Application to the Medicines Classification Committee to widen the classification for bilastine to include all oral forms

Executive Summary

Bilastine is a non-sedating antihistamine used in adults and children from 6 years (minimum 20kg weight). It has the licensed indications of symptomatic treatment of allergic rhino-conjunctivitis (seasonal and perennial) and urticaria.

It is currently a 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.

The Medicines Classification Committee in late 2022 agreed this classification remained appropriate to allow pharmacy-only access for a new application for bilastine children's orodispersible tablets.

To allow other children's formulations to be available without prescription, e.g. liquids, and to align the pharmacy-only classification with other non-sedating antihistamines in New Zealand, this application seeks to change the pharmacy-only wording to "for oral use", and leave the strength and indications to the product labelling.

There is no additional risk from this classification because it does not change who is eligible for pharmacy-only access. However, it has the benefit of choice for the consumer who may desire a liquid formulation. It also has the benefit of alignment across all marketed non-sedating antihistamines for the pharmacy-only category, which is logical.

Part A

1. **International Non-proprietary Name of the medicine**

   Bilastine.

2. **Proprietary name (s)**

   Bilastine is marketed in New Zealand under the brand name Labixten.

3. **Name of company/organisation/individual requesting reclassification**

   A. Menarini New Zealand Pty Ltd

   4 Whetu Place

   Rosedale

   Auckland 0632

   Ph: 0800 102 349

   A.Menarini New Zealand is the sponsor of Labixten.

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

   Dose form: oral formulations.
   No strength change – note: no strength is on the classification statement for the pharmacy-only availability for other non-sedating antihistamines, but only in the exception from pharmacy-only, ie general sales. We propose following this same wording of "for oral use" for the pharmacy-only classification without specifying the strength.

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

   It is recommended that there are no qualifications included in the classification statement for pharmacy-only availability, in line with other non-sedating antihistamines, but suggest these are managed in product registration.

   Pack size is not currently in the classification statement, and we do not recommend a pack size be added to this statement.

6. **Indications for which change is sought**

   Bilastine has the licensed indications of symptomatic treatment of allergic rhino-conjunctivitis (seasonal and perennial) and urticaria.

However, in line with other non-sedating antihistamines, it is proposed that the indications are not included in the classification statement but managed through the product licence.

7. Present classification of the medicine

The wording as at the time of this application preparation is as follows:

Prescription: except when specified elsewhere in the schedule

Pharmacy only: 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.

At the 69th Medicines Classification Committee meeting, when considering the current classification in light of a new medicine application for a child formulation, the minutes recommended the current classification remain, allowing a bilastine solid oral dose formulation for children in the process of registration to be marketed as a pharmacy medicine.

8. Classification sought

To allow for patient choice and convenience and alignment with other pharmacy-only classification wording for other marketed second-generation antihistamines, we seek the following wording for the classification:

Pharmacy only: for oral use

The above classification would match the pharmacy-only entry for the other second-generation antihistamines (Table 1 below), and minimum age and indications would be managed by the product licence and labelling.

The below comparison (Table 1) is limited to second-generation oral antihistamines currently marketed in New Zealand. The five oral antihistamines concerned are all available without prescription for children. The wording varies for the general sales classification, but all are pharmacy-only medicines for oral use, with no limitations on indications, strength or formulation. Thus, liquid formulations for children are already marketed as pharmacy-only medicines

Table 1 - Classification of other second-generation oral antihistamines on the New Zealand market

Medicine	Pharmacy Only	General Sales
Loratadine	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	For oral use	N/A
Cetirizine	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	For oral use	N/A
Fexofenadine	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 20 dosage units or less and not more than 10 days' supply; for the treatment of seasonal allergic rhinitis in adults and

		children 12 years of age and over when in tablets containing 180mg or less of fexofenadine hydrochloride with maximum daily dose of 180 mg when sold in the manufacturer's original pack containing 5 dosage units or less and not more than 5 days' supply.

Source: Medsafe Classification Database, 20 September 2022

Other oral non-sedating antihistamines such as ebastine and epinastine are marketed as OTC medicines in some countries but are not marketed in New Zealand.

If, for some reason, the MCC does not wish to have alignment, an alternative would be: Pharmacy only: in dosage forms for oral use containing 20 milligrams or less per dose for the treatment of the symptoms of allergic rhinoconjunctivitis (seasonal and perennial) and urticaria.

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

Bilastine is OTC for adult use (or over 12 years) in various countries which include: Australia (pharmacist-only), Austria, Czech Republic, Germany, Poland, Lithuania, Switzerland, Russia, Moldavia Georgia, South Africa, Turkmenistan, Thailand and Malaysia and Latvia. It is a prescription medicine in Canada, it is not registered in the United States of America, and prescription only in the United Kingdom. Bilastine has not been submitted for reclassification in Canada or the United Kingdom, as decided by the market authorisation holder in these markets.

New Zealand is the first country to enable OTC status of bilastine for children. To our knowledge, other countries have been slower to apply for OTC status for children.

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

Bilastine 20 mg tablets were consented for the New Zealand market on 9 February 2018, and launched on the market around May-June in 2018. Bilastine 10 mg orodispersible tablets is in the process of evaluation for consenting for distribution in New Zealand, while bilastine 2.5 mg/mL oral solution is planned for a marketing authorisation application in the future.

[redacted]

[redacted]

Bilastine 20 mg tablets is licensed in 26 European countries, and 93 other countries including the United Kingdom, Canada, New Zealand, Singapore, Switzerland, Australia and Japan [redacted] The first countries to authorise bilastine were Spain, Sweden, the United Kingdom and Portugal in 2010.

Bilastine 10 mg orodispersible tablets (for children) is licensed in over 60 countries [redacted] The earliest authorisations occurred in 2017.

Bilastine 2.5 mg/mL oral solution (for children) is licensed in 26 European countries and 45 other countries including Canada, Switzerland and Singapore. [redacted] The earliest authorisations occurred in 2017 in European countries.

[redacted]

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

Non-sedating antihistamines are important non-prescription medicines used to treat allergic rhinitis and urticaria, conditions that are common worldwide, and particularly in New Zealand. Non-sedating antihistamines are well-known to the public and health care professionals in New Zealand, convenient in oral dosage forms, and are often used first-line by the public and health care professionals.

The New Zealand population is particularly affected by allergic rhino-conjunctivitis symptoms. For example 11% of children aged 6-7 years and 18% of children aged 13-14 years are affected[1]. This rate is similar to in the United Kingdom and Australia, but higher than most other countries. We are unaware of any national data indicating the prevalence of allergic rhinitis in Māori specifically.

Bilastine tablets were first marketed in New Zealand in 2018, providing an additional choice for patients over existing antihistamines. In 2022, the Medicines Classification Committee (69th meeting) agreed that the current classification with no age restrictions was appropriate with the upcoming registration of a bilastine formulation for children. To allow for introduction of a bilastine 2.5 mg/mL solution as a pharmacy-only medicine for patient convenience, particularly for children, we propose widening the classification statement. We recommend a statement "for oral use" to allow for liquid dosage forms, and align with other second-generation antihistamines for pharmacy-only classification.

Allergy medications available without prescription in New Zealand include oral, nasal and ocular antihistamines and nasal corticosteroids. Not all of these are OTC in children.

Pharmacists and pharmacy staff are very familiar with managing symptoms of allergic rhino-conjunctivitis and urticaria, as this has been a common reason for people to present in pharmacy for decades. Pharmacy students and pharmacy staff are very competent in distinguishing a cold from allergic rhinitis, and identifying urticaria and advising patients about the appropriate medication/s for them.

New Zealand consumers are also very familiar with safely self-managing symptoms of allergic rhino-conjunctivitis and urticaria for both themselves and their children; as evident by the long history of symptom-relieving medications being OTC and in grocery stores.

New Zealand consumers are likely to appreciate having a choice of second-generation antihistamine to use.

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

Draft labelling for the solution is attached. This is subject to being finalised before an application is made.

13. Proposed warning statements (if applicable)

The following warnings are included on the proposed packaging for the solution:

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

Do not take Labixten Syrup:

- If you are allergic to bilastine or any other ingredients in this medicine
- If you are under 6 years of age and/or weigh less than 20 kg

Consult a pharmacist or doctor if:

- If you have kidney problems
- If you are breastfeeding, pregnant or likely to become pregnant
- If symptoms persist or appear to worsen
- If you experience any side effects that concern you

Contains hydroxybenzoates and sucrolose

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

The affected products are mentioned above.

Part B

Reasons for requesting classification change including benefit-risk analysis

The Medicines Classification Committee considered solid oral formulations for bilastine in the 69th meeting with respect to a new bilastine product being registered for use in children. The committee recommended the current classification remain, allowing the children's formulation (10 mg orodispersible tablets) to be available as a pharmacy only medicine. However, the current classification is for oral solid formulations and does not allow for a liquid formulation, it is also inconsistent with the majority of non-sedating antihistamines in New Zealand in the wording used.

This present application would allow parents to have the choice of liquid or solid formulations for their children, when purchasing bilastine from the pharmacy. It would also allow a liquid formulation to be purchased for an adult who could not swallow a tablet. It would align the pharmacy-only availability wording with other non-sedating antihistamines "for oral use", e.g. for loratadine, fexofenadine, cetirizine, desloratadine (see Table 1 above).

Bilastine is a fast-acting non-sedating long-acting second-generation antihistamine with selective peripheral H1 receptor antagonist affinity and no affinity for muscarinic receptors. As such, bilastine is a similar medicine to other oral second-generation antihistamines marketed in New Zealand or elsewhere, e.g. loratadine, desloratadine, cetirizine, levocetirizine, fexofenadine, ebastine and epinastine. Bilastine is administered once a day for its licensed indications of symptomatic treatment of allergic rhino-conjunctivitis (seasonal and perennial) and urticaria.

The primary benefit of this reclassification is the provision of choice to New Zealand consumers suffering from a common and troubling condition for which they already self-treat themselves and their children.

Allergic rhinitis impairs quality of life, cognitive function, productivity, sleep and causes irritability and disruption[2]. In children, allergic rhinitis affects the quality of sleep, often resulting in day-time fatigue[3]. Increased distraction in class or absenteeism is increased by allergic rhinitis. A recent Australian study found that having allergic rhinitis significantly reduced ability to perform schoolwork and other activities, being significantly worse in those children who were not treating their allergic rhinitis[4].

For the use in children, the choice is important in terms of palatability including the ability to choose a syrup or an orodispersible tablet. Australian Market Research has shown that people like to try different antihistamines, but want their antihistamine to be non-drowsy, fast-working, effective, without side effects, once a day, reasonable in price and accessible (without prescription)[5]. Having multiple bilastine paediatric formulations available for children adds choice. Other research has confirmed people want efficacy, fast onset of action, safety and lack of side effects[2]. Bilastine delivers on these requirements, but needs to be available in multiple children's formulations to aid access.

The medicines and benefit-risk of the reclassification

1. **Indications and dose**

   Indications: Symptomatic treatment of allergic rhino-conjunctivitis (seasonal and perennial) and urticaria.

   Dosing:

   Children 6-11 years, who weigh at least 20 kg: 10 mg once a day as required to manage symptoms.

   Adults and adolescents (12 years of age and over): 20 mg bilastine once daily.

   Take one hour before or two hours after intake of food or fruit juice.

   No dosage adjustments are required in elderly patients.

   No dosage adjustment is required in patients with renal impairment.

   These indications and dosing are appropriate for pharmacy-only supply.

2. **Presentation**

   Bilastine tablets 20 mg

   Bilastine 10 mg orodispersible tablets with a recommended minimum age of 6 years and bodyweight of 20 kg.

   A second children's formulation of bilastine 2.5 mg/mL oral solution will be submitted to Medsafe in time with the same recommended minimum age and bodyweight.

3. **Consumer benefits**

   The primary benefit of this reclassification is the provision of choice to New Zealand consumers suffering from a common and troubling condition which they already self-treat for themselves and their children. The Medicines Classification Committee has already agreed that pharmacy-only status is suitable for children for whom this medicine is licensed. However, this is for solid dosage forms, and we request that the classification statement for bilastine is aligned with other non-sedating antihistamines, allowing the oral solution to be available as a pharmacy-only medicine.

   Allergic rhinitis is usually a long-term condition that may come at the same time every year. Consumers are very familiar with the condition and what works for them, while being interested in trying new medicines for the condition[5]. They are keen to have choice for safe self-management for themselves[5] and this is also likely to apply to their management of their children. Urticaria is a condition commonly presenting in the

pharmacy which will be familiar to many consumers who would reach for an antihistamine to manage it.

As outlined above, allergic rhinitis impairs quality of life, cognitive function, productivity, sleep and causes irritability and disruption[2]. In children, allergic rhinitis affects the quality of sleep, often resulting in day-time fatigue[3]. Increased distraction in class or absenteeism is increased by allergic rhinitis and having allergic rhinitis significantly reduced ability to perform schoolwork and other activities, particularly in those children who were not treating their allergic rhinitis[4]. Urticaria is also causes discomfort and is likely to disturb sleep.

Lyseng[6] reported that "[Bilastine] has a favourable pharmacological profile, with a rapid onset of action and sustained efficacy over the 24-h dosing interval period, as well as a lack of CNS and cardiotoxic effects and clinically relevant drug interactions. In clinical trials, the efficacy of bilastine in treating rhino-conjunctivitis and urticaria was greater than that with placebo and generally similar to that of other second-generation antihistamines, and the overall tolerability profile of bilastine was similar to that of placebo."

4. Contraindications and precautions

The only contraindication is hypersensitivity to bilastine or excipients – as is typical for these medicines.

From the UK Summary of Product Characteristics (17 May 2021) for bilastine solution is the following for precautions in the paediatric population:

Efficacy and safety of bilastine in children under 2 years of age have not been established, and there is little clinical experience in children aged 2 to 5 years, therefore bilastine should not be used in these age groups.

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

Labixten solution contains methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) which may cause allergic reactions (possibly delayed).

These minor precautions have been managed in the product labelling stating the product is not for use in children under 6 years or children weighing under 20 kg. It also recommends consulting a pharmacist or doctor if you have kidney problems. The packaging states that the medicine contains hydroxybenzoates and sucralose. Precautions are not particularly different whether the classification wording is changed to allow all oral formulations or not.

5. Undesirable effects

Please see the attached SMPC from the UK for the side effects. These are typical for non-sedating antihistamines, which are known to be well-tolerated.

There is no greater risk for adverse effects to consumers through the proposed change in classification, as the same patient population will be exposed.

Bilastine is a fast-acting non-sedating long-acting second-generation antihistamine with selective peripheral H1 receptor antagonist affinity and no affinity for muscarinic receptors. As such, bilastine is a similar medicine to other oral second-generation antihistamines marketed in New Zealand or elsewhere, e.g. loratadine, desloratadine, cetirizine, levocetirizine, fexofenadine, ebastine and epinastine. Bilastine is administered once a day for its licensed indications of symptomatic treatment of allergic rhino-conjunctivitis (seasonal and perennial) and urticaria. Bilastine was deliberately developed for a sustained 24-hour effect devoid of central nervous system and cardiovascular side effects, and convenient pharmacokinetics (i.e. rapid absorption, high bioavailability, prolonged half-life, and lack of hepatic metabolism).

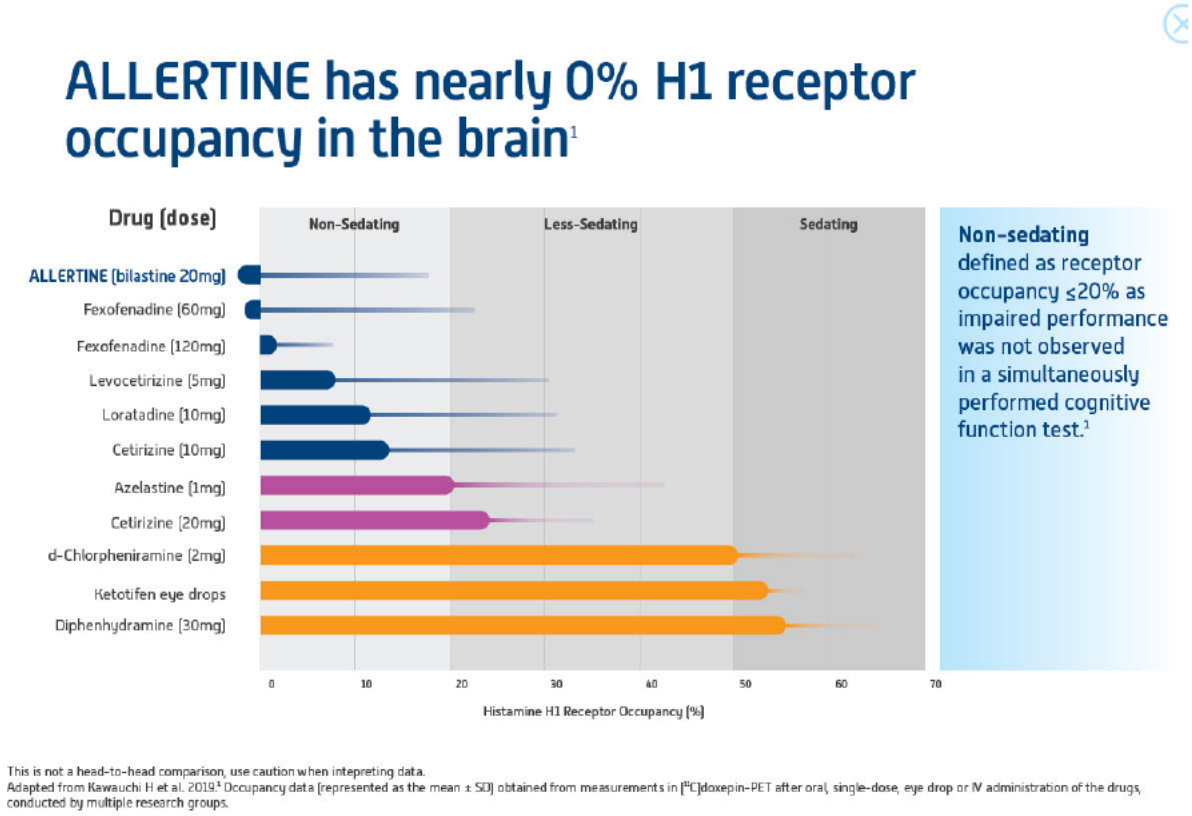
Lyseng[6] reported that "[Bilastine] has … a lack of CNS and cardiotoxic effects and clinically relevant drug interactions. In clinical trials, … the overall tolerability profile of bilastine was similar to that of placebo." Studies in children also show good tolerability that is not different from placebo. Serious adverse events occurred in 0.4% of those taking bilastine and 1.8% of those taking placebo but none was considered to be related to the study treatment (data on file).

The AUC and Cmax in children administered 10 mg bilastine are highly comparable to corresponding values in adults at the therapeutic dose of 20 mg, and far below the safety thresholds established for bilastine. There is a lack of age-related tendencies of bilastine pharmacokinetics. The drug does not accumulate.

Bilastine has a large therapeutic index. Administration of 220 mg as a single dose or 200 mg daily for 7 days to healthy volunteers was not associated with serious adverse events or significant prolongation in the QTc interval[7]. The cardiological safety of bilastine was proven in a thorough QT/QTc study performed according to ICH E142. Adverse effects were two times higher in frequency than with placebo, with dizziness, headache and nausea most frequently reported.

Brain H1 receptor occupancy (H1RO) has been used to help indicate potential for sedation[8]. Correlations are evident between proportional impairment ratio, incidence rate of sedative effects and H1RO measured by positron emission tomography. Bilastine and fexofenadine have the lowest brain H1 receptor occupancy of the second-generation antihistamines (Figure 1 below; adapted from Kawauchi et at, 2019), and therefore should have the lowest chance of sedation and impact on cognition[8].

Figure 1 - Brain histamine H1 receptor occupancy of various antihistamines and sedation classifications – adapted from Kawauchi et al, 2019



n.b. – "Allertine" refers to Labixten (bilastine) in New Zealand

Bilastine does not affect CNS function, cause driving impairment, or interact with alcohol[6]. The lack of effect on CNS function is important in children for managing school and activities.

It is important for patients (and parents) to have choices to treat allergic rhinitis and urticaria, both in terms of ingredient and formulation.

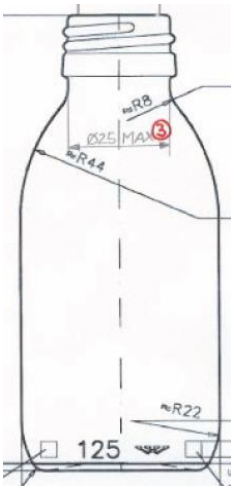
[redacted]

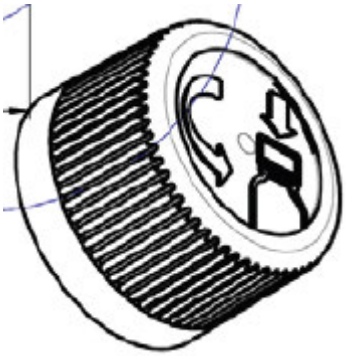
6. Overdose

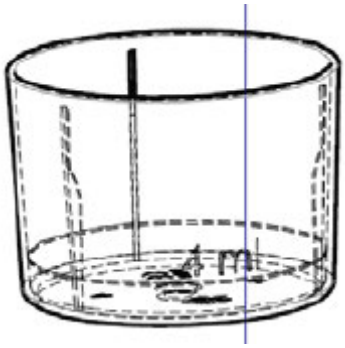
Widening the classification statement to all oral formulations would include liquid preparations, as for some other second-generation antihistamines on the market in New Zealand. There is not expected to be any greater risk of overdose for bilastine liquid than for other second-generation antihistamines.

The 2.5 mg/mL oral solution is packaged in an amber glass bottle (125mL, type III), sealed with a polypropylene child-proof cap, including a measuring cup.

The bottle is placed in a carton box.







Brimful capacity 130.5-136.5 mL

Dosage cup (25 mL, with 4 mL markings)

Bilastine has a wide therapeutic index, and the following information comes from the UK SMPC for bilastine liquid[9]:

There are no data for overdose in children.

Information regarding acute overdose of bilastine is retrieved from the experience of clinical trials conducted during the development in adults and the post-marketing surveillance. In clinical trials, after administration of bilastine at doses 10 to 11 times the therapeutic dose (220 mg as single dose or 200 mg/day for 7 days) to 26 adult 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. The information collected in the post-marketing surveillance is consistent with that reported in clinical trials.

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

In the event of overdose symptomatic and supportive treatment is recommended.

There is no known specific antidote to bilastine.

7. Medication errors and abuse/misuse potential

The liquid has a child-proof cap, it will be marketed in a pack of 125 mL and it has a measure contained in the packaging for accurate and easy dosing.

8. **Communal harm and/or benefit**

   Communal benefit is expected to arise from not needing to take a prescriber's time to arrange a prescription for a liquid bilastine formulation. General practitioners are in short supply and reducing unnecessary work for them is helpful.

   No communal harm is expected from this reclassification.

9. **Integrated benefit-risk statement**

   There is a benefit of choice, and no additional risk compared with the current situation with bilastine allowing children's oral solid dose formulations to be marketed as pharmacy-only medicines, and compared with other non-sedating antihistamines which are available as pharmacy-only medicines in oral liquid formulations.

10. **Risk mitigating strategies**

    The pack clear instructions about dosing and warnings and precautions.

    The liquid pack will have a child-resistant lid, and a measure for accurate dosing. The packaging notes to "Tighten cap after use to engage child resistant closure". It also includes the instruction: "Use the enclosed measuring cup to measure the dose correctly."

    The medicine has a large therapeutic index.

    New Zealanders are familiar with using non-prescription non-sedating antihistamines in liquid formulations.

    Pharmacy staff are familiar with bilastine and other non-sedating antihistamines and well able to provide advice where needed.

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

    There is no additional risk of harm to the consumer compared to the current situation of non-sedating antihistamines in liquid formulations being pharmacy-only medicines.

Summary

This reclassification application requests a minor change to the classification statement for bilastine that aligns with other non-sedating antihistamines, and with the benefit-risk profile of the medicine. We request that the pharmacy-only classification statement change to "for oral use" for bilastine.

References

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