomitant medications known to have the potential for QT prolongation.

## 9 DRUG INTERACTIONS

### 9.2 Drug Interactions Overview

The psychomotor performance after concomitant intake of alcohol and bilastine was similar to that observed after intake of alcohol and placebo (see DETAILED PHARMACOLOGY / Human Pharmacodynamics / Psychomotor Pharmacodynamics).

Particular care should be exercised when administering antihistamines, including APO-BILASTINE ORODISPERSIBLE TABLETS, APO-BILASTINE TABLETS and APO-BILASTINE ORAL SOLUTION to patients who are suspected to be at an increased risk of experiencing torsade de pointes during treatment with a QTc-prolonging drug (see [CONTRAINDICATIONS](#), [WARNINGS AND PRECAUTIONS](#), [DRUG INTERACTIONS](#), [ACTION](#) and [CLINICAL PHARMACOLOGY](#)).

### 9.3 Drug-Behavioral Interactions

A study was performed to assess the effects of bilastine and bilastine 40 mg on real time driving performance compared to placebo and hydroxyzine 50 mg. Bilastine did not affect driving performance differently than placebo following day one or after one week of treatment. However, patients should be informed that very rarely some people experience drowsiness, which may affect their ability to drive or use machines.

### 9.4 Drug-Drug Interactions

#### **Ketoconazole and erythromycin**

Concomitant administration of bilastine and ketoconazole or erythromycin increased bilastine AUC 2-fold and  $C_{max}$  2-3 fold. These changes can be explained by interaction with intestinal efflux transporters, since bilastine is a substrate for P-gp and not metabolized.

In a randomised, double-blind, placebo- and positive-controlled, 5-way crossover ECG assessment study in 30 healthy adult subjects, bilastine 20 mg/day administered alone for four days was associated with statistically significant positive mean differences from placebo in the QTcF interval at 1 and 3 h post-dosing on day 4, with a maximum mean difference from placebo of 4.0 ms (90% CI 1.20, 6.73) at 1 h, whereas bilastine 20 mg/day and ketoconazole 400 mg administered concomitantly for four days produced statistically significant QTcF

prolongation at all time points from 0.5-12 h, inclusive, on day 4 with a maximum mean difference from placebo of 10.0 ms (90% CI 6.49, 13.43) at 1 h. 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.

### **Diltiazem**

Concomitant administration of bilastine and diltiazem 60 mg 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.

### **Lorazepam**

Concomitant intake of bilastine and lorazepam 3 mg for 8 days did not potentiate the depressant CNS effects of lorazepam.

### **QTc-Prolonging Drugs:**

The concurrent use of APO-BILASTINE ORODISPERSIBLE TABLETS, APO-BILASTINE TABLETS and APO-BILASTINE ORAL SOLUTION with other QTc prolonging drugs is not recommended.

### **Inhibitors of P-Glycoprotein:**

Plasma levels of bilastine can be increased by inhibitors of P-glycoprotein; the concomitant use of these drugs with bilastine is not recommended. Drugs that inhibit P-glycoprotein include, but are not limited to certain azole antifungal, macrolide antibiotics, and HIV protease inhibitors (see [WARNINGS AND PRECAUTIONS](#)).

### **Drugs that Cause Electrolyte Depletion:**

The use of APO-BILASTINE ORODISPERSIBLE TABLETS, APO-BILASTINE TABLETS and APO-BILASTINE ORAL SOLUTION with drugs that can cause electrolyte imbalance is not recommended (see [WARNINGS AND PRECAUTIONS](#)).

### **Pediatrics**

No interaction studies have been performed in children with APO-BILASTINE ORODISPERSIBLE TABLETS or APO-BILASTINE ORAL SOLUTION. 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 taken into consideration when prescribing bilastine to children.

## **9.5 Drug-Food Interactions**

### **20 mg tablet**

Plasma bilastine  $C_{max}$ ,  $AUC_T$ , and  $AUC_I$  values were approximately 33%, 17%, and 18% lower, respectively, for subjects receiving bilastine following consumption of a high-fat, high calorie meal compared to bilastine administered under fasted conditions. Plasma bilastine  $C_{max}$ ,  $AUC_T$ , and  $AUC_I$  values were approximately 25%, 26%, and 25% lower, respectively, for subjects receiving bilastine following consumption of a low-fat, low calorie breakfast compared to bilastine administered under fasted conditions. The Phase 3 clinical trials were conducted under fasting conditions to ensure clinically appropriate exposure to bilastine.

### **10 mg orodispersible tablet**

Plasma bilastine  $C_{max}$ ,  $AUC_T$ , and  $AUC_I$  values were approximately 46%, 21%, and 21% lower,

respectively for subjects receiving bilastine following a moderate-fat, moderate calorie meal compared to bilastine administered under fasted conditions.

### **2.5 mg/mL oral solution**

Plasma bilastine  $C_{max}$ ,  $AUC_T$ , and  $AUC_I$  values for the bilastine oral solution were approximately 36%, 21% and 21% lower, respectively, for subjects receiving bilastine following a moderate-fat, moderate calorie meal compared to bilastine administered under fasted conditions.

### **Grapefruit Juice**

Concomitant administration of bilastine and grapefruit juice decreased bilastine bioavailability by approximately 30%. Concomitant administration of bilastine with other fruit juices may also decrease bioavailability. The degree of bioavailability decrease may vary between producers and types of fruit juice. 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.

## **9.6 Drug-Herb Interactions**

Interactions with herbal products have not been studied.

## **9.7 Drug-Laboratory Test Interactions**

Interactions with laboratory tests have not been observed.

# **10 CLINICAL PHARMACOLOGY**

## **10.1 Mechanism of Action**

Bilastine is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H<sub>1</sub> receptors. The antihistaminic activity of bilastine has been documented in a variety of animal and human models. It shows moderate to high affinity for histamine H<sub>1</sub>-receptors and no affinity for muscarinic, serotonergic, dopaminergic and noradrenergic receptors. Bilastine has been demonstrated to have limited distribution to the brain following oral administration.

## **10.2 Pharmacodynamics**

### **Nonclinical Pharmacology**

#### **Pharmacodynamics**

Bilastine has shown selective antagonism of H<sub>1</sub> receptor mediated effects *in vitro*, in isolated organs, and *in vivo* in nonclinical pharmacology studies. *In vitro*, bilastine displaced the H<sub>1</sub> receptor antagonist pyrilamine from the human recombinantly expressed H<sub>1</sub> receptor with a  $K_i$  of 64 nM (30 ng/mL). Bilastine did not modify H<sub>2</sub> and H<sub>3</sub> mediated effects in isolated animal organs at 100  $\mu$ M and 30  $\mu$ M, respectively, and did not bind to human recombinant H<sub>4</sub> receptors at 10  $\mu$ M. In *in vivo* animal models of anaphylaxis, single dose oral administration of bilastine dose-dependently reduced the allergen-induced increase in capillary permeability with ED<sub>50</sub> values of approximately 6 mg/kg. Bilastine showed no efficacy in mouse models of type III and IV hypersensitivity reactions.

#### **Safety Pharmacology**

Nonclinical safety pharmacology studies conducted with bilastine investigated the main organ systems, cardiovascular, pulmonary, and central nervous system, but also effects on the gastrointestinal system. In two separate studies, bilastine caused a concentration-dependent suppression of hERG tail currents in stably transfected HEK 293 cells with IC<sub>50</sub> values of 6.5 μM and 17.17 μM, respectively, based on nominal concentrations. In the isolated guinea pig heart atrium, bilastine at a concentration of 100 μM did not affect heart beat strength or frequency. In conscious telemetered dogs, bilastine given once orally at dose levels of 10, 30, or 100 mg/kg caused dose-dependent QTc prolongation at 30 and 100 mg/kg and reductions in systolic and diastolic blood pressure at the high dose only. Decreased heart rate and PR interval prolongation were also observed at 30 and 100 mg/kg. In a second study in dogs, no effect on these parameters was seen at the same dose levels. After a single oral dose, bilastine had minimal/ no effects on the central nervous system. An oral dose of 1,000 mg/kg transiently increased alertness in rats and 800 mg/kg caused a moderate decrease of motor activity in mice. Bilastine did not affect respiratory parameters at oral doses up to 1,000 mg/kg in rats. Bilastine had no effect on gastric secretion after 100 mg/kg administered intraduodenally in the rat or on intestinal motility in the mouse after oral doses up to 300 mg/kg.

### **Clinical Pharmacology**

Studies in adult healthy subjects showed that 20 mg bilastine inhibited the skin wheal and flare reactions induced with a histamine prick test for 24 hours, as well as the wheal and flare reactions in cold induced urticaria.

In an environmental chamber study, the onset of action of bilastine was demonstrated to be 1 hour after treatment administration and the effect lasted for 26 hours.

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 once daily did not affect psychomotor performance in clinical trials and did not affect driving performance in a standard driving test.

**Cardiac Electrophysiology:** A randomized, double-blind, placebo- and positive-controlled, 5-way crossover study of the electrocardiographic effects of bilastine was performed in 30 healthy adult subjects. Bilastine was tested at a therapeutic dose of 20 mg/day and a supratherapeutic dose of 100 mg/day, each administered for four days.

The bilastine 20 mg/day and 100 mg/day treatments were associated with a concentration-related prolongation of the QTcF (QTcF=QT/RR<sup>1/3</sup>) interval. On day 4 of treatment with the therapeutic 20 mg/day dose, statistically significant positive mean differences from placebo were observed at 1 and 3 h post-dosing, with a maximum mean difference from placebo of 4.0 ms (90% CI 1.20, 6.73) at 1 h.

On day 4 of treatment with the supratherapeutic bilastine 100 mg/day dose, statistically significant QTcF prolongation was observed at 5 consecutive time points from 0.5 to 3 h post-dose, with a maximum mean difference from placebo of 6.0 ms (90% CI 2.59, 9.48) at 2 h (see [CONTRAINDICATIONS](#), [WARNINGS AND PRECAUTIONS](#), [ADVERSE REACTIONS](#), [DRUG INTERACTIONS](#), [OVERDOSAGE](#)).

Bilastine administered at doses of 20 mg/day and 100 mg/day for four days was not observed to affect the QRS duration, the PR interval, or heart rate.



## 10.3 Pharmacokinetics

### Pre-Clinical Pharmacokinetics

Bilastine is orally bioavailable in mice, rats, rabbits, and dogs. There is large interanimal variability in the plasma concentrations with some studies reporting multiple peaks after oral administration. In rats, exposure after gavage dosing appeared higher in females than in males. Distribution studies with <sup>14</sup>C labelled bilastine in rat indicate limited peripheral distribution, in which concentrations of radioactivity were highest in the liver and kidney. In pigmented rats, detectable levels persisted in the eye and uveal tract for up to 14 days, indicating binding to melanin. In pregnant rats, there was low-level passage of radioactivity across the placental barrier into the tissues of the fetus. The mechanisms have not been elucidated, but pretreatment of rats with a potent P-gp inhibitor significantly increased exposure. Bilastine plasma protein binding was moderate with limited distribution into red cells. Bilastine is minimally metabolized *in vitro* and *in vivo* in animals. After oral dosing, bilastine was rapidly excreted in rats and dogs, with 7-12% and 4-6% of the dose was recovered in urine of rats and dogs, respectively, and the balance recovered in feces. In bile duct cannulated rats, 17% of the administered dose was excreted in the bile.

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.

### Clinical Pharmacokinetics

Bilastine pharmacokinetics were studied following a single oral dose of 20 mg to healthy volunteers. The results are presented in Table 4 below.

**Table 4 Bilastine pharmacokinetic parameters after a single oral dose of 20 mg (n=12)**

Parameter	Mean ± standard deviation
AUC <sub>(0-t)</sub> (ng*h/ml)	993.99 ± 279.93
AUC <sub>0-∞</sub> (ng*h/ml)	997.40 ± 279.81
% AUC <sub>0-∞</sub> extrapolation	0.37 ± 0.26
C <sub>max</sub> (ng/mL)	219.67 ± 62.06
t <sub>max</sub> (h) <sup>#</sup>	1.13 ± (0.75-3)
t <sub>1/2</sub> (h)	5.47 ± 2.13
Ae (mg)	8.39 ± 4.70
Cl <sub>r</sub> (l/h)	9.20 ± 7.35

<sup>#</sup>: median and range

The pharmacokinetic data obtained in 310 healthy volunteers enrolled in several Phase 1 studies were combined in a population pharmacokinetic two compartment model. t<sub>1/2β</sub> was 14.53 hrs, AUC was 1104.97 ng.h/mL and C<sub>max</sub> was 220.08 ng/mL, with a t<sub>max</sub> of 1.29 h.

**Absorption:** Bilastine is rapidly absorbed after oral administration with a time to maximum plasma concentration of around 1.13 hours. No accumulation was observed in subjects treated with bilastine from 20 to 100 mg daily after 14 days. The absolute bioavailability of bilastine is 61%.

Administration of bilastine following consumption of a meal with a fat and calorie content ranging from low-fat, low calorie to high-fat, high calorie results in a significant decrease in  $C_{max}$ ,  $AUC_T$  and  $AUC_I$  [see [DRUG INTERACTION, Drug-Food Interactions](#)].

**Distribution:** *In vitro* and *in vivo* studies have shown that bilastine is a substrate of P-gp (see [DRUG INTERACTIONS / Drug-Drug Interactions](#)) and OATP (see [DRUG INTERACTIONS / Drug-Food Interactions](#)). 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: MRP2, BCRP, BSEP, OATP1B3, OATP2B1, OAT1, OAT3, OCT2 and NTCP. Mild inhibition was detected for P-gp, OATP2B1 and OCT1, with an estimated  $IC_{50} \geq 300 \mu M$ , much higher than the calculated clinical plasma  $C_{max}$ . 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 is not significantly metabolized in humans (see Excretion). Bilastine does not induce or inhibit activity of CYP450 isoenzymes in *in vitro* and *in vivo* studies. Studies examining hepatic tissues (microsomes and hepatocytes) of human origin using different doses of bilastine demonstrated that there was little to no interaction with CYP isoenzymes.

**Elimination:** In a mass balance study performed in healthy volunteers, after administration of a single dose of 20 mg <sup>14</sup>C-bilastine, almost 95% of the administered dose was recovered in urine (28.3%) and faeces (66.5%) as unchanged bilastine. The mean elimination half-life calculated in healthy volunteers in the population pharmacokinetic model was 14.5 h.

**Linearity:** Bilastine presents linear pharmacokinetics in the dose range studied (5 to 220 mg), with a low inter-individual variability.

### Special Populations and Conditions

**Pediatrics:** Bilastine should not be administered to children below 4 years of age and under 16 kg due to limited data in this population. The mean AUC for children 4-11 years of age is 1084 ng\*h/mL from bilastine 10 mg after once daily oral administration.

**Geriatrics:** The safety and efficacy of bilastine have been demonstrated in a limited number of subjects > 65 years of age (n=34) enrolled in controlled clinical studies. A further open label study provided safety data for 150 patients treated for urticaria and/or allergic rhinitis. The pharmacokinetic parameters of bilastine are comparable in healthy subjects > 65 years of age and younger subjects, and no dosage adjustments are considered necessary in this patient population.

**Sex:** No statistically significant gender-related differences have been observed with regard to the pharmacokinetic parameters of bilastine.

**Hepatic Insufficiency:** There are no pharmacokinetic data in subjects with hepatic impairment. Bilastine is not significantly metabolized in humans, with the vast majority of the administered dose excreted unchanged. Since the results of the renal impairment study indicate renal elimination to be a major contributor in the elimination of bilastine, biliary excretion is expected to be only marginally involved. Changes in liver function are not expected to have a clinically relevant influence on bilastine pharmacokinetics.

**Renal Insufficiency:** A study of bilastine was performed in 24 male and female adults: 6 healthy controls and 6 each with mild, moderate, and severe renal impairment. The mean plasma bilastine concentrations in subjects with renal impairment generally exceeded those in the control group during the first 12 hours after dose administration. The subjects with renal impairment had higher mean bilastine AUC and  $C_{max}$  values than the healthy subjects. The mean  $AUC_{0-\infty}$  ranged from 737.4 to 1708.5 ng·hr/mL in healthy subjects and severely impaired subjects, respectively. The mean  $C_{max}$  ranged from 144.0 to 271.1 ng/mL in healthy subjects and moderately impaired subjects, respectively. There did not appear to be any substantial differences in median  $T_{max}$  or in the mean elimination rate constants for bilastine. Renal clearance was highest in healthy subjects, 8.7 L/hr and lowest in subjects with severe renal impairment, 4.0 L/hr. Urinary excretion of bilastine was essentially complete by the end of the 48 to 72 hour collection interval for all subjects, and the urinary excretion plots show essentially parallel excretion rate curves across groups.

## **11 STORAGE, STABILITY AND DISPOSAL**

Recommended storage conditions: Store between 15°C – 30°C.

## **12 SPECIAL HANDLING INSTRUCTIONS**

Keep out of reach and sight of children.

## PART II: SCIENTIFIC INFORMATION

### 13 PHARMACEUTICAL INFORMATION

#### Drug Substance

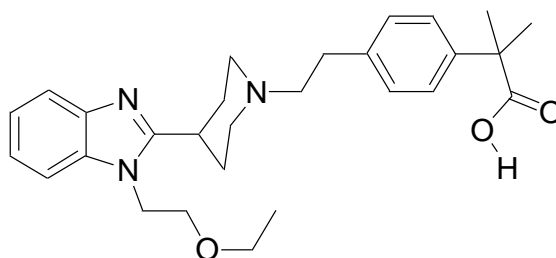
Proper name: bilastine

Chemical name: 2-[4-(2-(4-(1-(2-ethoxyethyl)-1H-benzimidazol-2-yl)piperidin-1-yl)ethyl)phenyl]-2-methylpropionic acid

or

p-[2-[4-[1-(2-ethoxyethyl)-2-benzimidazolyl]piperidino]ethyl]- $\alpha$ -methylhydratropic acid

Molecular formula and molecular mass:  $C_{28}H_{37}N_3O_3$  463.61 g/mol



Structural formula:

Physicochemical properties:

Physical Form: White, crystalline powder

Solubility:

Practically insoluble	acetonitrile
Very slightly soluble	water, buffer pH=6, buffer pH=4.5, buffer pH=8, acetone and isopropyl alcohol, glycerin
Slightly soluble	NaOH 0.01N, ethanol, methanol and dimethylsulfoxide (DMSO), 1,2-propylene glycol
Sparingly soluble	dimethylformamide (DMF), 0.1N hydrochloric acid (HCl) and buffer pH=3.5
Freely soluble	chloroform, HCl 1N and NaOH 1N

pKa Value:  $4.15 \pm 0.06$ , when determined by ultraviolet spectrophotometry and  $4.18$  by HPLC.

Hygroscopicity: Bilastine is not hygroscopic tested under ambient temperature ( $25.1 \pm 0.1$  °C) and relative humidity (85 % RH) conditions.

## 14 CLINICAL TRIALS

### 14.1 Trial Design and Study Demographics

#### Efficacy in Seasonal Allergic Rhinitis

##### Study demographics and trial design

The clinical efficacy of bilastine 20 mg tablets in the treatment of seasonal allergic rhinitis (SAR) was examined in three double-blind, randomized, placebo- and active-controlled parallel group clinical trials (BILA 1003/RAE, BILA 1704/RAE, and BILA 0802/RAE). A total of 2359 patients were randomized to treatment with bilastine, placebo or active comparator (desloratadine 5 mg and cetirizine 10 mg).

**Table 5 Summary of patient demographics for clinical trials in seasonal allergic rhinitis**

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
BILA 1003/RAE (Bachert et al, 2009)	Double-blind, randomized, placebo- and active-controlled parallel group	Bilastine 20 mg Desloratadine 5 mg Placebo  Oral, once daily for 14 days	233 242 245  ITT Total: 720	30  (12-70)	121/112 126/116 118/127
BILA 1704/RAE (Kuna et al, 2009)	Double-blind, randomized, placebo- and active-controlled parallel group	Bilastine 20 mg Cetirizine 10 mg Placebo  Oral, once daily, for 14 days	226 227 225  ITT Total: 678	31  (12-69)	108/118 107/120 108/117
BILA 0802/RAE	Double-blind, randomized, placebo- and active-controlled parallel group	Bilastine 20 mg Bilastine 40 mg Cetirizine 10 mg Placebo  Oral, once daily, for 14 days	240 239 240 242  ITT Total: 961	35.1  (12-70)	101/139 85/154 86/154 83/159

In the pivotal Phase 3 SAR studies the primary efficacy variable was the change in the area under the curve (AUC) of the total symptom score (TSS) from baseline to the end of the study (Day 14).

TSS was comprised of the reflective total nasal symptom score (rTNSS) and the reflective total non-nasal symptom score (rTNNSS).

rTNSS was based on the twice daily, AM and PM, reflective assessment of four nasal symptoms: rhinorrhea, nasal congestion, nasal itching, and sneezing, using a four point (0 [none] to 3 [severe]) scoring scale.

rTNNSS included four non-nasal symptoms: ocular itching, tearing, ocular redness, itching of ears and/or palate (the latter being scored only in study BILA 1003/RAE), and was assessed in a similar manner.

In one study, patients also recorded these symptoms in an instantaneous manner.

Change from baseline in rTNSS, rTNNSS, TSS, and Quality of Life (QofL) were assessed as secondary variables.

In two of the trials (BILA 1003/RAE & BILA 1704/RAE), bilastine demonstrated superior efficacy to placebo. In the third trial, BILA 0802/RAE, neither bilastine nor the active control, cetirizine, could be distinguished from placebo. Therefore, the results from this study are not presented here.

## 14.2 Study Results

### BILA 1003/RAE

The primary efficacy end-point, change in AUC of TSS from baseline to the end of the study in bilastine-treated patients was statistically significantly different from placebo (Table 6). At the same time, it did not differ from the active comparator (results not shown).

**Table 6 SAR Study BILA 1003/RAE - Total Symptom Score - Area under the Curve (ITT Population)**

	<b>Placebo N=245</b>	<b>Bilastine N=233</b>	<b>P value<sup>1</sup></b>
<b>Mean (SD)</b>	118.4 (62.7)	98.4 (58.1)	<0.001
<b>95% CI</b>	110.5, 126.3	90.9, 105.9	

<sup>1</sup> Tukey test

The individual component symptom scores that comprise the total symptom complex were also different for bilastine treated patients compared to placebo (Table 7).

**Table 7 SAR Study BILA 1003/RAE - Summary of Key Secondary Results (ITT Population)**

Variable – Mean (SD) Change from Baseline to Day 14	Placebo N=245	Bilastine N=233	Difference from Placebo	
			Estimate	95% CI
<b>rTNSS</b>	-2.3 (2.3)	-2.9 (2.2)	0.67	0.27, 1.07
<b>rTNNSS</b>	-1.3 (2.3)	-2.0 (2.1)	0.70	0.30, 1.10
<b>TSS</b>	-3.5 (4.2)	-4.9 (3.9)	1.35	0.62, 2.08
<b>RQLQ Total Score</b>	-1.3 (1.3)	-1.6 (1.2)	0.3	0.07, 0.52

TSS – Total Symptom Score; rTNSS – reflective Nasal Symptoms Score; rTNNSS – reflective Non Nasal Symptom Score; RQLQ – Rhinoconjunctivitis Quality of Life Questionnaire

## **BILA 1704/RAE**

**Table 8 SAR Study BILA 1704/RAE - Total Symptom Score - Area under the Curve (ITT Population)**

	<b>Placebo N=225</b>	<b>Bilastine N=226</b>	<b>P value<sup>1</sup></b>
<b>Mean (SD)</b>	100.66 (51.71)	76.49 (47.85)	<0.001
<b>95% CI</b>	93.86, 107.45	70.21, 82.76	

<sup>1</sup> Tukey test

The individual component symptom scores that comprise the total symptom complex were also different for bilastine treated patients compared to placebo (Table 9).

**Table 9 SAR Study BILA 1704/RAE - Summary of Key Secondary Results (ITT Population)**

<b>Treatment Variable</b>	<b>Placebo N=225</b>	<b>Bilastine N=226</b>	<b>Difference from Placebo</b>	
			<b>Estimate</b>	<b>95% CI</b>
rTNSS (mean change from baseline)	-2.0 (2.5)	-3.1 (2.3)	1.15	0.70, 1.59
rTNNSS (mean change from baseline)	-0.9 (1.9)	-1.6 (1.9)	0.73	0.38, 1.08
TSS (mean change from baseline)	-2.9 (4.1)	-4.8 (3.8)	1.88	1.15, 2.61

TSS – Total Symptom Score; rTNSS – reflective Nasal Symptoms Score; rTNNSS – reflective Non Nasal Symptom Score;

Onset of action was evaluated in one environmental exposure unit study in allergic rhinitis patients with a single dose of bilastine. Bilastine was found to have an onset of action 1 hour after oral intake.

## **Efficacy in Chronic Spontaneous Urticaria**

### **Study demographics and trial design**

The efficacy of bilastine for the treatment of chronic spontaneous urticaria was evaluated in two multi-center, randomized, placebo-controlled, double-blind clinical trials of 4 weeks duration in adult patients 18 to 76 years of age with chronic spontaneous urticaria. The two trials included one 4-week dose-ranging trial (BILA 0601/UCI) and one 4-week single dose level efficacy trial (BILA 2006/UCI). These trials included 742 patients (229 males and 513 females). Most patients (>90%) were Caucasian and the mean age was 41.5. A total of 339 patients received bilastine (of these patients, 230 received bilastine 20 mg once daily), and 237 received placebo.



**Table 10 Summary of patient demographics for clinical trials in chronic spontaneous urticaria**

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Gender M/F
BILA 0601/UCI	Double-blind, randomized, dose-ranging, placebo-controlled, parallel-group	Bilastine 10 mg Bilastine 20 mg Bilastine 30 mg Placebo Oral, once daily for 4 weeks	53 58 56 53  ITT Total = 219	43  (18-76)	15/33 13/25 9/28 8/21  PP Total* =152
BILA 2006/UCI (Zuberbier et al, 2010)	Double-blind, randomized, placebo- and levocetirizine-controlled parallel-group	Bilastine 20 mg **Levocetirizine 5 mg Placebo Oral, once daily for 4 weeks	172 163 181  ITT Total = 516	40  (18-75)	63/109 54/109 40/141

Efficacy was assessed based on the patients' diary card on reflective urticaria symptoms - itching intensity, wheals number and maximum size of wheals - each scored on a 0-3 interval scale. The primary efficacy variable was the change from baseline in the mean of the morning (AM) and evening (PM) Total Symptom Score (TSS), defined as the sum of the itching intensity score, the wheals number score, and the maximum size of the wheals score, over the 28 days of the treatment period.

### Study results

#### BILA 0601/UCI

**Table 11 CSU Study BILA 601/UCI – Total Symptom Score Change from Baseline at Day 28 (PP Population)**

	Placebo n=29	Bilastine n=38	P-value <sup>1</sup>
Mean (SD)	-1.9 (2.8)	-4.1 (2.9)	0.003
95% CI	-2.92, -0.88	-5.02, -3.18	

<sup>1</sup> T-test

The individual component symptom scores that comprise the total symptom complex were also different for bilastine treated patients compared to placebo (Table 12).

**Table 12 CSU Study BILA 0601/UCI - Summary of Secondary Results (PP Population)**

Variable – Mean (SD) Change from Baseline to Day 28	Placebo N=29	Bilastine 20 mg N=38	Difference from Placebo	
			Estimate	95% CI
IIS	-0.8 (1.1)	-1.5 (1.1)	0.7	0.17, 1.23
WNS	-0.6 (1.1)	-1.3 (1.1)	0.7	0.17, 1.23
MSWS	-0.6 (1.1)	-1.2 (1.2)	0.6	0.04, 1.15
Investigator’s CGI (median(range))	9 (1-15)	3.5 (1-15)	---	----

IIS: Itching Intensity Score, WNS: Wheal Number Score, MSWS: Maximum Size of Wheal Score, CGI: Clinical Global Impression

**BILA 2006/UCI**

**Table 13 CSU Study BILA 2006/UCI - Change from Baseline in the AM/PM TSS over the 28 Days of Treatment Period (ITT Population)**

	Placebo n=181	Bilastine n=172	P-value <sup>1</sup>
Mean (SD)	-2.99 (2.16)	-4.23 (2.1)	<0.001
95% CI	-3.67, -2.31	-4.89, -3.57	

<sup>1</sup> Tukey test

**Table 14 CSU Study BILA 2006/UCI - Summary of Secondary Results (ITT Population)**

Variable – Mean (SD) Change from Baseline to Day 28	Placebo N=181	Bilastine 20 mg N=172	Difference from Placebo	
			Estimate	95% CI
IIS	-1.01 (0.78)	-1.48 (0.73)	0.47	0.31, 0.63
WNS	-1.00 (0.74)	-1.37 (0.73)	0.37	0.22, 0.52
MSWS	-0.97 (0.80)	-1.37 (0.83)	0.40	0.23, 0.57
Investigator’s CGI (median(range))	6 (1-13)	5 (1-9)	---	----

IIS: Itching Intensity Score, WNS: Wheal Number Score, MSWS: Maximum Size of Wheal Score, CGI: Clinical Global Impression

**Efficacy in Children**

The efficacy of bilastine has been studied in adults and adolescents. According to guidelines, the proven efficacy in adults and adolescents for seasonal allergic rhinitis can be extrapolated to children, having demonstrated that the systemic exposure with 10 mg bilastine in children

from 4 to 11 years is equivalent to the exposure in adults with 20 mg bilastine. The proven efficacy in adults for chronic spontaneous urticaria can be extrapolated to adolescents, having demonstrated that the systemic exposure with 20 mg bilastine in adolescents from 12 to 17 years is equivalent to the exposure in adults with 20 mg bilastine. The extrapolation from adult and adolescent data is deemed appropriate for this product as the pathophysiology of allergic rhinitis and urticaria is the same for all age groups.

### 14.3 Comparative Bioavailability Studies

A single center, randomized, open-label, four-treatment, four-period, four sequence, single dose crossover study was conducted in 23 healthy adult male and female subjects under fasting conditions to compare the bioavailabilities of a 10 mg dose (4 mL) of bilastine oral solution, a 10 mg dose of bilastine orodispersible tablet administered with and without water and a 10 mg dose of a developmental formulation of the 10 mg orodispersible tablet administered with water. A summary of the bioavailability data comparing bilastine oral solution and the bilastine orodispersible tablets is presented in the following tables.

**Table 115 Summary of comparative bioavailability study**

Study #	Trial design	Trial Objectives	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Gender M/F
BILA 3414/BE	Open label, randomized, crossover, single-dose study with four treatments, four periods and four sequences	To assess the relative bioavailability (BA) of several bilastine formulations after oral administration in tablet form (ODT1) and in oral solution form (SOL) vs. the control formulation of the same drug in orodispersible tablets (ODT2) in healthy volunteers. The secondary objective is to assess the relative BA of the ODT administered with and without accompanying liquid, as well as tolerance to the drug.	Bilastine 10 mg orodispersible tablet (ODT1), Bilastine 10 mg orodispersible tablet (ODT2) Bilastine 2.5 mg/mL oral solution Oral, single dose	23 healthy subjects	21.6 (18-30)	11/12

**Table 16 Summary Table of the Comparative Bioavailability Data**

Bilastine 10 mg (4 mL x 2.5 mg/mL oral solution or 1 x 10 mg orodispersible tablet) From measured data Geometric Mean Arithmetic Mean (CV%)				
Parameter	Oral solution <sup>1</sup>	Orodispersible tablet <sup>2</sup>	Ratio of Geometric Means (%)	Confidence Interval (90%)
AUC <sub>T</sub> (ng*h/mL)	515.18 542.22 (33.28%)	527.95 552.94 (31.28%)	97.76	89.52 – 106.77
AUC <sub>I</sub> (ng*h/mL)	517.68 544.61 (33.15%)	531.78 556.57 (30.98%)	97.51	89.37– 106.39
C <sub>max</sub> (ng/mL)	107.39 117.94 (42.7%)	108.92 120.13 (46.60%)	98.76	85.23 – 114.45
T <sub>max</sub> <sup>3</sup> (h)	1.25 (0.75 – 4.00)	1.25 (0.50 – 2.50)		
T <sub>½</sub> <sup>4</sup> (h)	4.12 (41.8%)	4.88 (91.73%)		

<sup>1</sup>Bilastine oral solution, 2.5 mg/ml.

<sup>2</sup>Bilastine orodispersible tablets, 10 mg administered with water (Reference).

<sup>3</sup>Expressed as median (range) only.

<sup>4</sup>Expressed as the arithmetic mean (CV%) only.

**Table 17 Summary Table of the Comparative Bioavailability Data**

Bilastine 10 mg (1 x 10 mg orodispersible tablet administered with or without water) From measured data Geometric Mean Arithmetic Mean (CV%)				
Parameter	Orodispersible tablet <sup>1</sup>	Orodispersible tablet <sup>2</sup>	Ratio of Geometric Means (%)	Confidence Interval (90%)
AUC <sub>T</sub> (ng*h/mL)	525.26 559.87 (38.47%)	527.95 552.94 (31.28%)	99.99	92.51 – 108.08
AUC <sub>I</sub> (ng*h/mL)	527.80 562.36 (38.36%)	531.78 556.57 (30.98%)	99.72	92.31 – 107.72
C <sub>max</sub> (ng/mL)	115.69 129.46 (46.52%)	108.92 120.13 (46.60%)	106.77	93.04 – 122.53
T <sub>max</sub> <sup>3</sup> (h)	1.50 (0.75 – 3.00)	1.25 (0.50 – 2.50)		
T <sub>½</sub> <sup>4</sup> (h)	4.50 (64%)	4.88 (91.73%)		

<sup>1</sup>Bilastine orodispersible tablets, 10 mg administered without water.

<sup>2</sup>Bilastine orodispersible tablets, 10 mg administered with water (Reference).

<sup>3</sup>Expressed as median (range) only.

<sup>4</sup>Expressed as the arithmetic mean (CV%) only.

## 15 NON-CLINICAL TOXICOLOGY

### Single-Dose Toxicity

Bilastine has a low order of acute oral toxicity and there were no clinical signs or deaths after a single oral dose of 2000 mg/kg in rats and 5000 mg/kg in mice. After single i.v. dose

administration, bilastine was lethal at  $\geq 60$  mg/kg in rats and at  $\geq 30$  mg/kg in mice. In both rats and mice, death occurred within 5 minutes of dosing and was preceded by signs such as tonic-clonic convulsions, prostration, and/or dyspnea. The lowest non-lethal dose was 45 mg/kg in rats and 20 mg/kg in mice. Plasma bilastine concentrations were determined after i.v. dosing in the rat; at 50 mg/kg, concentrations at the earliest sampling point (10 min after i.v. dosing) were  $>190$  times the clinical  $C_{max}$  at maximum recommended human dose (MRHD).

### **Repeat-Dose Toxicity**

Repeat oral dose toxicity studies were performed in mice, rats, and dogs for up to 13, 26 and 52 weeks, respectively. Toxicity of bilastine administered i.v. daily for 4 weeks was evaluated in rats and dogs.

Oral bilastine administration of up to 2000 mg/kg/day in mice and rats and 800 mg/kg/day in dogs resulted in no signs in mice and transient clinical signs in rats and dogs (salivation in rats; vomiting, salivation, soft feces/diarrhea, and decreased activity in the dog). QTc was slightly increased in dogs at the end of 52 weeks of oral dosing at 800 mg/kg/day. Clinical pathology changes in rats and dogs were generally mild, occurred at high doses, and were reversible after 2 to 8 weeks without dosing. Liver and thyroid changes were noted in mice and rats and were considered adaptive responses. In the dog, at 800 mg/kg after dosing for 52 weeks, there was an increase in epididymal spermatozoa with abnormal morphology and one male had reduced spermatozoa motility. There were no histopathological changes in testes and prostate in the 52 week dog study.

After daily i.v. dosing for 4 weeks at doses up to 50 mg/kg/day in the rat, there were no clinical signs noted, but 4 out of 58 rats given 50 mg/kg/day were found dead. In the kidney at 50 mg/kg/day, there was minimal to slight proximal tubule hypertrophy in the cortico-medullary region of the kidney. All dogs survived 60 mg/kg/day i.v. for 4 weeks, there were dose related increased incidences of tremor and lip smacking post dose at all doses ( $\geq 30$  mg/kg/day), and vomiting was seen during and after administration of 40 and 60 mg/kg/day. Increased severity of venous thrombosis at and around the injection sites was noted at 60 mg/kg/day. After i.v. dosing in the dog, there were no effects on cardiovascular parameters or changes in epididymal spermatozoa morphology and motility.

No Adverse Effect Levels (NOAELs) were determined for all findings in repeat oral and i.v. dose studies. The margin to clinical  $C_{max}$  and AUC at the MRHD is at least 10 times and for most findings several hundred times.

### **Genotoxicity**

Bilastine was not mutagenic in bacterial mutation assays at concentrations up to 2000  $\mu\text{g}/\text{plate}$  or clastogenic in a human lymphocyte chromosome aberration assay at concentrations up to 500  $\mu\text{g}/\text{mL}$ . In the *in vivo* mouse micronucleus test, single oral bilastine doses of 2000 mg/kg did not induce clastogenicity.

### **Carcinogenicity**

In carcinogenicity studies in mice and rats, there were no bilastine related increases in tumor incidence at dose levels up to 2,000 mg/kg/day in mice and 1,200 mg/kg/day in rats administered in the diet for up to 104 weeks at which AUCs were  $>100$  times higher than at the MRHD. In the rat carcinogenicity study, urolithiasis was noted in females at 1200 mg/kg/day. At the NOAEL of 700 mg/kg/day for this finding, AUCs were  $>200$  times that of clinical values at MRHD.

## **Reproductive Toxicity**

In rats, daily oral administration of bilastine prior to and during mating and early pregnancy had no effect on female and male fertility, epididymal sperm count, motility and morphology and early embryonic development at doses up to 1000 mg/kg/day. Bilastine administered daily by oral gavage to pregnant rats and rabbits during the period of major organogenesis did not result in maternal or embryofetal toxicity in the rat at doses up to 1000 mg/kg/day. At a maternally toxic dose in rabbits (400 mg/kg/day), findings consistent with delayed skeletal ossification in the fetuses were probably related to reduced food consumption by the does, with 110 mg/kg/day identified as a NOAEL. In a peri- and post-natal development study, bilastine was administered orally to pregnant rats (F0 generation) at 75, 275, and 1000 mg/kg/day from gestation day 6 to lactation day 21. There were no clinical signs in the treated females and no effects on mating or pregnancy duration and index, and all the females delivered, nursed, and cared for their offspring normally. At the high dose, there was a slight reduction in body weight and body weight gain during lactation and one female had 100% postimplantation loss. There were no effects of bilastine treatment of the dams on pup development, sensory function, and motor development (F1 generation). The treatment of the dams had no effects on the offspring's reproductive capacity or their offspring (F2 generation). The NOAEL for the F0 generation was 275 mg/kg/day and the NOAEL for the offspring was 1000 mg/kg/day. The NOAELs for all reproductive endpoints in rats and rabbits were associated with AUCs >50 times higher than the clinical exposure at the MRHD.

## **17 SUPPORTING PRODUCT MONOGRAPHS**

1. BLEXTEN® (bilastine orodispersible tablets 10 mg, tablets 20 mg, and oral solution 2.5 mg/mL), submission control 241318, Product Monograph, Aralez Pharmaceuticals Canada Inc. (AUG 10, 2021)

## PATIENT MEDICATION INFORMATION

### READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

#### <sup>Pr</sup>**APO-BILASTINE TABLETS** **Bilastine tablets**

Read this carefully before you start taking **APO-BILASTINE TABLETS** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APO-BILASTINE TABLETS**.

#### **What is APO-BILASTINE TABLETS used for?**

APO-BILASTINE TABLETS (tablets) are used to relieve the symptoms of:

- **Seasonal Allergic Rhinitis:** Hayfever (sneezing, itchy, runny, blocked-up nose, red and watery eyes) in patients 12 years of age and older.
- **Chronic Spontaneous Urticaria:** Hives and itching in patients 12 years of age and older.

#### **How does APO-BILASTINE TABLETS work?**

APO-BILASTINE TABLETS is an antihistamine - it blocks the action of histamine and relieves hayfever symptoms, itchiness and hives.

#### **What are the ingredients in APO-BILASTINE TABLETS?**

Medicinal ingredient: bilastine

Non-medicinal ingredients: colloidal anhydrous silica, magnesium stearate, microcrystalline cellulose, sodium starch glycolate

#### **APO-BILASTINE TABLETS comes in the following dosage forms:**

Tablets: 20 mg

Bilastine is also available as a 10 mg orodispersible tablet and a 2.5 mg/mL oral solution for use in children 4 to 11 years of age, weighing at least 16 kg.

#### **Do not use APO-BILASTINE TABLETS if:**

- You are allergic (hypersensitive) to bilastine or any of the other ingredients of APO-BILASTINE TABLETS.
- You have a history of irregular heartbeat.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-BILASTINE TABLETS. Talk about any health conditions or problems you may have, including if you:**

- have kidney problems.
- have heart problems or a family history of heart problems.
- are pregnant or planning to become pregnant.
- are breastfeeding.

#### **Other warnings you should know about:**

**Driving and using machines**

While taking APO-BILASTINE TABLETS you may experience a feeling of tiredness, which can affect your ability to drive or use machines. If you experience tiredness, do not drive or operate machinery.

APO-BILASTINE TABLETS (20 mg) are not suitable for use by children under 12 years of age.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with APO-BILASTINE TABLETS:**

- ketoconazole (used to treat fungal infections)
- erythromycin and rifampicin (used to treat bacterial infections)
- diltiazem (used to treat heart problems)
- cyclosporine (used to suppress the immune system)
- ritonavir (used to treat HIV/AIDS)
- grapefruit and other fruit juices

**How to take APO-BILASTINE TABLETS:**

- Swallow the tablet with water.
- Take APO-BILASTINE TABLETS on an empty stomach, one hour before eating or drinking or two hours after. Food and fruit juice will lower the amount of medicine available to treat your symptoms.
- Do not take more APO-BILASTINE TABLETS than your healthcare professional has told you to. If your symptoms do not improve, consult your healthcare professional.

**Usual dose:**

**Seasonal Allergic Rhinitis**

Patients 12 years of age and older: 1 tablet (20 mg) once daily.

**Chronic Spontaneous Urticaria**

Patients 12 years and older: 1 tablet (20 mg) once daily.

**Overdose:**

If you think you, or a person you are caring for, have taken too much APO-BILASTINE TABLETS, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.
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**Missed Dose:**

If you forget to take your dose on time, take it as soon as possible, and then go back to your regular dosing schedule. Do not take a double dose to make up for a forgotten dose.

**What are possible side effects from using APO-BILASTINE TABLETS?**

These are not all the possible side effects you may have when taking APO-BILASTINE TABLETS. If you experience any side effects not listed here, tell your healthcare professional.

- headache
- sleepiness
- dizziness



- stomach pain

APO-BILASTINE TABLETS can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

<b>Serious side effects and what to do about them</b>			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>RARE</b> <b>Heart problems:</b> heart racing or slowing, cold sweats, feeling faint, feeling your heart beat, light headed, nausea, shortness of breath			√
<b>UNKNOWN</b> <b>Allergic reactions:</b> difficulty in breathing, swelling of your face, lips, tongue or throat, and/or swelling and redness of the skin			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

<p><b>Reporting Side Effects</b></p> <p>You can report any suspected side effects associated with the use of health products to Health Canada by:</p> <ul style="list-style-type: none"> <li>• Visiting the Web page on Adverse Reaction Reporting (<a href="https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html">https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html</a>) for information on how to report online, by mail or by fax; or</li> <li>• Calling toll-free at 1-866-234-2345.</li> </ul> <p><i>NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.</i></p>
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**Storage:**

Store between 15°C - 30°C.

Do not use APO-BILASTINE TABLETS after the expiry date which is stated on the carton and the blisters after EXP. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

Keep out of reach and sight of children.

**If you want more information about APO-BILASTINE TABLETS:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website (<http://www.apotex.ca/products>), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario M9L 1T9.

Last Revised: XXXX

## PATIENT MEDICATION INFORMATION

### READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

#### <sup>Pr</sup>APO-BILASTINE ORODISPERSIBLE TABLETS

#### Bilastine orodispersible tablets

Read this carefully before your child starts taking **APO-BILASTINE ORODISPERSIBLE TABLETS** and each time you get a refill for your child's prescription. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your child's medical condition and treatment and ask if there is any new information about **APO-BILASTINE ORODISPERSIBLE TABLETS**.

#### **What is APO-BILASTINE ORODISPERSIBLE TABLETS used for?**

APO-BILASTINE ORODISPERSIBLE TABLETS (orodispersible tablets) are used to relieve the symptoms of:

- **Seasonal Allergic Rhinitis:** Hayfever (sneezing, itchy, runny, blocked-up nose, red and watery eyes) in patients 4 to 11 years old, weighing at least 16 kg.
- **Chronic Spontaneous Urticaria:** Hives and itching in patients 4 to 11 years old, weighing at least 16 kg.

#### **How does APO-BILASTINE ORODISPERSIBLE TABLETS work?**

APO-BILASTINE ORODISPERSIBLE TABLETS is an antihistamine - it blocks the action of histamine and relieves hayfever symptoms, itchiness and hives.

#### **What are the ingredients in APO-BILASTINE ORODISPERSIBLE TABLETS?**

Medicinal ingredient: bilastine

Non-medicinal ingredients: croscarmellose sodium, mannitol, red grape flavour, sodium stearyl fumarate, sucralose (E955)

#### **APO-BILASTINE ORODISPERSIBLE TABLETS comes in the following dosage forms:**

Orodispersible Tablets: 10 mg

#### **Do not use APO-BILASTINE ORODISPERSIBLE TABLETS if:**

- Your child is allergic (hypersensitive) to bilastine or any of the other ingredients of APO-BILASTINE ORODISPERSIBLE TABLETS.
- Your child has a history of irregular heartbeat.

**To help avoid side effects and ensure proper use, talk to your child's healthcare professional before your child starts taking APO-BILASTINE ORODISPERSIBLE TABLETS. Talk about any health conditions or problems your child may have, including if your child has:**

- kidney problems.
- heart problems or a family history of heart problems.

#### **Other warnings you should know about:**

##### **Doing tasks that require special attention:**

APO-BILASTINE ORODISPERSIBLE TABLETS is not likely to affect your child's ability to do tasks. However, when they first start treatment, see how APO-BILASTINE ORODISPERSIBLE

TABLETS affects their ability to do tasks such as riding a bicycle or using a machine.

APO-BILASTINE ORODISPERSIBLE TABLETS (orodispersible tablets) (10 mg) are not suitable for use by children under 4 years of age or weighing under 16 kg.

**Tell your child's healthcare professional about all the medicines your child is using or receiving, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with APO-BILASTINE ORODISPERSIBLE TABLETS:**

- ketoconazole (used to treat fungal infections)
- erythromycin and rifampicin (used to treat bacterial infections)
- diltiazem (used to treat heart problems)
- cyclosporine (used to suppress the immune system)
- ritonavir (used to treat HIV/AIDS)
- grapefruit and other fruit juices

**How to take APO-BILASTINE ORODISPERSIBLE TABLETS:**

- The orodispersible tablet is for oral use.
- Place the orodispersible tablet in the mouth of your child. It will disperse rapidly in saliva and can then be easily swallowed.
- The tablet should **not** be taken with food or any fruit juices. Give your child the tablet one hour before or two hours after your child takes food or fruit juice.
- Alternatively, you may disperse the orodispersible tablet in a teaspoon of water before giving it to your child. Make sure that none of the orodispersible tablet remains in the spoon.
- **Only use water for dispersion**, do not use grapefruit juice or any other fruit juices.
- Do not give your child more APO-BILASTINE ORODISPERSIBLE TABLETS than your child's healthcare professional has told you to give them. If your child's symptoms do not improve, talk to your child's healthcare professional.

**Usual dose:**

**Seasonal Allergic Rhinitis:**

**Patients 4-11 years of age, weighing at least 16 kg:** 1 orodispersible tablet (10 mg) once daily.

**Chronic Spontaneous Urticaria:**

**Patients 4-11 years of age, weighing at least 16 kg:** 1 orodispersible tablet (10 mg) once daily.

**Overdose:**

If you think your child has taken too much APO-BILASTINE ORODISPERSIBLE TABLETS, contact a healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.
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**Missed Dose:**

If you forget to give your child their dose on time, give your child the dose as soon as possible, and then go back to the regular dosing schedule. Do not give your child a double dose to make up for a forgotten dose.

**What are possible side effects from using APO-BILASTINE ORODISPERSIBLE TABLETS?**

These are not all the possible side effects your child may have when taking APO-BILASTINE ORODISPERSIBLE TABLETS. If your child experiences any side effects not listed here, tell your child’s healthcare professional.

- headache
- stomach pain
- eye irritation
- nasal irritation
- diarrhea
- nausea
- lip swelling
- fatigue
- eczema or hives

APO-BILASTINE ORODISPERSIBLE TABLETS can cause abnormal blood test results. Your child’s healthcare professional will decide when to perform blood tests and will interpret the results.

<b>Serious side effects and what to do about them</b>			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>UNCOMMON</b> <b>Syncope</b> (temporary loss of consciousness)			√
<b>RARE</b> <b>Heart problems:</b> heart racing or slowing, cold sweats, feeling faint, feeling your heartbeat, lightheaded, nausea, shortness of breath			√
<b>UNKNOWN</b> <b>Allergic reactions:</b> difficulty in breathing, swelling of your face, lips, tongue or throat, and/or swelling and redness of the skin			√

If your child has a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your child’s daily activities, tell your child’s healthcare professional.

## Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

### Storage:

Store between 15°C - 30°C.

Do not use APO-BILASTINE ORODISPERSIBLE TABLETS after the expiry date which is stated on the carton and the blisters after EXP. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

Keep out of reach and sight of children.

### If you want more information about APO-BILASTINE ORODISPERSIBLE TABLETS:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website (<http://www.apotex.ca/products>), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario M9L 1T9.

Last Revised: XXXX

## PATIENT MEDICATION INFORMATION

### READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

#### **Pr** **APO-BILASTINE ORAL SOLUTION** **Bilastine oral solution**

Read this carefully before your child starts taking **APO-BILASTINE ORAL SOLUTION** and each time you get a refill for your child's prescription. This leaflet is a summary and will not tell you everything about this drug. Talk to your child's healthcare professional about your child's medical condition and treatment and ask if there is any new information about **APO-BILASTINE ORAL SOLUTION**.

#### **What is APO-BILASTINE ORAL SOLUTION used for?**

APO-BILASTINE ORAL SOLUTION (oral solution) is used to relieve the symptoms of:

- **Seasonal Allergic Rhinitis:** Hayfever (sneezing, itchy, runny, blocked-up nose, red and watery eyes) in patients 4 to 11 years old, weighing at least 16 kg.
- **Chronic Spontaneous Urticaria:** Hives and itching in patients 4 to 11 years old, weighing at least 16 kg.

#### **How does APO-BILASTINE ORAL SOLUTION work?**

APO-BILASTINE ORAL SOLUTION is an antihistamine – it blocks the action of histamine and relieves hayfever symptoms, itchiness and hives.

#### **What are the ingredients in APO-BILASTINE ORAL SOLUTION?**

Medicinal ingredient: bilastine

Non-medicinal ingredients: betadex, hydrochloric acid 37% (for pH-adjustment), hydroxyethylcellulose, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), purified water, raspberry flavour, sodium hydroxide (for pH-adjustment), sucralose (E955)

#### **APO-BILASTINE ORAL SOLUTION comes in the following dosage forms:**

Oral solution: 2.5 mg bilastine in one milliliter of the oral solution

#### **Do not use APO-BILASTINE ORAL SOLUTION if:**

- Your child is allergic (hypersensitive) to bilastine or any of the other ingredients of APO-BILASTINE ORAL SOLUTION.
- Your child has a history of irregular heartbeat.

**To help avoid side effects and ensure proper use, talk to your child's healthcare professional before your child starts taking APO-BILASTINE ORAL SOLUTION. Talk about any health conditions or problems your child may have, including if your child has:**

- kidney problems.
- heart problems or a family history of heart problems.

#### **Other warnings you should know about:**

#### **Doing tasks that require special attention:**

APO-BILASTINE ORAL SOLUTION is not likely to affect your child's ability to do tasks. However, when they first start treatment, see how APO-BILASTINE ORAL SOLUTION affects their ability to do tasks such as riding a bicycle or using a machine.

APO-BILASTINE ORAL SOLUTION (oral solution 2.5 mg/mL) is not suitable for use by children under 4 years of age or weighing under 16 kg.

**Tell your healthcare professional about all the medicines your child is using or receiving, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with APO-BILASTINE ORAL SOLUTION:**

- ketoconazole (used to treat fungal infections)
- erythromycin and rifampicin (used to treat bacterial infections)
- diltiazem (used to treat heart problems)
- cyclosporine (used to suppress the immune system)
- ritonavir (used to treat HIV/AIDS)
- grapefruit and other fruit juices

**How to take APO-BILASTINE ORAL SOLUTION:**

- The oral solution is accompanied by a dosing cup with a mark of 4 mL, which will help you to pour the right amount of oral solution
- Fill the cup with 4 mL of oral solution and give the medicine to your child by mouth, directly from the cup
- Wash the cup after use
- APO-BILASTINE ORAL SOLUTION should **not** be taken with food or any fruit juices. Give your child the oral solution one hour before or two hours after your child takes any food or fruit juice.
- Your healthcare professional will determine how long to give your child APO-BILASTINE ORAL SOLUTION

**Usual dose:**

**Seasonal Allergic Rhinitis**

**Patients 4-11 years of age, weighing at least 16 kg:** 4 mL of oral solution (equal to 10 mg bilastine) once daily

**Chronic Spontaneous Urticaria**

**Patients 4-11 years of age, weighing at least 16 kg:** 4 mL of oral solution (equal to 10 mg bilastine) once daily

**Overdose:**

If you think your child has taken too much APO-BILASTINE ORAL SOLUTION, contact a healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.
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**Missed Dose:**

If you forget to give your child the daily dose on time, give your child the dose as soon as possible, and then go back to your child's regular dosing schedule. Do not give your child a double dose to make up for a forgotten dose.



**What are possible side effects from using APO-BILASTINE ORAL SOLUTION?**

These are not all the possible side effects your child may have when taking APO-BILASTINE ORAL SOLUTION. If your child experiences any side effects not listed here, tell your child’s healthcare professional.

- headache
- stomach pain
- eye irritation
- nasal irritation
- diarrhea
- nausea
- lip swelling
- fatigue
- eczema or hives

APO-BILASTINE ORAL SOLUTION can cause abnormal blood test results. Your child’s healthcare professional will decide when to perform blood tests and will interpret the results.

<b>Serious side effects and what to do about them</b>			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>UNCOMMON</b> <b>Syncope</b> (temporary loss of consciousness)			√
<b>RARE</b> <b>Heart problems:</b> heart racing or slowing, cold sweats, feeling faint, feeling your heartbeat, lightheaded, nausea, shortness of breath			√
<b>UNKNOWN</b> <b>Allergic reactions:</b> difficulty in breathing, swelling of your face, lips, tongue or throat, and/or swelling and redness of the skin			√

If your child has a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your child’s daily activities, tell your child’s healthcare professional.

## Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

### Storage:

Store between 15°C - 30°C.

Do not use APO-BILASTINE ORAL SOLUTION after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

Keep out of reach and sight of children.

### If you want more information about APO-BILASTINE ORAL SOLUTION:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website (<http://www.apotex.com/products>), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario M9L 1T9.

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