Submission for the classification of Labixten (bilastine) 20 mg tablets (20 tablet pack) as Pharmacy Only

Te Arai BioFarma Ltd.
to
Medicines Classification Committee (MCC)

For the 53rd Meeting

Contents

Introduction

BILASTINE 20 mg was first authorized in 28 countries of the European Union, amongst which United Kingdom, via the decentralized procedure, with Germany as the Reference Member State. The agreed International Birth Date was 08 September 2010.

To date, BILASTINE 20 mg tablets is also registered via national procedure in 58 countries:

Albania (2013)
Algeria (2012)
Argentina (2012)
Armenia (2012)
Azerbaijan (2013)
Benin (2014)
Bosnia Herzegovina (2012)
Brazil (2011)
Burkina Faso (2012)
Cambodia (2014)
Cameroon (2012)
Central African Republic
Chile (2011)
Columbia (2011)
Congo (2013)
Costa Rica (2012)
Croatia (2012)
Democratic Republic of Congo (2013)
Dominican Republic (2012)
Ecuador (2012)
El Salvador (2012)
Gabon (2011)
Georgia (2012)
Guatemala (2011)
Guinea (2012)
Honduras (2012)
Ivory Coast (2013)
Kingdom of Saudi Arabia (2012)
Kazakhstan (2014)
Kosovo (2014)
Kyrgystan (2013)
Lebanon (2013)
Madagascar (2014)
Malaysia (2014)
Mali (2012)
Mauritania (2013)
Mexico (2012)
Nicaragua (2012)
Niger (2013)
Panama (2012)
Paraguay (2012)
Peru (2012)
Philippines (2014)
Republic of Chad (2014)
Republic of Mauritius (2013)
Republic of Moldova (2012)
Rwanda (2012)
Senegal (2012)
Serbia (2013)
Singapore (2014)
Switzerland (2011)
Tanzania (2014)
Togo (2013)
Turkmenistan (2012)
Ukraine (2014)
Uzbekistan (2012)
Venezuela (2013)
Vietnam (2013, temporary import license)

Bilastine is a new oral highly selective H1-receptor antagonist developed for the symptomatic treatment of allergic rhino-conjunctivitis and urticaria. It is an antiallergic agent whose main mechanism of action is the inhibition of immune system reactions mediated by the interaction of histamine on its H1-receptor. Many but not all hypersensitivity and allergic reactions are mediated by histamine, such as asthma or anaphylactic reactions. However, those mostly dependent on the release of histamine can be inhibited by blocking the H1 receptor with specific antihistamine drugs such as Bilastine.

To achieve optimal efficacy, the affinity for the H1 receptor should be high. A high specificity for the H1 receptor potentially reduces unwanted side effects. The affinity and selectivity of Bilastine for the human H1 receptor was investigated in vitro. Bilastine was shown to have high affinity and selectivity to the H1 receptor. The inhibition of histamine-mediated reactions by Bilastine was also assessed in various experimental tests both in vitro and in vivo.

BILASTINE 20 mg tablets is indicated for the symptomatic treatment of allergic rhinoconjunctivitis and urticaria.

As of mid-2014 (the cut off of sales data is slightly different country by country), approximately 20,281,557 packets of the available presentations of BILASTINE 20 mg tablets were distributed since the first launch, occurred in Spain on March 2011. Assuming a DDD for oral Bilastine of 20 mg, and mean treatment duration of 3 weeks, at least 22,292,737 patients (or number of therapeutic cycles) are estimated to have been exposed to bilastine in the same period (patient exposure = Package sold×tablets×strength/DDD/21 days).

Overview

Clinical trials have demonstrated that as a group, the second generation antihistamines have a much more favourable therapeutic index and a significantly lower incidence of sedative effects than their predecessors. Second generation antihistamines are less sedating than the first generation agents for their limited penetration across the blood-brain barrier. In addition, they are more selective for H1 receptors and are not associated with adverse events arising from interactions to other receptor types [1].

Bilastine goes beyond the requirements for a second-generation antihistamine. Bilastine is a potent, effective antihistamine, without sedation, without cardiac toxicity, it has absence of metabolism and does not interact with cytochrome P450.

Pharmacological studies have shown that bilastine binds specifically and selectively to histamine H1 receptor. At high concentrations there is no apparent affinity for 30 different receptors that have been assessed (including muscarinic, adrenergic, serotonergic, other histamine receptors, bradykinin, leukotriene D4, or calcium). Bilastine has a moderate-high affinity for histamine H_1 receptors, with values 3 times higher than those of cetirizine and 5 times higher than those of fexofenadine [2]. In experimental models bilastine has shown an excellent dose-dependent activity when administered by oral or intravenous route always higher than that of fexofenadine and, in certain models, also higher than that of cetirizine [3].

Bilastine studies in rats show the absence of radioactivity in the CNS; this suggests that bilastine does not cross the blood-brain barrier (BBB) [4]**.** Bilastine is a substrate for P-gP [5], a multidrug efflux transport system that also exists in the BBB and that limits the access of that drug to certain tissues and regulates its bioavailability [6]. Indeed, bilastine has been shown to have no sedative effects in man [7, 8]. In addition, bilastine (20 mg and 40 mg), unlike Cetirizine, does not increase alcohol effects on the CNS [9]. A positron emission tomography (PET) study in healthy volunteers showed a very low occupation of H1 receptors (value closed to zero value) and no subjective effects of sedation. These data indicated that bilastine 20 mg did not cross the blood–brain barrier in humans [10].

Despite greater incidence of sedation with first generation antihistamines, the NDPSC and MCC agreed that this group is available as Over-The-Counter medicines. The following non-sedating antihistamines are currently available in New Zealand:

Active ingredients	**Product names**	**Presentation**	**Dosage**	**Classification**
Cetirizine	Allerid C Apo-Cetirizine Cetirizen Hayfever Relief Histaclear Razene Your Pharmacy Cetirizene Zanlan Zetop Zyrtec	Tablet, or Film coated tablet	10mg	Pharmacy only, or General sale (5 tablet pack size)
Desloratadine	Aerius Deslor	Film coated tablet	5mg	Pharmacy only
Fexofenadine	Fexaclear Fexofast Fexofenadine Fexofenadine Rex Telfast Xergic	Tablet, or Film coated tablet	30mg, 60mg, 120mg and 180mg	Pharmacy only, or General sale (5 tablet pack size)

Loratadine	Allertyne Apo-Loratadine Claratyne Loraclear Hayfever Relief Lorafix Lora-tabs Lora-Tabs Allergy and Hayfever Lorfast Your Pharmacy Loratadine	Tablet, or Film coated tablet	10mg	Pharmacy only, or General sale (5 pack size)

The efficacy of 20 mg bilastine o.d. for the symptomatic treatment of patients suffering from seasonal allergic rhinoconjunctivitis and perennial allergic rhinoconjunctivitis (SAR/PAR) has been demonstrated according to the Guideline on the Clinical Development of Medicinal Products for the Treatment of Allergic Rhinoconjunctivitis (CHMP/EWP/2455/02).

The following table presents the results of phase III studies in terms of primary efficacy variables and EMEA efficacy endpoint. From the phase III clinical trials it can be concluded that the efficacy of bilastine for the symptomatic treatment of allergic rhinoconjunctivitis was significantly superior to placebo and similar to the active comparators in each of the composite symptom scores TSS (Total Symptom Score), TNSS (Total Nasal Symptom Score) and TNNSS (Total Non-Nasal Symptom Score).

Table 1. Results of phase III studies in terms of study primary efficacy endpoints and EMEA primary efficacy endpoints

Study No.	Treatment	N (ITT)	Study primary efficacy endpoint		EMEA primary efficacy endpoint		
			AUC_{TSS} from baseline to end of study	Test, p (ANOVA) (pairwise t-test)	TSS baseline	TSS Change from baseline over entire double blind period	Test, p (ANCOVA adjusting by baseline TSS) (pairwise t-test)
BILA 0802/RAE	Bilastine 20 mg	240	105.3 (60.0)	Overall p-value=0.9642 Bila 20 mg vs. Cet 10 mg p=0.9349 Bila 20 mg vs. Pbo p=0.6436 Cet 10 mg vs. Pbo p=0.7036	14.3 (4.2)	-5.9 (4.8)	Overall p-value=0.4964 Bila 20 mg vs. Cet 10 mg p=0.8823 Bila 20 mg vs. Pbo p=0.2982 Cet 10 mg vs. Pbo p=0.3726
	Cetirizine 10 mg	240	105.8 (65.6)		14.3 (4.2)	-5.8 (4.7)	
	Placebo	242	108.0 (58.8)		13.6 (4.2)	-5.2 (4.4)	
BILA 1003/RAE	Bilastine 20 mg	233	98.4 (58.1)	Overall p-value=0.0002 Bila 20 mg vs. Desl 5 mg p=0.6973 Bila 20 mg vs. Pbo p=0.0002 Desl 5 mg vs. Pbo p=0.0008	12.9 (3.9)	-4.9 (3.9)	Overall p-value<0.0001 Bila 20 mg vs. Desl 5 mg p=0.9283 Bila 20 mg vs. Pbo p=<.0001 Desl 5 mg vs. Pbo p=<.0001
	Desloratadine 5 mg	242	100.5 (54.6)		13.0 (4.0)	-5.0 (4.2)	
	Placebo	245	118.4 (62.7)		12.8 (4.1)	-3.6 (4.2)	
BILA 1704/RAE	Bilastine 20 mg	226	76.5 (47.9)	Overall p-value<0.0001 Bila 20 mg vs. Cet 10 mg p=0.3626 Bila 20 mg vs. Pbo p=<.0001 Cet 10 mg vs. Pbo p=<.0001	11.9 (3.42)	-4.8 (3.8)	Overall p-value<0.0001 Bila 20 mg vs. Cet 10 mg p=0.1633 Bila 20 mg vs. Pbo p<.0001 Cet 10 mg vs. Pbo p<.0001
	Cetirizine 10 mg	227	72.3 (46.6)		12.0 (3.5)	-5.3 (4.2)	
	Placebo	225	100.7 (51.7)		11.7 (3.7)	-2.9 (4.1)	
BILA 1503/RAP	Bilastine 20 mg	212	184.6 (93.1)	Overall p-value=0.2098 Bila 20 mg vs. Cet 10 mg p=0.8217 Bila 20 mg vs. Pbo p=0.1609 Cet 10 mg vs. Pbo p=0.1029	10.8 (3.2)	-3.6 (3.4)	Overall p-value=0.1750Bila 20 mg vs. Cet 10 mg p=0.8133 Bila 20 mg vs. Pbo p=0.0854 Cet 10 mg vs. Pbo p=0.1371
	Cetirizine 10 mg	214	182.7 (89.1)		10.5 (3.1)	-3.5 (3.4)	
	Placebo	215	196.8 (85.9)		10.8 (3.2)	-3.2 (2.8)	

For urticaria, as opposed to allergic rhinitis, no Clinical Development of Medicinal Products ICH or EMEA guideline has been published. Efficacy of bilastine was shown in the Phase II study BILA 0601/UCI [11] and confirmed versus placebo and active comparator (levocetirizine) in the pivotal multicenter Phase III study BILA 2006/UCI [12]. Differences between bilastine and placebo were highly statistically significant ($p<0.001$) for the main efficacy variable and for all secondary variables.

The safety data of all controlled Phase II and Phase III studies, performed in patients with either allergic rhinoconjunctivitis (SAR or PAR) or chronic idiopathic urticaria are presented below, in table 2. The overall incidence of adverse events and related adverse events during the Phase II and Phase III clinical studies was similar in patients treated with bilastine and in the patients receiving active comparators or placebo.

Table 2. Treatment emergent AEs reported in ≥1% of the patients treated with bilastine in the double-blind Phase II and Phase III studies

Body System/AE	Bilastine 20mg N=1358	Bilastine All Doses N=2186	Cetirizine 10mg N=686	Desloratadine 5mg N=242	Levocetirizine 5mg N=165	Placebo N=1362
Gastrointestinal disorders						
Abdominal pain	36 (2.65%)	51 (2.33%)	12 (1.79%)	6 (2.48%)	6 (3.64%)	30 (2.21%)
Diarrhoea	16 (1.18%)	24 (1.10%)	8 (1.17%)	1 (0.41%)	2 (1.21%)	13 (0.95%)
Nausea	10 (0.74%)	22 (1.01%)	5 (0.73%)	5 (2.07%)	1 (0.61%)	24 (1.76%)
General disorders and administration site conditions						
Fatigue	19 (1.40%)	24 (1.24%)	8 (1.17%)	1 (0.41%)	2 (1.21%)	13 (0.95%)
Infections and infestations						
Nasopharyngitis	17 (1.25%)	28 (1.28%)	8 (1.17%)	0 (0.0%)	2 (1.21%)	20 (1.47%)
Nervous system disorders						
Dizziness	24 (1.77%)	43 (1.97%)	9 (1.31%)	4 (1.65%)	0 (0.0%)	27 (1.98%)
Headache	212 (15.61%)	327 (14.96%)	77 (11.22%)	28 (11.57%)	27 (16.36%)	199 (14.61%)
Somnolence	55 (4.05%)	94 (4.30%)	55 (8.02%)	9 (3.72%)	11 (6.67%)	44 (3.23%)
Respiratory, thoracic and mediastinal disorders						
Pharyngolaryngeal pain	15 (1.10%)	26 (1.19%)	9 (1.31%)	2 (0.83%)	0 (0.0%)	17 (1.25%)

Based on safety findings collected during the clinical development, no important identified risks were detected.

Overall, the safety findings collected during about 4 years of marketing experience have confirmed the optimal safety and tolerability profile found in clinical studies.

Conclusion

Bilastine is a H1-receptor antagonist, the same pharmaceutical mechanism of action as other Pharmacy only classified medicines in New Zealand.

The Benefit/Risk ratio for Bilastine has been shown through clinical trials to be equivalent, and potentially superior in terms of the absence of sedation, to second generation products such as cetirizine and fexofenadine which are currently classified in New Zealand as Pharmacy only medicines.

The absence of sedation with Bilastine is an important advantage in terms of patient safety, including for example road safety [13].

PSUR data across a large patient exposure of more than twenty-two million support the clinical trial safety data of Bilastine.

Bilastine received regulatory approval from the Medsafe recognized authorities of Germany and the United Kingdom in 2010. Bilastine has been approved and available for a period greater than three (3) years.

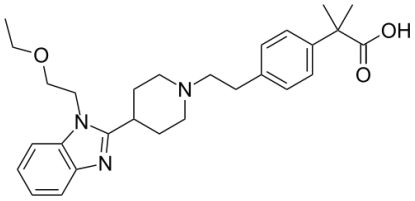
For these reasons we propose Bilastine is to be classified Pharmacy Only.

PART A

1. International Non-proprietary Name (or British Approved Name or US Adopted Name) of the medicine.

Name: Bilastine

Chemical Structure:



Molecular Formula: $C_{28}H_{37}N_3O_3$

CAS Registry Number: 202189-78-4

2. Proprietary name(s).

Labixten

3. Name of the company / organisation / individual requesting a reclassification.

Te Arai BioFarma Limited
Auckland, New Zealand

4. Dose form(s) and strength(s) for which a change is sought.

Dose Form: Tablet
Strength: Bilastine 20mg

5. Pack size and other qualifications.

4 tablet Al-Al Blister pack within a carton.
10 tablet Al-Al Blister pack within a carton.
20 tablet Al-Al Blister pack within a carton.
30 tablet Al-Al Blister pack within a carton.

6. Indications for which change is sought.

Treatment of symptoms of allergic rhinoconjunctivitis (seasonal and perennial).
Treatment of symptoms of urticaria.

7. Present classification of the medicine.

Currently Labixten is unclassified in New Zealand.

8. Classification sought.

This application seeks to classify Bilastine 20mg oral tablets as a Pharmacy Only Medicine.

9. Classification status in other countries (especially Australia, UK, USA, Canada).

Bilastine 20mg tablets are currently available as Prescription Only Medicine in many countries, including the United Kingdom.

10. Extent of usage in New Zealand and elsewhere (eg, sales volumes) and dates of original consent to distribute.

BILASTINE 20 mg was first authorized in 28 countries of the European Union, via the decentralized procedure, amongst which United Kingdom, with Germany as the Reference Member State and the agreed International Birth Date was 08 September 2010.

As of mid-2014 (the cut off of sales data is slightly different country by country), approximately 20,281,557 packets of the available presentations of BILASTINE 20 mg tablets were distributed since the first launch, occurred in Spain on March 2011. Assuming a DDD for oral Bilastine of 20 mg, and mean treatment duration of 3 weeks, at least 22,292,737 patients (or number of therapeutic cycles) are estimated to have been

exposed to bilastine in the same period (patient exposure = Package sold×tablets×strength/DDD/21 days).

Bilastine does not currently have marketing approval in New Zealand.

11. Labelling or draft labelling for the proposed new presentation(s).
A copy of the proposed labelling is available in Appendix 1.

12. Proposed warning statements if applicable.
The following warning statement will be presented on the carton label for Labixten (Bilastine):

- Although this medicine is unlikely to affect your ability to drive or operate machinery, a few people may be impaired and care should be taken.

The warning to take care when driving or operating machines is a precautionary measure. Experiencing drowsiness is a very rare side effect.

Driving and operating machinery are not contraindicated as there is an absence of CNS effects associated with Labixten (Bilastine).

13. Other products containing the same active ingredient(s) and which would be affected by the proposed change.
No other products containing the same active ingredient are registered in New Zealand. Therefore, no other products would be affected by the proposed change.

Part B

1. A statement of the benefits to both the consumer and to the public expected from the proposed change

Labixten 20mg is a single daily oral dose for the treatment of prevalent allergic disorders such as allergic rhinoconjunctivitis and urticaria. [14]. Labixten 20mg tablets contain the active ingredient Bilastine, which is a newer non-sedating antihistamine, entering the worldwide market 4 years ago. Bilastine goes beyond the requirements for a second-generation antihistamine. Bilastine is a potent, effective antihistamine, without sedation (it does not cross the blood-brain-barrier), without cardiac toxicity, it has absence of metabolism and does not interact with cytochrome P450. It is similar to Pharmacy Only classified H 1 antihistamines (such as Cetirizine, Desloratadine, Fexofenadine and Loratadine), in terms of qualitative tolerability profile, minimal clinically significant drug interactions and no contraindications other than hypersensitivity to the active ingredient and excipients [14].

The OTC classification of other second generation antihistamines from the same class (Cetirizine, Desloratadine, Fexofenadine and Loratadine) supports the potential public need for ready access of patients to treatment for their allergic conditions [15]. Seasonal allergic rhinoconjunctivitis (SAR) can have a detrimental effect on a patients' quality of life. Despite severe symptoms, people with SAR tend not to seek medical advice regarding treatment. Patients already have an awareness of their allergic conditions (particularly with SAR) and/or knowledge of how to manage these allergies with little assistance or counselling from a pharmacist or doctor. A study conducted in the US has found that only 12.4% of patients with allergic rhinitis (AR) consulted a physician, choosing instead to self-treat with home remedies and over-the-counter (OTC) medications [16].

SAR is often considered a nuisance rather than a major disease and most people will self-treat [15]. The condition is easily self-diagnosed by the characteristic symptoms of rhinorrhoea, sneezing and nasal stuffiness, as well as occasional itching of the eyes, nose, ears and/or palate. It is a recurring yet self-limiting disorder, which requires no special investigations, and is unlikely to mask a more serious underlying disease.

Indeed, AR has long been recognised as being appropriate for self-diagnosis, as reflected by the extensive range of oral antihistamine and intranasal decongestant products that have been marketed worldwide for many years on an OTC basis.

2. Potential risk of harm to the consumer as a result of the proposed change, and factors to mitigate this risk.

The safety and efficacy of Bilastine is well established. The complete clinical program of bilastine investigated over 5000 individuals, either healthy volunteers or patients with either seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), or chronic idiopathic urticaria (CIU), 12-83 years old, in 18 Phase I studies, 5 Phase II and 5 Phase III clinical studies.

Information regarding acute overdose is provided 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 [1].

Critical evaluation of bilastine's multiple dose (100 mg x4 days) effect on ventricular repolarization by a "thorough QT/QTc cross-over study" involving 30 healthy volunteers did not show significant QTc

prolongation [17].

There is no possibility of community harm resulting from wider use of Bilastine.

The benefits of Bilastine being classified as Pharmacy Only medicine significantly outweigh the risk. A Pharmacy Only medicine classification is logical given the Pharmacy Only classification of second generation antihistamines and presents a low risk.

3. Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated.

Allergic Rhinoconjunctivitis refers to inflammation of the lining of the nose; an allergen comes into contact with the sensitive, moist lining in your nose and sinuses and sets off the allergic response [15]. Allergic Rhinoconjunctivitis can be either Seasonal or Perennial. Seasonal allergic rhinitis (SAR) is associated with spring and early summer, triggered by pollen (outdoor allergens), but not only, when pollens that bloom in winter are present. Individuals suffering from perennial allergic rhinoconjunctivitis (PAR) have symptoms all year round, triggered by house dust mites, pets and mould (indoor allergens) [18].

Despite severe symptoms, people with SAR or PAR tend not to seek medical advice regarding treatment [16]. Patients already have an awareness of their allergic conditions (particularly with SAR) and/or knowledge of how to manage these allergies with little assistance or counselling from a pharmacist or doctor. The condition is easily self-diagnosed by the characteristic symptoms of sneezing (especially paroxysmal), congestion, watery anterior rhinorrhoea, itchy nose, eyes and throat, sinus pressure, facial pain and decreased sense of smell or taste [18]. In the case of SAR, the timing of symptoms is related to exposure to environmental aeroallergens [18]. It is a recurring yet self-limiting disorder, which requires no special investigations, and is unlikely to mask a more serious underlying disease.

Urticaria refers to a group of skin disorders affecting adults and children, in which red patches and wheals occur. Histamine or other vasoactive chemicals are released from mast cells and basophils in the skin causing small blood vessels to leak, resulting in the skin swelling or a “wheal”. The wheals can be a few millimetres or several centimetres in diameter, coloured white or red, often surrounded by a red flare, and frequently itchy. Each wheal may last a few minutes or several hours, and may change shape. [19].

In the majority of patients a specific cause for Urticaria will not be found. According to Best Practice Advocacy Centre (BPAC) Guidelines extensive diagnostic testing is not recommended unless there is strong evidence to suspect a specific trigger. Treatment is aimed at symptom relief, using oral non-sedating antihistamines first-line [18].

Indeed, Allergic Rhinoconjunctivitis and Urticaria have long been recognised as being appropriate for self-diagnosis, as reflected by the extensive range of oral antihistamine and intranasal decongestant products that have been marketed worldwide for many years on an OTC basis.

4. Relevant comparative data for like compounds.

Second generation antihistamines are widely regarded as an effective and safe treatment option to ease the symptoms of hay fever, hives and other allergies. As a class, second generation antihistamines are highly selective for the H1 receptor and bind to it with high affinity. They have a limited effect on the central nervous system and cause almost no drug interactions [1].

Bilastine was shown to bind to the H1 receptor with a high affinity and a very high specificity and

to inhibit effectively histamine-H1-mediated reaction in isolated organs and in vivo. The potency of bilastine in vitro was consistently greater than cetirizine and in vivo tests showed bilastine to have similar to greater potency than cetirizine where histamine was used to induce a response. The potency of bilastine where IgE was used to induce an allergic response was inferior to that of cetirizine. The potency of bilastine was greater than that of fexofenadine both in vitro and in vivo. A high and dose- dependent anti-anaphylactic activity of bilastine was demonstrated in the well-established animal model of active and passive cutaneous anaphylaxia.

The therapeutic index for Bilastine is in line with the second generation antihistamines Pharmacy only medicines currently available in New Zealand. Second generation H1 antihistamines are considered to have an improved risk/benefit ratio because of their low penetration into the brain and their low incidence of CNS depressant effects [20, 21]. Bilastine has proven to be superior to second generation antihistamines in terms of sedation – Bilastine does not cause drowsiness or sedation.

5. Local data or special considerations relating to New Zealand.

Allergy New Zealand approximates 20 per cent of the New Zealand population suffers from rhinitis. 50 per cent of those patients experience symptoms for more than four months per year and 20 per cent have symptoms for at least nine months per year.

The BPAC suggests seasonal allergic rhinitis may affect up to 30% with prevalence being higher in Western countries including New Zealand. In New Zealand the seasons are not very distinct and they vary throughout the country because of the different climates. The season starts about one month earlier at the top of the North Island than the bottom of the South Island. Thus the hay fever season is not very well defined.

Oral antihistamines have been used for many years for the prevention and treatment of AR. A number of these are available as Pharmacy Medicines or General Sale Medicines depending on pack size. They can be used to treat some of the histamine-mediated symptoms of rhinitis, such as nasal itching, sneezing and watery rhinorrhoea, by blockade of histamine H1-receptors.

Active ingredients	**Product names**	**Presentation**	**Dosage**	**Classification**
Cetirizine	Allerid C Apo-Cetirizine Cetirizen Hayfever Relief Histaclear Razene	Tablet, or Film coated tablet	10mg	Pharmacy only, or General sale (5 tablet pack size)
Desloratadine	Aerius	Film coated tablet	5mg	Pharmacy only

Appendix 4. (Scaglione, 2012)

Fexofenadine	Fexaclear Fexofast Fexofenadine Fexofenadine Rex	Tablet, or Film coated tablet	30mg, 60mg, 120mg and 180mg	Pharmacy only, or General sale (5 tablet pack size)
Loratadine	Allertyne Apo-Loratadine Claratyne Loraclear Hayfever Relief Lorafix Lora-tabs	Tablet, or Film coated tablet	10mg	Pharmacy only, or General sale (5 pack size)

6. Interactions with other medicines.

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

Interaction with grapefruit juice: concomitant intake of bilastine 20 mg and grapefruit juice decreased bilastine bioavailability by 30%. This effect may also apply to other fruit juices. The degree of bioavailability decrease may vary between producers and fruits. The mechanism for this interaction is an inhibition of OATP1A2, an uptake transporter for which bilastine is a substrate. Medicinal products that are substrates or inhibitors of OATP1A2, such as ritonavir or rifampicin, may likewise have the potential to decrease plasma concentrations of bilastine.

7. Contraindications and precautions.

Bilastine is contraindicated in patients who are hypersensitive to the active substance bilastine or to any of the excipients.

Special warnings and precautions:

Efficacy and safety of bilastine in children under 12 years of age have not been established.

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

Interaction with ketoconazole or erythromycin: Concomitant intake 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 substrate for P-gp and not metabolized. These changes do not appear to affect the safety profile of bilastine and ketoconazole o r erythromycin, respectively. Other medicinal products that are substrates or inhibitors of P-gp, such as cyclosporine, may likewise have the potential to increase plasma concentrations of bilastine.

Interaction with diltiazem: Concomitant intake of bilastine 20 mg and diltiazem 60 mg increased 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.

Appendix 4. (Scaglione, 2012)

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

8. Possible resistance

Not applicable.

9. Adverse events

The qualitative tolerability profile for bilastine is similar to other new H 1 antihistamines. Headache, drowsiness and lethargy are the commonest adverse events reported by patients, regardless of the dose in most studies.

Over twenty clinical trials that were conducted during the clinical development of bilastine have assessed its safety and tolerability as a primary or secondary endpoint. No statistically significant differences were found between any bilastine dose used and placebo. However, in some cases significant differences were found between bilastine and the antihistamine comparators, particularly in relation to drowsiness and lethargy.

Accumulated data from the phase I, II and III clinical studies completed so far include the safety analysis of 3,500 patients treated with bilastine, 513 of whom were given 20 mg daily for 12months (open-label extension phase of study BILA 1503/RAP)[23]. Taking all the completed studies into consideration, 36.7% of patients treated with bilastine 20 mg/day reported an adverse event (20% related to bilastine itself). These percentages were similar to patients treated with placebo or with desloratadine and slightly higher for those treated with cetirizine (table 3) [22].

Table 3. Percentage of patients with any adverse effect (AE) in phase II and III clinical studies.

Treatment	**Dose (mg/day)**	**Adverse effects (AE) Total**	**(%) of patients Treatment-related**
Bilastine	20	36.7	20.3
Cetirizine	10	40.7	28.6
Desloratadine	5	32.6	19.8
Placebo	-	34.4	18.8

Based on safety finding collected during the clinical development, no important identified risks were detected, whereas the following potential safety concerns were highlighted for a close monitoring during the post-marketing surveillance:

Important potential risks
1. Dizziness
2. Headache
3. Somnolence
4. Electrocardiogram QT prolonged

Missing information
5. Use in Pregnancy
6. Use in Children

Appendix 4. (Scaglione, 2012)

7. Use in the elderly

The post-marketing findings on the above safety concerns collected up to September 2014 are summarized below.

A total of 56 cases of dizziness, 78 cases of headache and 59 cases of somnolence were cumulatively received. The reporting rates for these events when calculated per 100,000 patients are: 0.25 (95% CI 0.19-0.33), 0.35 (95% CI 0.28-0.44) and 0.26 (95% CI 0.20-0.34) respectively. These events are generally mild and transient and resolve after drug withdrawal. Just four (4) cases of dizziness, four (4) of headache and five (5) of somnolence were reported into 13 serious cases. The outcomes were recovered for ten (10) cases and unknown for the remaining three (3). Only 1 case of electrocardiogram QT prolonged was cumulatively received; nevertheless, the values of the QT prolongation in this case seem to be within the normal range. The reporting rate for this event when calculated per 100,000 patients is: 0.0045 (95% CI 0.0001-0.025).

Therefore no safety alerts were detected in the post-marketing surveillance on potential risks.

As far as topics where the information is missing are concerned, safety of bilastine is currently being investigated in children between 2 and less than 12 years of age. A clinical trial in this population subset has demonstrated the primary hypothesis of non-inferiority from Bilastine 10 mg with respect to placebo regarding the proportion of children without treatment-emergent adverse events (TEAEs) during the study. Based on the confirmation of the primary hypothesis of non-inferiority of Bilastine 10 mg with respect to placebo regarding the proportion of children without treatment-emergent adverse events, and the similar safety and tolerability profile compared to placebo, the study results confirm Bilastine 10 mg as a good drug to treat children in the population subset from 2 to < 12 years of age with either allergic rhinoconjunctivitis or urticaria. Nevertheless, until paediatric indication is submitted for marketing approval, the use of bilastine in this paediatric population subset is not recommended.

The information collected in elderly patients also does not raise any important concerns. In the post-marketing surveillance, one hundred and sixty five (165) adverse reactions were reported in seventy (70) individual safety reports. One hundred and seventeen (117) adverse reactions were considered non-serious, and forty eight (48) adverse reactions were reported as serious. Under SOC cardiac disorders, ten (10) serious adverse reactions were reported (Extrasystoles 5; Tachycardia 3; Atrial fibrillation 2). These adverse reactions occurred in the context of patients with cardiac comorbidity (arrhythmia, hypertension) or concomitant medication that might have been associated to the events reported. The safety profile in this population subset of patients (≥65 years of age) is not different from that observed in the adult and adolescent populations, and it is consistent with the data observed in the post-authorization study performed in elderly patients. One hundred and fifty one (151) patients were included in this study, 150 patients in the safety population, and 146 patients in the modified safety population (excluding 4 patients 64 years old at the time of study inclusion). A total of 75 patients reported 131 TEAEs during the study period. All TEAEs were considered from mild to moderate intensity by the investigators. With regards to the most frequently reported TEAEs, these were nasopharyngitis, urinary tract infection and contusion reported by 5 patients each, and back pain and somnolence by 4 patients each. Only 8 out of the 131 TEAEs reported were considered related to Bilastine 20 mg. Regarding adverse events included in the Product Information of Bilastine (safety profile), somnolence was reported by 4 patients with a common frequency (≥ 1/100 to < 1/10), whilst dry mouth, dyspepsia, epigastric discomfort (stomach discomfort) and fatigue were reported by one patient each with an uncommon frequency (≥ 1 / 1000 to < 1/100), all matching the incidence described in the Product Information. A total of 5 serious TEAEs were reported by 3 patients. All of them were considered of moderate intensity, but none was related to the study medication. Based on the study results, the incidence of adverse events in patients ≥ 65 years old with either allergic rhinoconjunctivitis and/or urticaria who, following the usual clinical practice, took Bilastine 20 mg showed a favourable safety profile with a low incidence of treatment emergent adverse events (TEAEs) in accordance with results from previous studies and within the safety profile and incidence of adverse reactions described in the approved Product Information.

There are no data available on the use of bilastine in pregnant women and lactating women and it is unknown whether bilastine is excreted in human milk.

Overall, the safety findings collected during about 4 years of world-wide marketing experience have confirmed the optimal safety and tolerability profile found in clinical studies.

Nervous system and psychomotor performance

As mentioned earlier, the highest incidence of drug related adverse events is a result of mild changes in the CNS [23].The most common (higher than 0.5 %) in both the bilastine 20 mg group and in the placebo group were:

- Headache (3.7% versus 3.4%)
- Drowsiness (3.5% versus 2.9%)
- Lethargy (0.9% versus 1.3%)
- Dizziness (0.1% versus 0.6%)

In preclinical studies, bilastine administered at high doses did not alter any of the parameters that characterize the behaviour of the animals assessed in specific assays of motor activity and coordination. In addition, studies on tissue distribution using radiolabelled molecule ([14 C]-bilastine) in whole body autoradiography showed that measurable levels of radioactivity were not detected in the brain or spinal cord of rats, a fact that clearly demonstrates that bilastine has difficulty crossing the blood-brain barrier (BBB) in experimental animals [24] .

From a clinical perspective, the safety of bilastine in the CNS has been evaluated in all the clinical trials (with more than 3,500 patients treated). No statistically significant differences have been found between any bilastine dose and placebo. However, in some cases important and significant differences were found between bilastine and cetirizine and hydroxyzine, particularly in relation to drowsiness and lethargy.

At a therapeutic dose of 20mg/day Bilastine does not significantly affect psychomotor performance, it does not enhance the depressant effect of alcohol or lorazepam, nor does it affect the ability to drive. Also, Bilastine 40 mg/day, does not significantly affect the ability to drive under real conditions.

Cardiac safety

Changes in cardiac repolarisation caused by certain antihistamines (terfenadine, astemizole) have been related to their ability to inhibit the potassium ion currents in the myocardium, and in particular the so-called delayed rectifier potassium current (IKr), which cardiac action potential depends on.

This inhibition can alter repolarisation and prolong the duration of the QT/QTc interval on ECG, which is the biggest predisposing factor for this type of arrhythmia[25]. The IKr current depends in turn on several potassium channel subtypes most notably those encoded by the hERG gene. Bilastine shows very low potency for blocking this channel (IC50=6.5 μM), while that obtained with cetirizine, albeit low, is about four times higher(IC 50 =1.1 μM). The corresponding potency of fexofenadine to inhibit the hERG channel (IC 50 = 12 μM) is even lower than that obtained with bilastine.

10. Potential for abuse or misuse.

Appendix 4. (Scaglione, 2012)

The abuse potential for Bilastine is in line with second generation antihistamines Pharmacy only medicines currently available in New Zealand. The s econd generation non-sedating antihistamines are less likely to be abused than sedating antihistamines, although data on this issue is limited.

Buckley et al (1994) reported on all cases of antihistamine poisoning admitted to Newcastle Hospital Warratah NSW over 6 years; Non-sedating antihistamines accounted for only 2.4% of admissions [26].

The risk of inappropriate use for Bilastine is in line with the s econd generation antihistamine Pharmacy only medicines currently available in New Zealand.

No reports of off label use have been received.

Conclusion

Bilastine is a H1-receptor antagonist, the same pharmaceutical mechanism of action as other Pharmacy only classified medicines in New Zealand.

The Benefit/Risk ratio for Bilastine has been shown through clinical trials to be equivalent, and potentially superior in terms of sedation, to second generation products such as cetirizine which are currently classified in New Zealand as Pharmacy only medicines.

PSUR data across a large patient exposure of more than twenty-two million support the clinical trial safety data of Bilastine.

Bilastine received regulatory approval from the Medsafe recognized authorities of Germany and the United Kingdom in 2010. Bilastine has been approved and available for a period greater than three (3) years.

For these reasons we propose Bilastine is to be classified Pharmacy Only.

Appendix 4. (Scaglione, 2012)

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Appendix 4. (Church, 2011)

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