▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – ALLERTINE®, ALLERTINE® MELTLETS, ALLERTINE® KIDS MELTLETS, ALLERTINE® KIDS ORAL LIQUID (bilastine)

1 NAME OF THE MEDICINE

Bilastine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets: Each tablet contains 20 mg of bilastine.

Orally disintegrating tablets: Each orally disintegrating tablet contains 10 mg of bilastine, or 20 mg of bilastine.

Oral solution: Each mL contains 2.5 mg of bilastine.

Excipient with known effect: Each orally disintegrating tablet contains sucralose. The oral solution contains methyl hydroxybenzoate, propyl hydroxybenzoate and sucralose. For the full list of excipients, see section 6.1. LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Tablets: oval, biconvex, scored white tablets. The score line allows for splitting of the tablet to facilitate the ease of swallowing.

Orally disintegrating tablets:

20 mg orally disintegrating tablets: round, flat, white orally disintegrating tablets engraved with “20” on one side and 8 mm of diameter.

10 mg orally disintegrating tablets: round, slightly biconvex, white and of 8 mm diameter.

Oral solution: clear, colourless, slightly viscous aqueous solution of pH 3.0-4.0, without precipitate.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ALLERTINE 20 mg tablets and ALLERTINE MELTLETS 20 mg orally disintegrating tablets are indicated in adults and adolescents (12 years of age and over) for the symptomatic treatment of Allergic Rhinoconjunctivitis (AR - both Seasonal Allergic Rhinitis (SAR) and Perennial Allergic Rhinitis (PAR)) and/or urticaria.

ALLERTINE KIDS MELTLETS 10 mg orally disintegrating tablets and ALLERTINE KIDS ORAL LIQUID 2.5 mg/mL oral solution are indicated for the symptomatic treatment of Allergic Rhinoconjunctivitis and/or urticaria in children aged 6-11 years with a body weight of at least 20 kg.

4.2 DOSE AND METHOD OF ADMINISTRATION

For allergic rhinoconjunctivitis, the treatment should be limited to the period of exposure to allergens. For seasonal allergic rhinitis, treatment could be discontinued after the symptoms have resolved and reinitiated upon their reappearance. In perennial allergic rhinitis, continued treatment may be proposed to the patients during the allergen exposure periods. For urticaria, the duration of treatment depends on the type, duration and course of the complaints, and the treatment could be discontinued after the symptoms have resolved and reinitiated upon their reappearance.

Adults and adolescents (12-17 years of age)

Take a 20 mg tablet or a 20 mg orally disintegrating tablet once daily for the relief of symptoms of allergic rhinoconjunctivitis (SAR and PAR) and urticaria.

Children (6-11 years of age weighing at least 20 kg)

Take a 10 mg orally disintegrating tablet or 4 mL of oral solution once daily for the relief of symptoms of allergic rhinoconjunctivitis (SAR and PAR) and urticaria.

Renal impairment

No dosage adjustment is required in renal impairment in adults or in the elderly. The safety and efficacy of bilastine in renally impaired children have not been established. Studies conducted in adults in special risk groups (renally impaired patients) indicate that it is not necessary to adjust the dose of bilastine in adults (see section 5.2 PHARMACOKINETIC PROPERTIES).

Hepatic impairment

No dosage adjustment is required in hepatic impairment in adults or in the elderly. The safety and efficacy of bilastine in hepatically impaired children have not been established. There is no clinical experience in either adult or paediatric patients with hepatic impairment. However, since bilastine is not metabolised and is eliminated as unchanged in urine and faeces, hepatic impairment is not expected to increase systemic exposure above the safety margin in adult patients. Therefore, no dosage adjustment is required in adult patients with hepatic impairment (see section 5.2 PHARMACOKINETIC PROPERTIES).

Method of Administration

Tablets: The 20 mg tablets should be swallowed whole, with a glass of water.

Orally disintegrating tablets: The 10 mg or 20 mg orally disintegrating tablets should be placed in the mouth where it disperses rapidly in saliva, so it can be easily swallowed. Alternatively, the 10 mg or 20 mg orally disintegrating tablets may be dispersed in a teaspoon of water before administration. Grapefruit juice or any other fruit juices should not be used for dispersion. (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). May be followed by a glass of water if desired.

Oral solution: The oral solution is provided in a bottle with a child-proof cap and must be opened as follows: press the plastic screw-cap downwards and simultaneously turn anti-clockwise. This is accompanied by a measuring cup for dosage with a mark of 4 mL equivalent to 10 mg bilastine per dosing. The cap should be tightened after use to engage child resistant closure.

All presentations of ALLERTINE should be taken at least 1 hour before or 2 hours after intake of food or fruit juice (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

4.3 CONTRAINDICATIONS

Hypersensitivity to bilastine or to any of the excipients (see section 6.1 LIST OF EXCIPIENTS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use in hepatic impairment

The safety and efficacy of bilastine in hepatically impaired children have not been established. There is no clinical experience in both adult and paediatric patients with hepatic impairment. There is no clinical experience in adult patients with hepatic impairment. No dosage adjustment is required in patients with hepatic impairment (see section 5.2 PHARMACOKINETIC PROPERTIES) since bilastine is not metabolised and is eliminated unchanged in urine and faeces. Hepatic impairment is not expected to increase systemic exposure above the safety margin.

Use in renal impairment

The safety and efficacy of bilastine in renally impaired children have not been established. No dosage adjustment is required in patients with renal impairment (see section 5.2 PHARMACOKINETIC PROPERTIES).

In patients with moderate or severe renal impairment, co-administration of bilastine with P-glycoprotein inhibitors such as cyclosporine or diltiazem should be approached with caution as elevated bilastine plasma levels and higher incidence of adverse reactions such as dizziness, headache and nausea may occur (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Use in the elderly

No dosage adjustment is required in elderly patients (see sections 5.1 PHARMACODYNAMIC PROPERTIES and 5.2 PHARMACOKINETIC PROPERTIES). Data from Phase 2, 3 and post-authorisation studies found no difference in efficacy or safety in elderly patients over 65 years of age compared to younger adults.

Paediatric use

No difference in efficacy and safety was observed in clinical trials with ALLERTINE in adolescents 12 to 17 years compared to the adult population.

In a double blind, placebo-controlled safety and tolerability study children aged from 6 to 12 years dosed with 10 mg bilastine have demonstrated a safety profile consistent with that seen in adults and adolescents receiving 20 mg bilastine (see section 5.2 PHARMACOKINETIC PROPERTIES).

There is currently no data on the use of bilastine in children aged 2 years or under for allergic rhinoconjunctivitis or urticaria. There is little clinical experience in children aged 2 to 5 years, therefore ALLERTINE should not be used in these age groups.

ALLERTINE oral solution contains methyl hydroxybenzoate and propyl hydroxybenzoate, which may cause allergic reactions (possibly delayed).

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

Interaction with food

Food reduces the oral bioavailability of bilastine 20 mg tablets and 20 mg orally disintegrating tablets by 25% to 30%, and that of the 10 mg orally disintegrating tablets and the oral solution by 20%; although it is not certain if this interaction is clinically significant particularly when food has a low-fat content (see section 5.2 PHARMACOKINETIC PROPERTIES).

Interactions mediated by transporters or CYP450

In vitro and *in vivo* studies have shown that bilastine is a substrate of P-gp and OATP1A2. 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.

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

Interaction with grapefruit juice

Concomitant intake of bilastine 20 mg tablets or 20 mg orally disintegrating tablets and grapefruit juice decreased bilastine bioavailability by 30%. This effect may also apply to other fruit juices. 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 with ketoconazole or erythromycin increased bilastine AUC 2-fold and C_{max} 2-3 fold, but these changes do not appear to affect the safety profile of bilastine and ketoconazole or erythromycin, respectively. These changes can be explained by interaction with intestinal efflux transporters since bilastine is a substrate for P-gp and is not metabolised (see section 5.2 PHARMACOKINETIC PROPERTIES).

Other medicinal products that are substrates or inhibitors of P-gp, such as ciclosporin, may likewise have the potential to increase plasma concentrations of bilastine.

Importantly, no clinically relevant prolongation of the QTc interval or any other cardiovascular effect has been observed in interaction studies with ketoconazole and erythromycin, or when repeat doses of bilastine 200 mg daily (i.e. 10 times the therapeutic dose) are taken.

Interaction with diltiazem

Concomitant intake of bilastine 20 mg and diltiazem 60 mg increased C_{max} of bilastine by 50%, but it does not appear to affect the safety profile of ALLERTINE. This effect can be explained by interaction with intestinal efflux transporters (see section 5.2 PHARMACOKINETIC PROPERTIES).

Interaction with lorazepam

Concomitant intake of bilastine 20 mg and lorazepam 3 mg for 8 days did not potentiate the CNS depressant effects of lorazepam.

Interaction with alcohol

No differences were observed in psychomotor performance after intake of alcohol with either bilastine 20 mg or placebo.

Paediatric population

While interaction studies were performed in adults, similar effects are expected in adolescents 12 to 17 years of age.

No interaction studies have been performed in children with the ALLERTINE oral solution nor the orally disintegrating tablets. 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. There are no clinical data in children to state whether changes to the AUC or C_{max} due to interactions affect the safety profile of bilastine.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are limited clinical data available. In a fertility study in rats, bilastine administered orally up to 1000 mg/kg/day did not induce any effect on female or male reproductive organs. Mating, fertility and pregnancy indices were not affected. A reduction in sperm motility and abnormal sperm morphology were observed in dogs treated with bilastine for 52 weeks with oral doses of 800 mg/kg/day (approximately 380 times the clinical exposure based on AUC), with no effects at 125 mg/kg/day (approximately 130 times the clinical exposure based on AUC).

Use in pregnancy

PREGNANCY CATEGORY B3

There are limited data available on the use of bilastine in pregnant women.

Bilastine was studied for effects on embryofetal development in pregnant rats and rabbits given oral doses of 75, 275 and 1000 mg/kg/day and 30, 110 and 400 mg/kg/day respectively, during organogenesis. In rabbits, an increased incidence of skeletal variations (incomplete ossification of cranial bones, sternebrae and limbs) were observed at a maternotoxic dose of 400 mg/kg/day (approximately 250 times the clinical exposure based on AUC), with no effects on embryofetal development at 110 mg/kg/day (approximately 40 times the clinical exposure based on AUC). Bilastine had no effect on pre- and postnatal development of rats treated with oral doses up to

1,000 mg/kg/day. As a precautionary measure, it is preferable to avoid the use of ALLERTINE/ALLERTINE MELTLETS during pregnancy.

Use in lactation

The excretion of bilastine in milk has not been studied in humans. Available pharmacokinetic data in rats administered a single oral dose (20 mg/kg) has identified excretion of bilastine in milk. Concentrations of bilastine in milk were about half of those in maternal plasma. The relevance of those results for humans is unknown.

A decision on whether to use ALLERTINE/ALLERTINE MELTLETS should be made taking into account the benefit of breast-feeding to the child and the benefit of ALLERTINE/ALLERTINE MELTLETS therapy to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE OF MACHINES

The CNS safety profile and incidence of somnolence of bilastine 20 mg at the recommended dose was similar to placebo in clinical trials. Higher doses of bilastine up to 40 mg once daily did not affect psychomotor performance in clinical trials or driving performance in a standard driving test.

Although ALLERTINE/ALLERTINE MELTLETS is no more likely than placebo to cause sedation and/or decreased mental alertness, individual response should be determined before driving or using machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of safety profile in adults and adolescent patients (12 to 17 years of age)

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

Phase 2 and 3 clinical trials performed during the clinical development included 2599 patients treated with single or multiple doses of bilastine, up to 40 mg. Of these trials, double-blind multiple-dose trials included 1358 patients who received 20 mg (ALLERTINE), 1362 who received placebo, and 1093 who received active control. Adverse events most commonly reported for ALLERTINE were headache, somnolence and abdominal pain (see Table 1). These adverse events occurred with a frequency comparable to that for placebo.

Tabulated summary of adverse events in adults and adolescents

Adverse events with a frequency of very common (≥1/10) and common (≥1/100 to <1/10) related to ALLERTINE 20 mg during the clinical development in double-blind multiple-dose phase 2 and 3 studies (n = 1358) are tabulated below. Adverse events with a frequency less than 1% (<1/100) have not been included in Table 1.

Table 1 - Treatment emergent AEs reported in ≥ 1% of patients treated with ALLERTINE in double-blind multiple-dose Phase 2 and Phase 3 studies

Body System / AE	ALLERTINE 20 mg n = 1358	Cetirizine 10 mg n = 686	Desloratadine 5 mg n = 242	Levocetirizine 5 mg n = 165	Placebo n = 1362
Gastrointestinal disorders					
Abdominal pain	36 (2.65%)	12 (1.79%)	6 (2.48%)	6 (3.64%)	30 (2.21%)
Diarrhoea	16 (1.18%)	8 (1.17%)	1 (0.41%)	2 (1.21%)	13 (0.95%)
General disorders and administration site conditions					
Fatigue	19 (1.40%)	23 (3.35%)	3 (1.24%)	1 (0.61%)	27 (1.98%)
Infections and infestations					
Nasopharyngitis	17 (1.25%)	8 (1.17%)	0 (0.0%)	2 (1.21%)	20 (1.47%)
Nervous system disorders					
Dizziness	24 (1.77%)	9 (1.31%)	4 (1.65%)	0 (0.0%)	27 (1.98%)
Headache	212 (15.61%)	77 (11.22%)	28 (11.57%)	27 (16.36%)	199 (14.61%)
Somnolence	55 (4.05%)	55 (8.02%)	9 (3.72%)	11 (6.67%)	44 (3.23%)
Respiratory, thoracic and mediastinal disorders					
Pharyngolaryngeal pain	15 (1.10%)	9 (1.31%)	2 (0.83%)	0 (0.0%)	17 (1.25%)

Other adverse reactions at least possibly related to ALLERTINE 20 mg and reported at a frequency of uncommon (≥1/1,000 to <1/100) during the clinical development include:

Infections and Infestations: oral herpes
Metabolism and Nutrition Disorders: increased appetite
Psychiatric Disorders: anxiety, insomnia
Ear and labyrinth Disorders: tinnitus, vertigo
Cardiac Disorders: right bundle branch block, sinus arrhythmia, electrocardiogram QT prolonged, other ECG abnormalities
Respiratory, Thoracic and Mediastinal Disorders: dyspnoea, nasal discomfort, nasal dryness
Gastrointestinal Disorders: upper abdominal pain, nausea, stomach discomfort, dry mouth, dyspepsia, gastritis
Skin and Subcutaneous Tissue Disorders: pruritus
General Disorders and Administration Site Conditions: thirst, improved pre-existing condition, pyrexia, asthenia
Investigations: increased gamma-glutamyltransferase, alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased, blood triglycerides increased, increased weight.

Although ECG abnormalities and other cardiac disorders were reported during clinical trials of bilastine, the incidences were not significantly different from those reported when taking placebo (see also sections 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and 4.9 OVERDOSE).

Adolescent population

During the clinical development of ALLERTINE 20 mg the frequency, type and severity of adverse reactions in adolescents (12 years to 17 years) were the same as seen in adults. The safety

information collected in this population (adolescents) during post-marketing surveillance has confirmed clinical trial findings.

Post-marketing experience in adults and adolescents

Information collected during post-marketing surveillance confirmed the ALLERTINE 20 mg safety profile observed during clinical development.

Palpitations, tachycardia, hypersensitivity reactions (such as anaphylaxis, angioedema, dyspnoea, rash, localised oedema/local swelling, and erythema), vomiting and electrocardiogram QT prolonged have been observed during the ALLERTINE 20 mg post-marketing period.

Summary of safety profile in paediatric population

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

The related adverse events most commonly reported in 291 children (2-11 years) receiving bilastine 10 mg during clinical trials were headache, allergic conjunctivitis, rhinitis and abdominal pain. These related adverse events occurred with a comparable frequency in 249 patients receiving placebo.

Post-marketing experience in paediatric population

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Health professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

There are no data for overdose in children.

Information regarding acute overdose of bilastine is based on experience from clinical trials conducted during the development and 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 volunteers, frequency of treatment emergent adverse events was two times higher than with placebo, with dizziness, headache and nausea most frequently reported. No serious adverse events and no significant prolongation in the QTc interval were reported.

Critical evaluation of bilastine's multiple dose (100 mg x 4 days) effect on ventricular repolarization by a "thorough QT/QTc cross-over study" involving 30 healthy volunteers did not show significant QTc prolongation.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Bilastine is a non-sedating, long-acting histamine antagonist with selective peripheral H_1 receptor antagonist affinity and no affinity for muscarinic receptors. Single doses of bilastine 20 mg demonstrated sustained inhibition of histamine-induced wheal and flare skin reactions for 24 hours. Duration of activity in AR as measured by efficacy at 22-26 hours post-dose was at least 26 hours for ALLERTINE. This end of the dosing period efficacy was also significantly greater for ALLERTINE than for the active comparator fexofenadine (p= 0.0012). ALLERTINE also demonstrated a fast 1 hour onset of action equivalent to other non-sedating antihistamines (cetirizine, fexofenadine).

Clinical trials

The efficacy and safety studies were conducted with the tablet formulation ALLERTINE, to which ALLERTINE MELTLETS have been shown to be bioequivalent.

Allergic Rhinoconjunctivitis (SAR and PAR)

The efficacy of bilastine has been studied in adults and adolescents. According to guidelines, the proved efficacy in adults and adolescents can be extrapolated to children, having demonstrated that the systemic exposure with 10 mg bilastine in children from 6 to 11 years with a body weight of at least 20 kg is equivalent to the exposure in adults with 20 mg bilastine (see 5.2 PHARMACOKINETIC PROPERTIES). The extrapolation from adult and adolescent data is deemed appropriate for this product as the pathophysiology of allergic rhinoconjunctivitis and urticaria is the same for all age groups.

In a 12-week controlled clinical trial with children aged 2-11 years (total 509 children, 260 treated with bilastine 10 mg: 58 at age 2 to <6 years, 105 at age 6 to <9 years and 97 at 9 to <12 years and 249 treated with placebo: 58 at age 2 to <6 years, 95 at age 6 to <9 years and 96 at 9 to <12 years), at the recommended paediatric dose of 10 mg once daily, the safety profile of bilastine (n=260) was similar to placebo (n=249), with adverse drug reactions seen in 5.8% and 8.0% of patients taking bilastine 10 mg and placebo, respectively. Both bilastine 10 mg and placebo showed a slight decrease in somnolence and sedation scores on the Paediatric Sleep Questionnaire during this study, with no statistically significant differences between treatment groups. In these children aged 2 to 11 years, no significant differences in QTc were observed following 10 mg bilastine daily compared with placebo. Quality of Life questionnaires specific for children with allergic rhinoconjunctivitis or chronic urticaria showed a general increase in scores over 12 weeks with no statistically significant difference between the bilastine and placebo arms. The total population of 509 children encompassed: 479 subjects with allergic rhinoconjunctivitis and 30 subjects diagnosed with chronic urticaria. 260 children received bilastine, 252 (96.9%) for allergic rhinoconjunctivitis and 8 (3.1%) for chronic urticaria. In analogy, 249 children received placebo, 227 (91.2%) for allergic rhinoconjunctivitis and 22 (8.8%) for chronic urticaria.

In clinical trials with adults and adolescents (12-17 years) with AR (SAR and PAR), ALLERTINE 20 mg once daily for 14-28 days demonstrated effective relief of nasal (sneezing, nasal discharge, nasal itching and nasal congestion) and non-nasal symptoms (ocular redness and tearing ± itching of ears, palate and/or eyes) symptoms. Bilastine effectively controlled symptoms for 24 hours. The primary efficacy measurement was mean reduction in total symptom scores (TSS), with mean

reductions in sum of nasal symptom scores (NSS) and/or sum of non-nasal symptom scores (NNSS) included as secondary measures. Given SAR and PAR are considered pharmacodynamically comparable conditions that differ principally in symptom duration with many PAR patients having concomitant SAR, efficacy and safety data are considered for AR as a whole.

In study #1003, ALLERTINE 20 mg once daily was compared to the active comparator desloratadine 5 mg once daily and placebo in 720 SAR patients for 14 days. ALLERTINE had comparable efficacy to desloratadine from day 1, with mean reductions in TSS significantly greater than that for placebo ($p<0.001$) over the study period. In addition, the percentage reduction of NSS ($p=0.001$) and NNSS ($p=0.003$) from baseline to day 14 was significantly greater with ALLERTINE compared to placebo, supporting the efficacy of bilastine for the range of AR symptoms. No differences were observed when comparing the efficacy of ALLERTINE with the active comparator. ALLERTINE also demonstrated an excellent safety profile with an adverse events profile equivalent to that for placebo (28.3% vs 25.3%, $p=0.199$).

In study #1704, 683 SAR patients were treated with ALLERTINE 20 mg, placebo or the active comparator cetirizine 10 mg, once daily for 14 days. Mean reductions in TSS at 14 days were significantly greater with ALLERTINE and cetirizine compared to placebo ($p<0.001$). ALLERTINE also significantly decreased both NSS ($p<0.001$) and NNSS ($p<0.001$) compared to placebo. After 14 treatment days, the reported mean TSS at the end of the dose period (prior to the next morning dose) was compared to that measured the prior evening. As no difference in TSS was observed between these time points for ALLERTINE ($p=0.2032$) while a significant difference was observed for placebo ($p<0.0001$), there is strong evidence of ALLERTINE's sustained 24-hour efficacy and duration of action. In addition, ALLERTINE demonstrated a favourable safety profile, with an incidence of adverse events similar to that of placebo (14.5% vs 19.5% respectively), and superior adverse events profile to that of cetirizine 10 mg (overall incidence 24.7% vs 36.0% respectively, $p=0.031$).

In study #1503, 650 patients with PAR were randomised to ALLERTINE 20 mg, the active comparator cetirizine 10 mg or placebo, once daily for 28 days. Due to regional differences in the response, no significant differences in mean reduction of TSS across treatment groups were observed. However, when the data was reanalysed by excluding a region with very high placebo response, both ALLERTINE and cetirizine significantly reduced TSS compared to placebo over the 28-day treatment period ($p=0.039$). The 28 day double-blind phase was followed by an additional 12 month open-label safety extension in 513 patients receiving ALLERTINE. A trend in mean reduction of NSS and NNSS were observed throughout the 12 months follow-up, although there were no comparison groups. There were no significant differences in overall adverse events incidence with ALLERTINE compared to cetirizine or placebo. No serious adverse reactions were reported with ALLERTINE.

Urticaria

In clinical study #2006, 522 adults suffering from Chronic Idiopathic Urticaria (CIU) with a documented history of symptoms for at least 6 weeks were treated with either ALLERTINE 20 mg, the active comparator levocetirizine 5 mg or placebo once daily for 28 days. Efficacy was defined as mean reduction in TSS (which is comprised of number and size of wheals as well as itching intensity and discomfort due to urticaria) at 4 weeks. Both ALLERTINE and levocetirizine significantly reduced TSS compared to placebo ($p<0.001$), with similar secondary quality of life outcomes reported for both active treatments. Results obtained for the secondary efficacy variables were consistent with those reported for the primary efficacy variable and in general, efficacy of both ALLERTINE and

levocetirizine were superior to placebo with high statistical significance. Similarly, ALLERTINE demonstrated a favourable safety profile, with similar incidence of adverse events to that for levocetirizine (overall incidence 35.8% vs 37.0% respectively, p=0.319).

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetic properties were studied on the tablet formulation ALLERTINE.

Two pharmacokinetic studies were carried out in healthy volunteers to compare ALLERTINE MELTLETS and ALLERTINE, which have demonstrated the bioequivalence of the two formulations.

Absorption

Bilastine is rapidly absorbed after oral administration with a time to maximum plasma concentration of around 1.3 hours. No accumulation has been observed. Mean bilastine oral bioavailability is 61%.

The effect of food on bioavailability of bilastine was investigated in two Phase 1 studies. The first assessed the influence of a high fat meal on bioavailability compared to a fasted state. The second study compared bioavailability after a high-fat meal, a standard (low-fat) meal and in a fasted state. It appears that high-fat and standard low-fat meals significantly reduce the oral bioavailability of bilastine by 30% and 25% respectively (see section 4.2 DOSE AND METHOD OF ADMINISTRATION and section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS “Interaction with grapefruit juice”). Nevertheless, as the low-fat meal studied included orange juice and the apparent bioavailability reduction with low-fat meals and with juices is similar, it is possible that low-fat meal interactions are not clinically significant.

Distribution

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

Metabolism

Metabolism of bilastine was limited in animal species and humans. Minimal to no metabolism of bilastine by animal or human microsomes or hepatocytes. No metabolism was detected in Caco-2 cells, with and without induction of CYP1A1 and CYP3A4, indicating the absence of intestinal metabolism.

Excretion

In a mass balance study performed in healthy volunteers, after administration of a single dose of 20 mg ^{14}C-bilastine, almost 95% of the administered dose was recovered in urine (28.3%) and faeces (66.5%) as unchanged bilastine, confirming that bilastine is not significantly metabolised in humans. The mean elimination half-life in healthy volunteers was 14.5 h.

Linearity

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

Patients with Renal Impairment

The effects of bilastine in patients with renal impairment have been studied in adults.

In a study in subjects with renal impairment the mean (SD) $AUC_{0-\infty}$ increased from 737.4 (±260.8) ng.hr/mL in subjects without impairment (GFR: >80 mL/min/1.73 m^2) to: 967.4 (±140.2) ng.hr/mL in subjects with mild impairment (GFR: 50 - 80 mL/min/1.73 m^2), 1384.2 (±263.2) ng.hr/mL in subjects with moderate impairment (GFR: 30 - <50 mL/min/1.73 m^2), and 1708.5 (±699.0) ng.hr/mL in subjects with severe impairment (GFR: < 30 mL/min/1.73 m^2). 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.

Patients with Hepatic impairment

There are no pharmacokinetic data in subjects with hepatic impairment. Bilastine is not metabolised in humans. Since the results of the renal impairment study indicate renal elimination to be a major contributor in the elimination, biliary excretion is expected to be only marginally involved in the elimination of bilastine. Changes in liver function are not expected to have a clinically relevant influence on bilastine pharmacokinetics.

Elderly Patients

There are limited pharmacokinetic data for subjects older than 65 years which shows no statistically significant differences in pharmacokinetics compared to adults aged between 18 and 35 years.

Paediatric population

No pharmacokinetic data are available in adolescents (12 years to 17 years) as the extrapolation from adult data was deemed appropriate for this product.

Pharmacokinetic data in children were obtained in a Phase II pharmacokinetic study including 31 children aged 4 to 11 years with allergic rhinoconjunctivitis or chronic urticaria, administered once daily with bilastine 10 mg orally disintegrating tablet. This formulation has been shown to be bioequivalent to bilastine 2.5 mg/mL oral solution. Pharmacokinetic analysis of plasma concentration data showed that the paediatric dose of bilastine 10 mg once daily results in systemic exposure equivalent to that seen after a 20 mg dose in adults and adolescents, being the mean AUC value 1014 ng*hr/mL for children 6 to 11 years. These results were largely below the safety threshold based on data from 80 mg once daily dose in adults in accordance to the drug safety profile. These results confirmed the choice of bilastine 10 mg taken orally once daily as the appropriate therapeutic dose for the paediatric population in the age range 6 to 11 years with a body weight of at least 20 kg.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Bilastine was not mutagenic in a bacterial reverse mutation assay (Ames test) using *S. typhimurium*, or clastogenic in human lymphocytes *in vitro*. Systemic exposure to bilastine did not induce chromosomal aberrations in an *in vivo* micronucleus assay conducted in mice.

Carcinogenicity

Bilastine was not carcinogenic to mice or rats when administered orally for 2-years in the diet at dose levels up to 2000 mg/kg/day in mice and 1200 mg/kg/day in rats (greater than 100 times the clinical exposure based on AUC).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablets:

Microcrystalline cellulose
Sodium starch glycollate type A
Colloidal anhydrous silica
Magnesium stearate

Orally disintegrating tablets:

Mannitol
Croscarmellose sodium
Sodium stearylfumarate
Sucralose
Luctadry Red Grape 29665A (PI No. 146208)

Oral solution:

Betadex
Hyetellose
Methyl hydroxybenzoate
Propyl hydroxybenzoate
Sucralose
Soless Raspberry Colourless 0616 (PI No. 148236)
Hydrochloric acid
Sodium hydroxide
Purified water

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF-LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Oral solution: Discard the oral solution 6 months after first opening.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

This medicine does not require any special storage conditions.

6.5 NATURE OF CONTENTS OF CONTAINER

Tablets: PVC-PVAC-Al blister packs containing 4, 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 tablets*.

Orally disintegrating tablets: *20 mg orally disintegrating tablets:* Al/Al perforated unit-dose blister packs containing 2, 4, 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 orally disintegrating tablets*. *10 mg orally disintegrating tablets:* OPA/Al/PVC/Al blister packs containing 4, 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 orally disintegrating tablets*.

Oral solution: amber glass bottle (Type III glass), sealed with a polypropylene cap, with child-proof closure and LDPE liner. Packs include a 25 mL polypropylene cup for dosage graduated at 4 mL. Each bottle contains 120 mL oral solution.

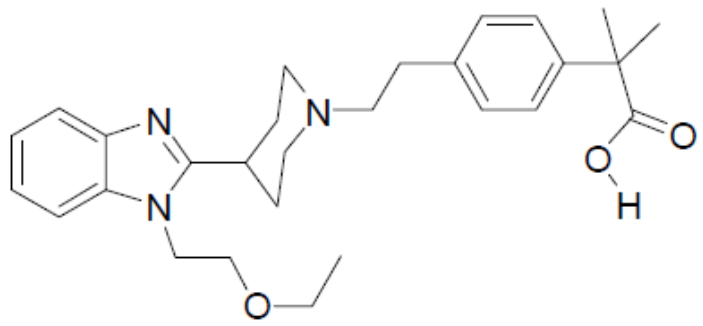
* Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



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]-α-methylhydratropic acid*
Molecular formula:	$C_{28}H_{37}N_3O_3$
Molecular weight:	463.61 g/mol
AAN:	Bilastine

CAS number

202189-78-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Bilastine 20 mg tablets and 20 mg orally disintegrating tablets – Schedule 2 (Pharmacy Medicine)

Bilastine 10 mg orally disintegrating tablets – Schedule 3 (Pharmacist Only Medicine)

Bilastine 2.5 mg/mL oral solution – Schedule 3 (Pharmacist Only Medicine)

8 SPONSOR

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Australia
Telephone: 1800 644 542

9 DATE OF FIRST APPROVAL

ALLERTINE bilastine 20 mg tablets: 27 April 2022

ALLERTINE MELTLETS bilastine 20 mg orally disintegrating tablets: 26 February 2025

ALLERTINE KIDS MELTLETS bilastine 10 mg orally disintegrating tablets: 20 August 2026

ALLERTINE KIDS ORAL LIQUID bilastine 10 mg/4 mL oral solution: 19 August 2026

10 DATE OF REVISION

20 August 2026

Summary table of changes

Section Changed	Summary of new information
2, 3, 4.1, 4.2, 4.4, 4.6, 4.7, 5.1, 5.2, 6.1, 6.5	Inclusion of information relating to new dosage form, ALLERTINE MELTLETS (orally disintegrating tablet).
All sections	Addition of new presentations for oral solution and 10 mg orally disintegrating tablets and associated information
4.1, 7	Down-scheduling of 20 mg tablets applied, following TGA notice of final decision to amend the current Poisons Standard in relation to bilastine (November 2023)
4.5	Correction of hyperlink to cross-referenced section under ‘Interaction with food’
9	Addition of new ARTG entries