Executive Summary

Bilastine is a non-sedating antihistamine (second generation) with a strong safety profile which is marketed in around 100 countries around the world.

In New Zealand, bilastine is already a pharmacy medicine in solid dosage forms containing up to 20 mg in up to 30 dosage units, since 2015. We are proposing a minor wording change that aligns with the other non-sedating antihistamines, and would remove the upper limit of dosage units able to be provided as a pharmacy-only medicine.

Other non-sedating antihistamines have no upper limit as pharmacy-only medicines. Pharmacy staff and the public are very familiar with these medicines, and the indications (allergic rhinoconjunctivitis and urticaria) are already self-managed in adults and children. Furthermore, misuse and abuse does not occur with non-sedating antihistamines, they have an excellent tolerability profile, and they do not mask underlying conditions or have concerning contraindications, precautions or drug interactions.

The rationale for not having a maximum pack size is two-fold. The first is that it allows consumers to get a better price for a treatment they will often need to use for two to four months over the spring and summer period. The second is that allergic rhinitis runs in families, and a pack of 30 tablets would not last long in the middle of hayfever season in a family of five adults and teenagers.

Part A Changes Proposed

1. International Non-proprietary Name of the medicine.

   Bilastine

2. Proprietary name(s).

   Labixten®

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

   A. Menarini New Zealand Pty Ltd

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

   Solid dosage forms up to 20 mg.

5. Proposed pack size, storage conditions and any other qualifications.

   The only proposed change for the classification statement is to remove the maximum pack size as a pharmacy-only medicine, in line with other non-sedating antihistamines.

6. Indications for which change is sought.
   As currently classified, for the treatment of the symptoms of allergic rhinoconjunctivitis (seasonal and perennial) and urticaria.

7. Present classification of the medicine.

   Pharmacy only medicine: in divided solid dosage forms for oral use containing 20 milligrams or less for the treatment of the symptoms of allergic rhinoconjunctivitis (seasonal and perennial) and urticaria when sold in a pack containing not more than 30 dosage units

8. Classification sought:

   Pharmacy only medicine: in divided solid dosage forms for oral use containing 20 milligrams or less for the treatment of the symptoms of allergic rhinoconjunctivitis (seasonal and perennial) and urticaria.

   Note: This statement is more aligned with the pharmacy-only classifications for other non-sedating antihistamines, loratadine, fexofenadine and cetirizine.

   Loratadine, fexofenadine and cetirizine include “for oral use” for their pharmacy only medicine classification, with no maximum pack size. All of these three antihistamines have an exception from pharmacy-only for specific dosage forms, strengths and pack sizes for general sales. We are not applying for general sales status in this application.

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

   Bilastine is a prescription medicine in Canada, UK, and Europe. Bilastine is not yet registered in Australia and the United States of America. It has non-prescription status in Malaysia, Thailand, Cambodia, and Turkmenistan.

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

    Labixten® (bilastine) was registered in New Zealand on 9 February 2018, and launched in June 2018. In NZ around [redacted] have been distributed to date.

    The international birthdate of bilastine was 8 Sep 2010 when it was authorised in Europe under the decentralised procedure. Additional to the 28 countries of the European Union, bilastine is registered in 89 countries. It is not yet registered in Australia and the United States of America, but it is registered in Canada.

    In May 2019 it was reported that worldwide [redacted]. [

11. Local data or special considerations relating to New Zealand (if applicable)

    Bilastine 20 mg tablets were registered in New Zealand on 9 February 2018, and marketed since June 2018.

    Other second generation H1 antagonists on the NZ market, and their classification wording are in Table 1 below. Please note that all other non-sedating antihistamines have no pack size restrictions in the pharmacy only medicine classification.

Table 1 - Classification Statements for the non-sedating antihistamines available in New Zealand, and the proposed bilastine statement

	Prescription	Pharmacy-only	General Sales
Loratadine	**except** when specified elsewhere in this schedule	for oral use; **except** in divided solid dosage forms for oral use containing 10 milligrams or less per dose form for the treatment of seasonal allergic rhinitis when sold in the manufacturer's original pack containing not more than 10 days' supply	in divided solid dosage forms for oral use containing 10 milligrams or less per dose form for the treatment of seasonal allergic rhinitis when sold in the manufacturer's original pack containing not more than 10 days' supply
Desloratadine	**except** for oral use	for oral use	
Fexofenadine	**except** for oral use	for oral use **except** for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when in capsules containing 60 milligrams or less of fexofenadine hydrochloride or in tablets containing 120 milligrams or less of fexofenadine hydrochloride with a maximum daily dose of 120 milligrams when sold in the manufacturer's original pack containing 10 dosage units or less and not more than 5 days' supply	for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when in capsules containing 60 milligrams or less of fexofenadine hydrochloride or in tablets containing 120 milligrams or less of fexofenadine hydrochloride with a maximum daily dose of 120 milligrams when sold in the manufacturer's original pack containing 10 dosage units or less and not more than 5 days' supply
Cetirizine	**except** for oral use	for oral use **except** in divided solid dosage forms for oral use containing 10 milligrams or less of cetirizine hydrochloride per dose form for the treatment of seasonal allergic rhinitis when sold in the manufacturer's original pack containing not more than 5 days' supply	in divided solid dosage forms for oral use containing 10 milligrams or less of cetirizine hydrochloride per dose form for the treatment of seasonal allergic rhinitis when sold in the manufacturer's original pack containing not more than 5 days' supply
Levocetirizine	**except** for oral use	for oral use	
Bilastine	**except** when specified elsewhere in this schedule	in divided solid dosage forms for oral use containing 20 milligrams or less for the treatment of the symptoms of allergic rhinoconjuctivitis (seasonal and perennial) and urticaria when sold in a pack containing not more than 30 dosage units	
Bilastine - proposed	**except** when specified elsewhere in this schedule	in divided solid dosage forms for oral use containing 20 milligrams or less for the treatment of the symptoms of allergic rhinoconjunctivitis (seasonal and perennial) and urticaria	

Source: Medsafe website, accessed 25 June 2019

12. Labelling or draft labelling for the proposed new presentation(s).

    The labelling would not change as the product remains a pharmacy-only medicine. The current labelling is attached.

13. Proposed warning statements (if applicable).

    No change. The current label is attached.

    The pack warning says the following:

    Consult your doctor or pharmacist if:
    - You are pregnant or trying to become pregnant
    - You have kidney problems
    - After taking Labixten symptoms persist.

    A warning is also included on driving (as required in the Medicines Regulations, see below):

    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.

14. Other products containing the same active ingredient(s) and which would be affected by the proposed change.

    Nil

Part B:
Evidence supporting the classification change proposal including benefit-risk analysis.

Bilastine is a non-sedating long-acting second-generation antihistamine with selective peripheral H1 receptor antagonist affinity and with no apparent affinity for muscarinic receptors. It has a good efficacy and tolerability similar to placebo.[1]

Antihistamines have long been available without a prescription, initially as first-generation sedating antihistamines e.g. diphenhydramine, chlorpheniramine, promethazine and triprolidine. With the arrival and reclassification of second-generation antihistamines, the first-generation antihistamines have largely fallen out of favour for the treatment of allergies given the lack of sedation particularly.[2]

Non-sedating (second-generation) antihistamines are very similar across the group with a few differences in pharmacokinetics (e.g. duration of action and absorption).[2] The key potential concern for this group is QT prolongation, compounded by drug interactions. Terfenadine and astemizole were upscheduled in NZ to prescription only during the 1990s for this reason. Similar to certain other second generation antihistamines listed below,[1, 2] no clinically relevant prolongation of the QTc interval or any other cardiovascular effect has been observed for bilastine in clinical trials, including studies of up to 220mg per day.[3] Such products are generally considered safe for self-medication, with the following oral medicines classified as non-prescription in various countries:

- Loratadine
- Desloratadine
- Fexofenadine
- Cetirizine
- Levocetirizine
- Ebastine

In some countries, reclassification may not have been applied for, e.g. ebastine in NZ.

Many other second generation H1 antagonists are available without prescription in multiple countries as eye or nasal preparations.

1. Indications and dose

Bilastine is used for symptomatic treatment of allergic rhino-conjunctivitis (seasonal and perennial) and urticaria. The current classification statement allows use in all licensed indications, and this application is also for all licensed indications.

Allergic rhinitis, seasonal or perennial, and urticaria have long been OTC indications in NZ and elsewhere. As a pharmacy medicine, guidance will remain available in the pharmacy. Pharmacists and pharmacy assistants are well-informed on these conditions. NZ sufferers of these conditions are generally used to self-management of these conditions, with advice from pharmacy staff and/or their doctor as required. For allergic rhinoconjunctivitis, antihistamines have been available as OTC medicine for decades, and nasal corticosteroids became available without prescription over 20 years ago. Topical products and systemic antihistamines have been available for urticaria for decades as well. There is no additional risk to consumers in terms of diagnosis and management with removing the maximum pack size for bilastine given the long history of self-management with similar products.

The treatment population is adults and adolescents over 12 years of age with allergic rhino-conjunctivitis or urticaria.

The dose is:

- 20 mg once daily in adults and adolescents over 12 years of age.

2. Presentation

Bilastine is currently classified as pharmacy only for solid dosage forms up to 20 mg in a pack of up to 30 dosage units. It is currently presented as tablets, with the same strength for both indications.

It is proposed to seek greater alignment of the pharmacy medicine classification with other non-sedating antihistamines to allow larger packs to be sold as a pharmacy-only medicine.

The treatment population remains the same as the current classification statement.

There is no special consideration around disposal different to any other antihistamine that would affect the non-prescription availability. Bilastine use in patients has no environmental concerns.[4]

The proposed presentation (tablets taken once daily) is practical and easy to use, as is currently the case.

3. Consumer benefits

The benefit of a greater pack size is to provide a choice to the consumer for this product, allowing them to treat more of their family members for longer and to be able to make some likely cost savings. This is in line with other non-sedating antihistamines.

Bilastine was first registered in 2010. Since then it has been registered in 117 countries, and marketed in 99 countries, many of which have good pharmacovigilance systems. It was reclassified to pharmacy medicine in NZ in 2015, but only launched in NZ in 2018.

Bilastine is an effective antihistamine with a long duration of action (26 hours) and once daily dosing that is suitable for a wide range of people. Patterson's Allergic Diseases [2] reports an onset of action of 1 hour versus 2 hours for some other OTC non-sedating antihistamines. The tolerability profile is very good, and Patterson's Allergic Diseases [2] and the Summary of Product Characteristics (SMPC) from the UK [3] reports clinically relevant QT prolongation has not been seen, even at very high doses. Studies indicate no cognitive impairment [5, 6], and better performance in this regard than cetirizine [5] and there is no additional CNS effects with alcohol or with lorazepam [7, 1].

Allergic rhinitis and urticaria can cause considerable discomfort and affect quality of life, and it is important to have a choice of agents to aid optimal self-management. Oral bilastine has a faster onset of action than some other second-generation anti-histamines, [2] and a lower risk of cognitive impairment than cetirizine [8] providing potential useful benefits for some patients. Quality of life in rhinitis sufferers improves with bilastine usage [9].

4. Contraindications and precautions

Bilastine is in a well-known class of drugs which generally have good tolerability and few contraindications and precautions. It does not have a low therapeutic index.

The pack warning says the following:

Consult your doctor or pharmacist if:

- You are pregnant or trying to become pregnant
- You have kidney problems
- After taking Labixten symptoms persist.

A warning is also included on driving (as required in the Medicines Regulations, see below):

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.

A consumer leaflet is available at www.labixten.co.nz.

The only contraindication is hypersensitivity to the active ingredient or excipients. This is a usual contraindication for non-prescription medicines.

The precautions are:

- Not to use bilastine 20 mg tablets in children under 12 years of age Note: this has been managed through packaging.
- Avoid use with p-glycoprotein inhibitors (e.g. ketoconazole, erythromycin, cyclosporine, ritonavir or diltiazem) in patients with moderate or severe renal impairment as they may increase plasma levels and therefore risk of adverse effects of bilastine. Note: this has been managed through the precaution on the label regarding seeing the pharmacist or doctor regarding kidney problems.
- Although this medicine is unlikely to affect the ability to drive or operate machinery, a few people may be impaired and care should be taken.
    - Whilst this precaution did not arise from the evaluation of bilastine safety data, Medsafe requires this warning for all non-sedating antihistamines under Medicines Regulations 1981 [regulation 13(1)(i)].

These precautions are on the packaging and straight-forward to understand. They are commonly seen on other non-prescription medicines.

Food significantly reduces the oral bioavailability of bilastine by 30% (high fat meals or grapefruit juice) for tablets. [3] Therefore, it is recommended to be taken one hour before or two hours after the intake of food or fruit juice. This is on the packaging. There is no risk to the consumer of taking it with food or grapefruit juice, except to be less effective.

The clinically non-significant drug interactions with ketoconazole, erythromycin, and diltiazem are discussed in the SmPC [3] attached, and it is noted that these “do not appear to affect the safety profile of bilastine”. However, note the precaution in people with moderate to severe renal impairment mentioned above.

These interactions are comparable to those of other non-prescription non-sedating antihistamines. Like bilastine, fexofenadine is also a substrate for p-glycoprotein and OATP, and Stockley’s Drug Interactions [10] reports that the effect of ketoconazole on fexofenadine is to increase the plasma concentration by 2.4 fold and the AUC by 2.6

fold. In comparison, ketoconazole with bilastine causes an increase of 81% in the AUC and 2.5 fold increase in maximum plasma concentration of bilastine[10].

Like other available second-generation antihistamines, bilastine has a wide therapeutic index with doses 220 mg as a single dose or 200 mg daily for seven days in healthy volunteers without serious adverse events.[3] No clinically relevant prolongation of QTc interval or other cardiovascular effect has been observed in clinical trials even at these doses or when coadministered with PGP inhibitors e.g. ketoconazole or erythromycin, or in a thorough QT/QTc cross-over study.

A potential class effect is QT prolongation with terfenadine and astemizole (both are no longer marketed for this reason) which has been investigated thoroughly as above for any of this class of drugs remaining on the market. Terfenadine and astemizole had significant cytochrome P450 drug interactions which contributed to this problem,[2] while bilastine is largely unmetabolized. [3]

There are no additional risks from the proposed widened access which simply allows a larger pack size to be provided. This would be similar to a person getting non-sedating antihistamines on prescription when they would be prescribed 90 tablets, or purchasing other non-prescription non-sedating antihistamines in the pharmacy.

There are no restrictions on driving. Bilastine is a non-sedating antihistamine, and even did not affect the ability of patients to perform in a Formula 1 car simulation test [11]. Whilst no effect has been seen by bilastine, Medicines Regulations 1981 [regulation 13(1)(i)] require the carton to contain the following precaution: Although this medicine is unlikely to affect the ability to driver or operate machinery, a few people may be impaired and care should be taken.

In phase II and III studies, patients 65 years or older had no difference in efficacy or safety than younger people.[3]

5. Undesirable effects

Bilastine is well-tolerated. See the attached Summary of Product Characteristics from the UK for the full list of adverse reactions and frequency.[3] The Summary of Product Characteristics states: “The incidence of adverse events in patients suffering from allergic rhinoconjunctivitis or chronic idiopathic urticaria treated with 20 mg bilastine in clinical trials was comparable with the incidence in patients receiving placebo (12.7% versus 12.8%).”[3]

Bilastine is not subject to any significant safety concerns, or withdrawals from markets for safety reasons. It does not have any withdrawal effects.

6. Overdose

In doses of 200 mg per day for 7 days or 220 mg as a single dose in healthy volunteers no serious adverse events or significant prolongation of the QTc interval were reported.[3] While there is limited experience with overdose (Appendix 1), overdose should be no more likely than with other non-sedating antihistamines.

Should overdose occur, there is no antidote, symptomatic and supportive treatment is recommended.[3]

7. Medication errors and abuse/misuse potential

Reclassification should not increase the risk of unnecessary use. It is hard to find reasons why someone would treat themselves with bilastine if they did not have allergic rhinoconjunctivitis or urticaria. If unsure, pharmacy staff would help a person identify if they had an allergic basis to their symptoms.

The wording change proposed to the classification will make little difference to import considerations.

There is no known addiction potential of the medicine.

The reports of medication error, abuse, misuse, accidental overdose are in Appendix 1, these are confidential.

8. Communal harm and / or benefit

There is no known or expected communal harm or benefit from widening the classification wording.

9. Integrated benefit-risk statement

The benefits of the proposed change in wording over the current wording are simply patient convenience and choice with an alignment of the bilastine classification statement to other non-sedating antihistamines currently supplied in NZ. Widening the classification wording is expected to benefit the community, and prevent unnecessary barriers for families who cannot go to a pharmacy every week or so during hayfever season.

There is no additional harm expected over the current classification.

Allergic rhinoconjunctivitis and urticaria are self-treated conditions, having multiple options of effective treatments in different forms provides choice and convenience and is in line with the benefit-risk profile of this medicine.

This change is in-line with the pharmacy-only classifications of other non-sedating antihistamines.

10. Risk mitigating strategies

There is little change from the current classification, only removal of the pack size restriction. The pharmacy staff will be able to provide guidance with a pharmacy-only medicine.

No post-market surveillance activities will be carried out above the usual pharmacovigilance activities.

This is a minor wording change to align with other products within the same therapeutic area, with minimal consequences for health professionals, and therefore we have not consulted with professional bodies.

Summary

This is a very straight-forward request to remove the maximum pack size from the bilastine pharmacy-only classification statement. This request is in line with other non-sedating

antihistamines currently available in NZ. Bilastine belongs to a group of medicines with excellent tolerability, and abuse and misuse are unlikely.

References

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