# Proposal for Reclassification of

# Claratyne®

## Loratadine in Children 6 – 12 Years of Age

## Pharmacy Medicine to General Sales Medicine

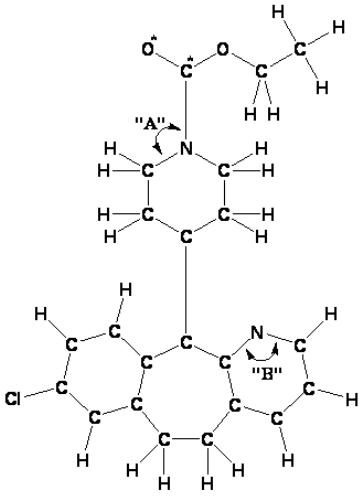
**January 2018**

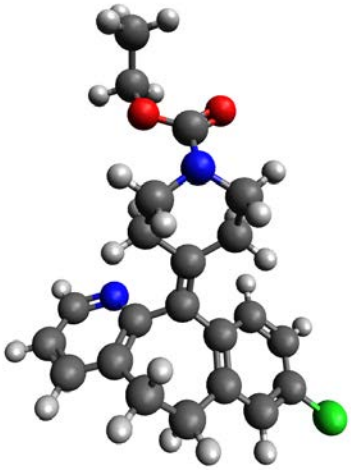
# INDEX

# PART A

## A1. Name of the Medicine

The International Non-Proprietary Name of the medicine is loratadine, which has the chemical formula $C_{22}H_{23}ClN_2O_2$.



The proprietary or brand name of the product in New Zealand is Claratyne® and Children's Claratyne®. In other countries the brand name Claritin® is also used.

## A2. Name of the Company

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## A3. Dose Forms, Strengths and Pack Sizes

The current classification of loratadine is:-

General Sale
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

Pharmacy Only
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

Prescription
Except where specified elsewhere

Medsafe further restricts the sale of loratadine as a General Sales medicine through the label statements database. The following warnings are required for loratadine as a General Sales Medicine (but not when it is distributed as a Pharmacy Medicine):-

- Do not use in children under 12 years old.
- Do not use for more than 5 days at a time.
- Do not use with other antihistamines.
- Do not use if you are pregnant except on the advice of a healthcare professional.
- Do not use if you are breastfeeding except on the advice of a healthcare professional.

These same warnings are required for cetirizine and fexofenadine when sold as General Sales Medicines. The warnings were required by MCC for fexofenadine when a General Sales option was recommended for this medicine at the 42nd meeting in November 2009.

Bayer New Zealand Limited currently markets Claratyne 10 mg tablets (packs of 30 and 60 tablets), Children's Claratyne 5 mg chewable tablets (packs of 10 and 30 tablets) and Children's Claratyne 1 mg/mL syrup (bottles of 100 mL [peach

flavoured] and 120 mL [grape flavoured]) within the Pharmacy Medicine classification available. Additionally, Claratyne 10 mg tablets (packs of 5 and 10 tablets) are currently marketed as General Sales Medicines.

The proposed reclassification can be summarised as requesting that the General Sales restriction on age be changed from "Do not use in children under 12 years old" to "Do not use in children under 6 years old".

In terms of dose form, strength and pack size, this proposal affects the Children's Claratyne range of chewable tablets, which contain 5 mg loratadine. Currently the range is labelled for children 2 – 12 years, whereas this proposal envisages creation of presentations labelled for children 6 – 12 years. The current pack size restriction of 10 days' supply is not proposed to change, meaning that only packs of 10 tablets would be available for General Sales supply.

## A4. Indications

The current approved indication for Children's Claratyne chewable tablets, as per the current label[1], is:-

**Who can use this product**
Adults Children 2 years and over

**Use this product for**
Rapid 24 hour relief from the symptoms of hayfever, year round allergies and chronic urticaria (hives). One daily dose provides relief from:

- Sneezing
- Watery, itchy eyes
- Runny nose
- Itchy rash (hives)

Labelling for the proposed General Sales Children's Claratyne 5 mg 10 pack presentation would be restricted to allergic rhinitis (not including chronic urticaria). The General Sales carton label[2] is proposed to state:-

Children 6+ years

**Use this product for**
Rapid 24 hour relief from the symptoms of hayfever allergy.

- Sneezing
- Watery, itchy eyes
- Runny nose

This modified indication for the General Sales presentation derives from a proposal regarding loratadine to the Medicines Classification Committee and considered at their meeting of November 2011 that the General Sales classification should only be for the indication of hayfever[3]. This current proposal includes maintaining the indication for a General Sales medicine as hayfever allergy only, and so represents no change to the indication for loratadine as a General Sales Medicine.

## ***A4.1 Dosage Recommendation***

The current dosage instructions on the carton label for Children's Claratyne chewable tablets[1], are:-

> How to use this product
>
> Age: Children 2 - 12 years:
> Up to 30 kg How much: 1 tablet Once daily as necessary
> Over 30 kg How much: 2 tablets Once daily as necessary
>
> Age: Adults and children over 12 years
> How much: 2 tablets
> How often: Once daily as necessary

An on-going project for Children's Claratyne chewable tablets, regardless of classification, is to change the basis of the children's dosage instructions from weight to age.

The Claratyne Children's products marketed in Australia and the United Kingdom has the same body-weight based dosing instructions as those currently used in New Zealand. In the United States of America, the recommended dose for a child 6 - 12 years of age is 10 mg loratadine daily. This USA dosing recommendation is based on the pharmacokinetic profile of a 10 mg dose of loratadine in children 6 - 12 years of age being similar to the pharmacokinetic profile of a 10 mg dose of loratadine in adults. The user experience in Australia, the UK and USA over 20 years suggests loratadine dosed by either body weight or age is efficacious and safe for children under 12 years of age.

In Australia, Merck submitted a rescheduling application for loratadine in children from 6 years of age during 2013 with a proposed weight-based dosage regime as currently approved. This rescheduling application was not successful, in part as the ACMS suggested that the body-weight dosage regimen for an unscheduled medicine might pose a risk of inappropriate dosing. To address this concern, a

new application in Australia, which was subsequently successful, proposed a clear age-based dosage regimen, based on the average body weight of Australian children at various age groups.

Accurate dosing for children is critical, especially in products with safety concerns such as analgesics. In Australia, the Medicine Evaluation Committee (MEC) and the latest TGA *Australian Regulatory Guideline for Over-the-Counter Medicines* (ARGOM)[4] have defined the average body weight of Australian children at various age groups to aid with accurate medicine dosing. According to the MEC/ARGOM data replicated below in Table 4, Australian children with an average body weight of 30 kg fall into the 9–10 years of age category.

**Table 1: Australian children age and body weight reference for accurate dosing of analgesics**

| Age | Average Body Weight (kg) |
|---|---|
| 1–3 months | 4–6 |
| 3–6 months | 6–8 |
| 6–12 months | 8–10 |
| 1–2 years | 10–12 |
| 2–3 years | 12–14 |
| 3–4 years | 14–16 |
| 4–5 years | 16–18 |
| 5–6 years | 18–20 |
| 6–7 years | 20–22 |
| 7–8 years | 22–25 |
| 8–9 years | 25–28 |
| 9–10 years | 28–32 |
| 10–11years | 32–36 |
| 11–12 years | 36–41 |

Similarly, the Australian Pharmaceutical Formulary and Handbook[5], an everyday guide for pharmacy practice, also states that Australian children with an average body weight of 30 kg fall between the 9 and 10 year age category (Table 2).

**Table 2: Australian children age and body weight reference for accurate dosing for pharmacy practice**

| Age<br>Last Birthday | Boys<br>Average Body Weight (kg) | Girls<br>Average Body Weight (kg) |
|---|---|---|
| Term | 3.3 | 3.2 |
| 2 months | 5.6 | 5.1 |
| 4 months | 7 | 6.4 |
| 6 months | 7.9 | 7.3 |
| 1 years | 9.6 | 8.9 |
| 2 years | 12.2 | 11.5 |
| 3 years | 14.4 | 13.9 |
| 4 years | 16.3 | 15.9 |
| 5years | 18.5 | 18 |
| 6 years | 20.8 | 20.3 |
| 7 years | 23.2 | 22.9 |
| 8 years | 25.8 | 25.8 |
| 9 years | 28.7 | 29.1 |
| 10 years | 32.1 | 33.1 |
| 11years | 36.1 | 37.4 |
| 12 years | 40.7 | 41.8 |
| 13 years | 45.8 | 46 |
| 14 years | 51.2 | 49.5 |

Given the relatively similar socio-economic and ethnic profiles of the Australian and New Zealand populations, it is reasonable to assume that the age-to-weight profile of New Zealand children is the same. This assumption is supported by the New Zealand Ministry of Health[6], who quote the average weight of 5 – 9 year olds in New Zealand is 28.3 kg for boys and 28.0 kg for girls.

Based on these references, Bayer proposes to change its current weight-based dosage regime (using 30 kg body weight as a decision point for either 1 tablet dosing [5mg loratadine] or 2 tablets dosing [10mg loratadine]) to an age-based dosage regime using the evidence above that New Zealand and Australian children weighing 30 kg will be, on average, 9.5 years old. Bayer will propose to Medsafe the following age-based dosing instructions for loratadine use in New Zealand, both for the current Pharmacy Medicine presentations and for future General Sales Medicines:

- Children 6-9 years of age: 5 mg/day
- Children over 9 years of age: 10 mg/day

Given this planned variation to the product, it is appropriate that the new dosage regime is taken into account as part of this proposal. Therefore, the dosage instructions for the proposed general sales Children's Claratyne presentations are:-

Age: Children 6 - 9 years:
How much: 1 tablet
How often: Once daily as necessary

Age: Adults and children 9+ years
How much: 2 tablets
How often: Once daily as necessary

This dosage regime is reflected in the proposed labelling[2].

## A5. Classification

The current classification of loratadine, taken from the Medsafe Web site on 6 November 2017, is:-

| | |
|---|---|
| Loratadine, except when specified elsewhere | Prescription |
| 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 | Pharmacy Only |
| Loratadine 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 | General Sales |

This proposal does not request changing the classification entry for loratadine in Schedule 1 of the Medicines Regulations i.e. the entry would remain as above. However, Medsafe further restricts over-the-counter classifications of loratadine through the Label Statements Database.

The labelling requirements for loratadine are:-

| Medicine/Group/Class | Conditions | Statements or requirements | Required by |
|---|---|---|---|
| **Antihistamines, non-sedating, loratadine/desloratadine**<br>Includes:<br>Desloratadine<br>Loratadine* | For oral use | • Some people might get drowsy on this medicine. You should make sure you are not affected before doing such activities that require full attention, such as driving or operating machinery.<br>[or]<br>• 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. | 1/08/2011 |
| | In cough and cold medicines | • Do not use in children under 6 years old.<br>• Consult a healthcare professional before using in children aged six years and over.<br>• Do not use with other antihistamines.<br>• Do not use with other medicines intended to treat the symptoms of the common cold except on the advice of a healthcare professional. | 1/08/2011 |
| **Loratadine** | When sold as a General Sale Medicine | • Do not use in children under 12 years old.<br>• Do not use for more than 5 days at a time.<br>• Do not use with other antihistamines.<br>• Do not use if you are pregnant except on the advice of a healthcare professional.<br>• Do not use if you are breastfeeding except on the advice of a healthcare professional. | 1/04/2014 |

This submission proposes that the label requirements for loratadine as a general sale medicine be changed to:-

> Do not use in children under 6 years old.
> Do not use for more than 5 days at a time.
> Do not use with other antihistamines.
> Do not use if you are pregnant except on the advice of a healthcare professional.
> Do not use if you are breastfeeding except on the advice of a healthcare professional.

Essentially, this proposal supports and embraces all of the current restrictions for the general sale of loratadine, with the only proposed change being that the age restriction on the General Sales medicine be reduced from "under 12 years old" to "under 6 years old".

In New Zealand loratadine was considered by the MCC several times between 1986 and 1997, with a recommendation for the product taken orally to be a Pharmacy Only medicine in 1990 (subsequent consideration did not find cause to change this decision). In 2011, MCC recommended that loratadine should be reclassified to a General Sale medicine when in packs containing sufficient tablets for five days' supply and when used for seasonal allergic rhinitis. This recommendation was subsequently extended to packs containing 10 days' supply in 2016. Thus, this proposal is a natural continuation of the established trend in New Zealand to further down-schedule loratadine, reflecting the on-going acceptance of loratadine as a safe and efficacious medicine suitable for self-treatment by consumers.

## ***A5.1 Classification Status in Other Countries***

Available global scheduling information indicates that loratadine is OTC in the majority countries considered similar to New Zealand[7]. Since January 2016, when global scheduling information was last presented to MCC by Bayer for loratadine, the following changes have taken place to this list:-

China – 10 mg orodispersible tablets and 5 mg granules added
Croatia – liquid at 1 m/mL has been added
Italy – maximum strength and maximum pack size restrictions removed
Norway – max. pack size increased from 10 tablets to 30 tablets
Netherlands – dosage changed from age-based to weight-based. Packs of 10 tablets as general sales medicines added.

The general sale classification details in overseas countries generally recognized by New Zealand are listed in the table below[7]:-

**Loratadine OTC/General Sale classification in other markets**

| Country | General Sale Classification Year | General Sale Classification details |
|---|---|---|
| Australia | 2012<br><br><br><br>2016<br>2017 | General sale approval for oral divided preparations for the treatment of seasonal allergic rhinitis, in adults and children aged 12 years and over. Maximum daily dose 10 mg. Maximum pack size 5 dosage units.<br>Maximum pack size increased to 10 tablets.<br>Age restriction reduced to 6 years and over. |
| Canada | 2002 | General sale approval for seasonal allergic rhinitis, perennial allergic rhinitis and chronic urticaria in children 12 years and over. |
| UK | 2002<br><br><br><br>2012 | General sale approval for tablets for the symptomatic relief of seasonal allergic rhinitis, perennial rhinitis, and chronic urticaria, in adults and children aged 2 years and over and weighing more than 30 kg. Maximum daily dose 10 mg. Max. pack size 7 tablets.<br>Maximum pack size increased to 30 tablets. |
| | 2012 | General sale approval for syrup for the symptomatic relief of seasonal allergic rhinitis, perennial rhinitis, and chronic urticaria, in adults and children aged 2 years and over. Maximum daily dose in adults and children weighing over 30 kg: 10 mg; maximum daily dose in children weighing 30 kg or less: 5 mg. Max. pack size 70 mg. |
| USA | 2002<br><br><br><br>2006 | Approved as OTC (equivalent to general sales in New Zealand) for the symptoms of hay fever or other upper respiratory allergies for tablets, orally disintegrating tablets (10 mg) and syrups. Syrups were approved to be used in children 2 years and over. No pack size limit.<br><br>Approved as OTC (equivalent to general sales in New Zealand) for the symptoms of hay fever or other upper respiratory allergies for chewable tablets and orally disintegrating tablets (5 mg) to be used in children 2 years and over. No pack size limit. |

Loratadine is available OTC in many countries. In 2 countries (Italy and Czech Republic) there is a pack size limit of 7 days' supply while in others the pack size limit is 10, 14, 30, 70 or unlimited[7].

In the UK, loratadine tablets have been available as an unscheduled medicine since 2002 in packs containing 7 dosage units for the symptomatic relief and treatment of seasonal allergic rhinitis, perennial allergic rhinitis and chronic urticaria in adults and children. The current unscheduled pack size limit for loratadine tablets is 30 dosage units when used for the symptomatic relief and treatment of seasonal allergic rhinitis, perennial allergic rhinitis and chronic urticaria in adults and children 2 years and over and weighing more than 30 kg. Liquid dosage forms are also available unscheduled for children 2 years and over with a pack size limit of 70 mg[7].

In the USA, loratadine was first approved for OTC use (equivalent to unscheduled in New Zealand) in 2002 in tablet (including orally disintegrating tablets) and syrup forms for children 2 years and over for hayfever or other upper respiratory allergies without pack size limitations. In 2006, loratadine in chewable tablets and orally disintegrating tablets (5 mg) was further approved for OTC use for when used in children 2 years and over for the symptoms of hayfever or other upper respiratory allergies without pack size limitation[7].

In Australia, Bayer submitted a re-scheduling proposal seeking to lower the age limit of the existing loratadine scheduling exemption from 12 to 6 years of age on 15 November 2016 i.e. essentially the same proposal that is the subject of this submission. At the time, unscheduled loratadine products for children from 12 years of age were limited to a maximum of 10 dosage units in Australia, and the submission proposed that unscheduled loratadine products for children between 6 and 12 years of age be limited to a maximum of 5 dosage units to minimise any potential risk to children in this age group. However, during evaluation of this proposal the delegates interim decision included increasing the pack size limit to 10 dosage units[8], and this recommendation was ultimately accepted (p58, p101)[9].

Clearly since the year 2000, there has been an ongoing world-wide trend to down-schedule loratadine, both for adults and for children. Bayer now seeks for New Zealand to follow this trend by making a general sales product for children aged 6 – 12 years available to New Zealand consumers.

# A6. Extent of Usage

## *A6.1 New Zealand*

Loratadine is a widely used product in New Zealand. Scan data from pharmacies gives the following sales volumes:-

| | | New Zealand Pharmacy | | |
|---|---|---|---|---|
| | | Total Loratadine (Adult & Children) | Total Loratadine (Children) | Total Loratadine (Adult) |
| Units | MAT To 01/11/15 | 191,505 | 26,877 | 164,628 |
| | MAT To 30/10/16 | 196,767 | 32,291 | 164,475 |
| | MAT To 29/10/17 | 187,334 | 31,662 | 155,672 |

These volumes need to be interpreted with some caution as pack sizes are not differentiated.

In the grocery sector, Bayer sales of Claratyne 10 mg tablets in packs of 5 totalled approximately $150,000 in 2015, and MAT to 30/4/17 was $357,314. Clearly, availability of the product in grocery has been a popular development with consumers who have rapidly adopted this new retail outlet for the product.

## *A6.2 World-Wide*

Total estimated sales volume for loratadine and loratadine combination formulations for the PSUR reporting period 02 Feb 2013 through 02 Feb 2016 was 8,289 million doses[10].

For the purposes of patient exposure estimation, for the loratadine tablet formulations, it was assumed that the average daily dose was 1 tablet per day. For the syrup/drops formulation, it was assumed that the average daily dose was 5 mL per day. Based on these assumptions, patient exposure for the reporting period was estimated as follows:

**Worldwide Patient Exposure to single ingredient Loratadine products from 2 February 2013 to 2 February 2016**

| Formulations | Distribution (dosage units) | Patient-Treatment Days | Patient-Treatment Years* |
|---|---|---|---|
| Tablets | 3,087,941,450 | 3,087,941,450 | 8,454,323 |
| Syrup/solution | 2,731,984,742 | 546,396,948 | 1,495,953 |
| Reditabs | 550,505,578 | 550,505,578 | 1,507,202 |
| Capsule | 136,061,565 | 136,061,565 | 372,516 |
| Powder | 7,090,550 | 14,181,100 | 38,826 |
| Oral Drops | 2,409,150 | 481,830 | 1,319 |
| **Total** | | **4,335,568,471** | **11,870,139** |

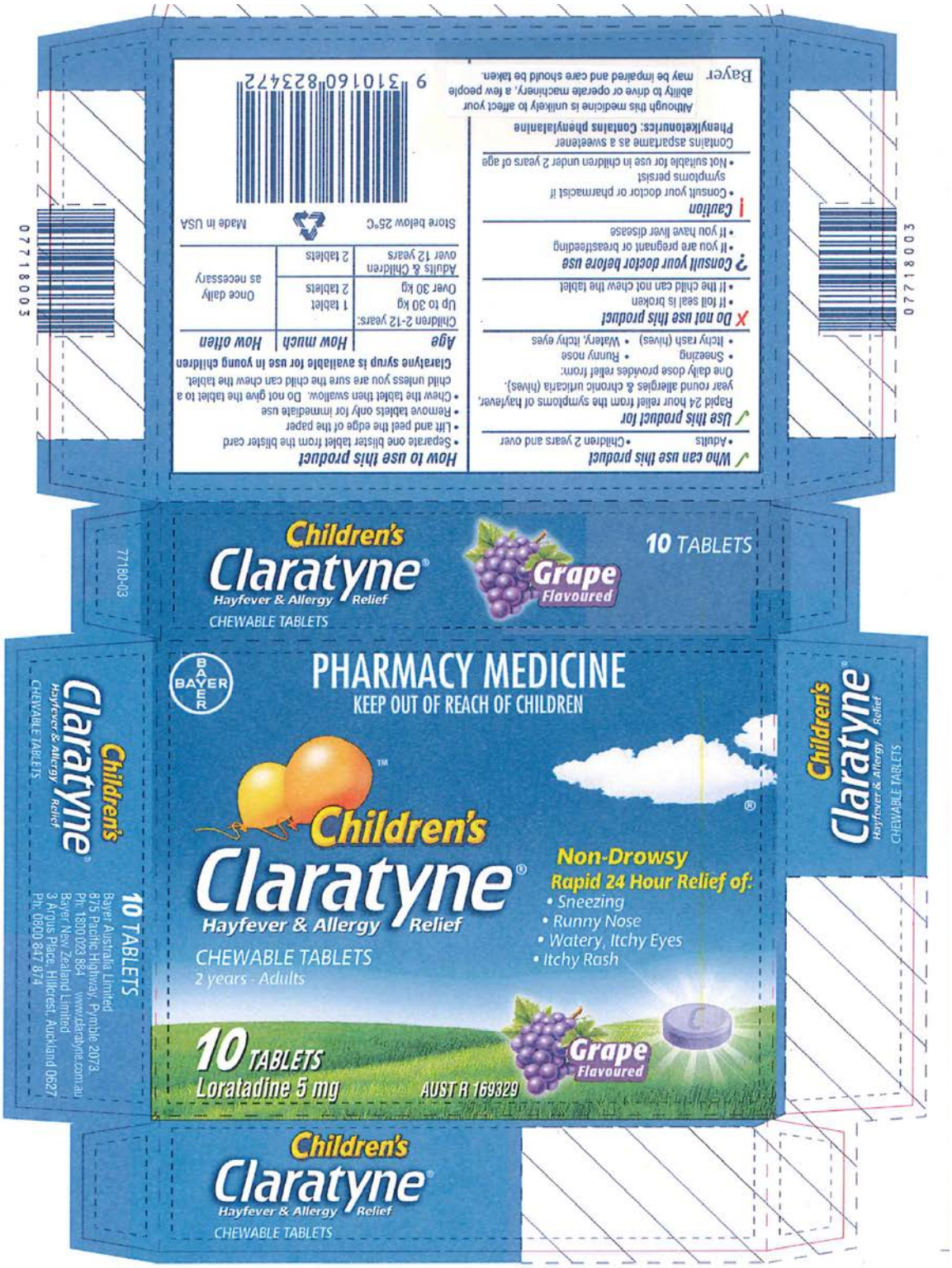
* Patient-treatment years = patient-treatment days / 365.25.

Total worldwide patient exposure for all loratadine oral formulations (including combination products) for the reporting period was estimated to be 5,546,106,023 patient-treatments days or 15,184,409 patient-treatment years. This represents an approximate usage of over five million patient-treatment years per annum. Clearly, loratadine is extensively used world-wide making the efficacy, adverse event profile and safety of this product very well understood.

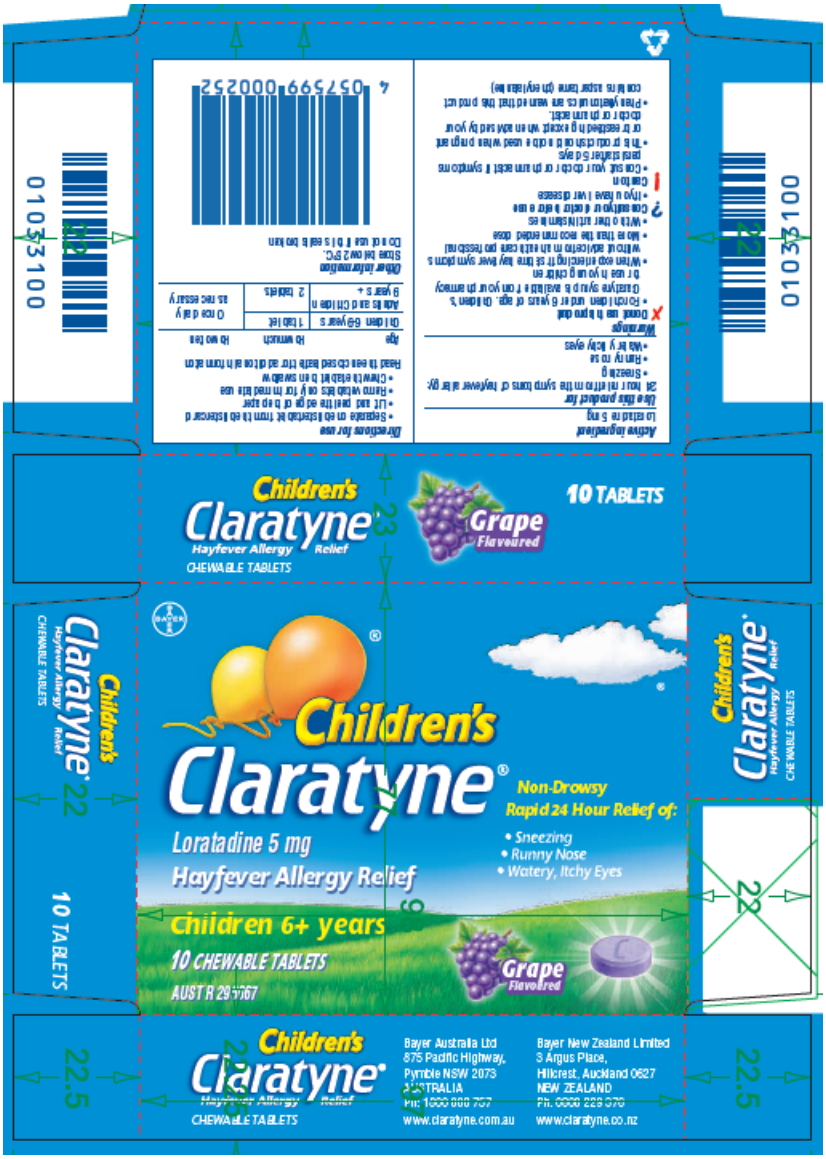
## A7. Labelling

On the following page is the currently approved labelling (10 chewable tablet pack) for Children's Claratyne 5 mg grape-flavoured chewable tablets. A more manipulable copy of this carton is provided as a reference for ease of reading[1]. The label meets all of the requirements for loratadine 5 mg as a Pharmacy Medicine. Furthermore, the design, layout and information format have been used for the Claratyne range of products for many years, and to Bayer's knowledge consumers do not experience problems with label comprehension and successfully use Claratyne in the New Zealand market.

*Children's Claratyne grape-flavoured chewable tablets loratadine 5 mg 10 pack*



The proposed label for this product as a General Sales Medicine is:-



A more manipulable copy of this carton is provided as a reference for ease of reading[2].

Details appropriate for the medicine as a General Sales Medicine have been incorporated, such as removal of the hives (itchy rash) indication and change of the age range to 6+ years.

The New Zealand specific warning “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.” is included on the current label. However, at the time of writing Bayer is planning to make a submission to Medsafe and the Medicines Adverse Reaction Committee proposing that this warning should no longer be required in New Zealand for selected second generation non-sedating antihistamines. This is the second such proposal Bayer will make to Medsafe and it is expected to be considered at an upcoming MARC meeting in 2018 - the outcome may or may not be known by the time the MCC meets. Bayer will provide an update to MCC shortly before their meeting regarding any outcomes resulting from this proposal. A copy of the submission made regarding removing this warning can be made available to the MCC on request. Clearly, any Children’s Claratyne chewable tablets labels would be maintained compliant with the requirements of the labelling statements database at the time.

## A8. Proposed Warnings

Medsafe requires the following warnings to be applied to loratadine sold as an over-the-counter medicine (Label Statements Database as of 2 December 2017):-

| Medicine/Group/ Class | Conditions | Statements or requirements |
|---|---|---|
| **Antihistamines, non-sedating** Includes:<br><br>Desloratadine<br>Loratadine* | For oral use | • Some people might get drowsy on this medicine. You should make sure you are not affected before doing such activities that require full attention, such as driving or operating machinery.<br>[or]<br>• 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. |
| | In cough and cold medicines | • Do not use in children under 6 years old.<br>• Consult a healthcare professional before using in children aged six years and over.<br>• Do not use with other antihistamines.<br>• Do not use with other medicines intended to treat the symptoms of the common cold.<br>[or]<br>Consult a doctor/pharmacist before using with other medicines intended to treat the symptoms of the common cold. |
| **Loratadine** | When sold as a General Sale Medicine | • Do not use in children under 12 years old.<br>• Do not use for more than 5 days at a time.<br>• Do not use with other antihistamines.<br>• Do not use if you are pregnant except on the advice of a healthcare professional.<br>• Do not use if you are breastfeeding except on the advice of a healthcare professional. |

The conditions for general sale of the medicine have been in place since 1 April 2014. Clearly, these additional label warnings/restrictions were considered necessary the product to ensure appropriate use when the product is sold as a General Sales medicine, and these are considered reasonable and appropriate.

Consequently, they have been transferred to the proposed general sales label for Children's Claratyne chewable tablets, which have the following warnings:-

**Do not use this product**

- With other antihistamines
- More than the recommended dose

**Consult your doctor before use**

- If you have liver disease

**Caution**

- Consult your doctor or pharmacist if symptoms persist after 5 days
- This product should not be used when pregnant or breastfeeding except when advised by your doctor

Furthermore, the following additional warning is proposed:-

**Do not use this product**

- When experiencing first-time hayfever symptoms without advice from a healthcare professional

This warning is considered appropriate for the product when indicated for children 6 years of age and over to minimise any potential risk of misdiagnosis or delay in diagnosis in this particular age group (see section B3 Safety in Use – Diagnosis).

As their primary source of information, the current carton label for the General Sales presentation of Claratyne tablets provides complete and balanced information regarding the medicine the consumer has chosen. With the additional warnings as proposed above, Bayer aims to achieve the same level of complete and balanced information for the younger patient age group within the general sales category for loratadine.

## A9. Other Products

There are no other loratadine medicines registered in New Zealand that are suitable for children 6 – 11 years old, since only Bayer has registered and markets a 5 mg oral dose form presentation.

However, because the proposed dosage regime is 10 mg (2 x 5 mg) for children over 9 years of age, the proposal could impact those products containing 10 mg if they chose to change the dosage recommendation to 9+ years. If sponsors chose to make this change, the following products currently available could be affected:-

| | | | |
|---|---|---|---|
| Claratyne Tablet, 10 mg (Pharmacy only) | Loratadine | Bayer New Zealand Limited | Consent given |
| Claratyne Tablet, 10 mg (General sale) | Loratadine | Bayer New Zealand Limited | Consent given |
| Loraclear Hayfever Relief Tablet, 10 mg (Pharmacy only) | Loratadine | AFT Pharmaceuticals Ltd | Consent given |
| Loraclear Hayfever Relief Tablet, 10 mg (General sale) | Loratadine | AFT Pharmaceuticals Ltd | Consent given |
| Lorafix Tablet, 10 mg (Pharmacy only) | Loratadine | Teva Pharma (New Zealand) Limited | Consent given |
| LoraPaed Oral solution, 5 mg/5mL (Pharmacy only) | Loratadine | AFT Pharmaceuticals Ltd | Consent given |
| Lora-Tabs Allergy & Hayfever Tablet, 10 mg (Pharmacy only) | Loratadine | Mylan New Zealand Ltd | Consent given |
| Lorfast Tablet, 10 mg (Pharmacy only) | Loratadine | Multichem NZ Limited | Consent given |
| Your Pharmacy Loratadine Tablets Tablet, 10 mg (Pharmacy only) | Loratadine | Orion Laboratories (NZ) Ltd | Consent given |

# PART B

## B1. SUBSTANCE SUMMARY

Loratadine is a potent, long-acting tricyclic antihistamine with selective peripheral $H_1$-receptor antagonistic activity[13]. Its efficacy as a first line treatment for the symptomatic treatment of allergic rhinitis and allergic skin conditions such as urticaria (hives) has long been established. Once a day treatment, as an effective control for allergic rhinitis, has been available in New Zealand and globally for more than 20 years.

Loratadine has a rapid onset of action after oral administration, usually within one hour[13]. It is well absorbed with peak plasma levels occurring at approximately 1 - 2 hours after dosing. It undergoes extensive first-pass metabolism to the active metabolite desloratadine and is then excreted in urine (~40%) and faeces (42%) in a 10 day period[13]. Renal impairment has no significant effect on loratadine clearance[13].

Loratadine exhibits greater affinity for peripheral $H_1$-receptors than for central $H_1$-receptors, and therefore loratadine and its metabolites do not readily cross the blood-brain barrier[13]. These properties account for its lack of sedation compared to first generation antihistamines.

Loratadine has a safety profile similar to that of placebo. It does not potentiate the central nervous system (CNS) effects of alcohol or diazepam, and there have been no reports of clinically significant interactions between loratadine and drugs such as erythromycin, cimetidine and ketoconazole[13]. Furthermore, loratadine has a similar safety profile in children; the incidence of loratadine-associated adverse effects in children appears to be similar to placebo[14,15].

Loratadine has a wide therapeutic index with no unusual neurological symptoms or signs of toxicity seen in cases of accidental overdose. In volunteer studies, single doses of loratadine up to 160 mg have been administered without any untoward effects[13]. Children who accidentally ingest large quantities of loratadine (up to 40 mg) may be adequately managed at home with the large dose being well tolerated[15].

Loratadine is not associated with cardiovascular toxicity[15]. Once daily administration of loratadine at therapeutic doses with or without erythromycin did not induce adverse cardiac effects in children 5-12 years[14,16].

No regulatory action has been taken world-wide since loratadine's launch due to safety concerns. Safety data contained in company Periodic Safety Update

Reports (PSURs) demonstrates that the overall benefit-risk balance for loratadine continues to be positive[10,11].

Loratadine is a second generation non-sedating antihistamine, and has an excellent safety profile. The toxicity and safety of loratadine have been well established over more than 20 years of product use in New Zealand and internationally.

# B2. RISKS AND BENEFITS ASSOCIATED WITH THE USE OF CLARATYNE (LORATADINE)

## *B2.1 Allergic Rhinitis*

### *B2.1.1 Incidence, Prevalence and Associated Costs*

Allergic rhinitis is a symptomatic disorder of the nose induced by inflammation mediated by immunoglobulin E (IgE) in the membrane lining of the nose after allergen exposure. It exhibits the symptoms of nasal drainage, nasal congestion, sneezing and/or nasal itching[17,18].

Allergic rhinitis may be seasonal or perennial. Individuals with seasonal allergic rhinitis have symptoms during the pollinating season of plants to which they are sensitive, such as grass, weeds, and trees[16,18]. Those with perennial allergic rhinitis have symptoms year round from exposure to allergens that have no seasonal variation, such as dust mites, moulds, or animal allergens[16,19].

Allergic rhinitis is a common condition affecting children[18,19]. In New Zealand, about 20% of the general population suffers from this condition, and of these about one third develops the problem before the age of 10 years (www.allergy.org.nz). In Australia, about 12-20% children aged 6-14 years are affected[17,20,21] and the prevalence could be up to 35-47% in some areas[20,21]. These Australian figures are comparable to the known incidence in New Zealand.

Allergic rhinitis significantly impacts the health and quality of life in children and their carers, and can lead to reduced school attendance, impaired cognitive functioning and reduced learning ability[17]. Persistent symptoms and poor quality sleep can result in lethargy, poor concentration and behavioural changes and impact on learning (www.allergy.org.nz). Cleary, these effects could have a significant long-term impact on individuals if allowed to persist.

Allergic rhinitis is one of the most common chronic respiratory conditions - affecting about 20% of the Australian population[17,18], it is likely that the incidence and prevalence is similar in New Zealand. Allergy New Zealand (www.allergy.org.nz) estimates that about 20% of the New Zealand population suffers from this disease, of which 50% experience symptoms for more than four months per year. However, prevalence may be as high as 40% in New Zealand and Australia (www.allergyclinic.co.nz). It significantly reduces the quality of life of affected consumers, impacts their work and study, and results in substantial healthcare costs[17,18]. Those affected by allergic rhinitis suffer more frequent and prolonged sinus infection, and there is the risk of developing infective conjunctivitis due to frequent eye rubbing. Persistent symptoms and poor quality sleep can result in lethargy, poor concentration and behavioural changes. It may predispose people to obstructive sleep apnoea and more frequent and prolonged respiratory infections.

Allergic rhinitis represents a substantial public health burden associated with significant healthcare costs[17,19,22]. In Australia, the cost of allergies to the economy was around $7.8 billion per annum in 2007, with lost productivity and health system expenditure the major contributing factors. Not only does Australia have one of the highest prevalence's of allergic disorders in the developed world, but recent studies have demonstrated a doubling in some conditions such as allergic rhinitis (hay fever) and eczema[22].

### *B.2.1.2 Ease of Self-Diagnosis*

Allergic rhinitis is readily self-diagnosed by consumers. Seasonal allergic rhinitis is typically easy to recognise as it coincides with the arrival of the relevant allergens in the environment with obvious symptoms[19,20]. However, individuals with perennial allergic rhinitis are very familiar with their symptoms and also have little trouble with self-diagnosis.

Most New Zealand adults are thought to self-medicate for allergic rhinitis, including parents and/or carers who buy products for the children in their care. A 2002 survey of hay fever and allergy sufferers in Australia revealed that nearly two-thirds of respondents did not consult their doctor about their allergic rhinitis treatment. This is confirmed by new data from an April 2015 Bayer Australia loratadine/Claratyne consumer study involving 880 consumers which showed that only 5 - 12% of loratadine purchases resulted from a recommendation by a doctor regardless of whether the medicine was obtained via pharmacy or non-pharmacy retailers[23]. It appears that over this time, the proportion of Australian consumers consulting their doctor for allergic rhinitis has shrunk, and that overall these consumers have become more independent with regards to their self-treatment of allergic rhinitis. It is likely that the situation is similar in New Zealand.

This potential for consumers to safely self-diagnose and self-medicate allergic rhinitis has been recognised for many years in New Zealand with the progressive down-scheduling of allergic rhinitis treatments such as loratadine. Since 2014 New Zealand has allowed for adults to self-diagnose and self-medicate in the complete absence of healthcare professional support by classifying some of the treatments as General Sales Medicines. Since it is well-recognised that parents purchase their children's medications, allowing purchases for older children to also occur without healthcare professional support appears a logical step that is unlikely to increase the risk associated with the use of these medicines.

Easy recognition of the familiar symptoms of seasonal allergic rhinitis and its seasonal nature leads to appropriate self-medication with loratadine containing products[19]. The scope for misdiagnosis or misuse is limited. Initial diagnosis is commonly made, or at least confirmed, by a healthcare professional but symptoms are reasonably self-understood and self-medicated. The British Society for Allergy and Clinical Immunology (BSACI) recognises that compliance with once-daily administration of a long-acting antihistamine (i.e. loratadine) is likely to be better than one requiring multiple daily dosing[24].

Seasonal allergic rhinitis is self-diagnosable because it is triggered by aero-allergens and has a seasonal nature and obvious symptoms. The symptoms are easily recognised because of the rapid and reproducible onset and offset of symptoms in association with pollen exposure[19], meaning that the symptoms are not likely to be indicative of a more serious underlying diagnosis. The seasonal nature of the symptoms leads to easy recognition by sufferers and carers, largely negating the need for professional advice.

In order to ensure there is no risk of delay in correct diagnosis or inappropriate use in children, Bayer proposes that the unscheduled product not be used for first-time sufferers unless there is a healthcare professional diagnosis of seasonal allergic rhinitis. Therefore, a safety statement 'Do not use this product when experiencing first-time hayfever symptoms without advice from a healthcare professional' is proposed to be included on the product labelling[2,12].

### *B2.1.3 Masking of Underlying Disease*

Diagnostic considerations for doctors, when considering a possible diagnosis of hayfever in children, are:-

- Vasomotor rhinitis or nonallergic rhinitis

- Gustatory rhinitis (vagally mediated)
- Rhinitis medicamentosa (rebound nasal congestion that may be brought on by extended use of topical decongestants, antihypertensives, cocaine abuse)
- Anatomic rhinitis (eg, deviated septum, choanal atresia, adenoid hypertrophy, foreign body, nasal tumor)
- NARES (nonallergic rhinitis with eosinophilia syndrome [high levels of white blood cells])
- Immotile cilia syndrome (ciliary dyskinesis)
- Cerebrospinal fluid leak. Patients typically complain of clear, watery drainage usually from only one side of the nose or one ear.
- Nasal polyps
- Granulomatous rhinitis (eg, Wegener granulomatosis, sarcoidosis)

However, a diagnosis of allergic rhinitis is usually confirmed when treatment starts – a positive symptomatic response to antihistamines means the cause was almost certainly an allergy (www.nhs.uk). The proposed unscheduled product will retain the same labelling information as the current unscheduled packs. A consumer information leaflet[13], similar to that included in the current unscheduled adult product[25], will be enclosed in the pack, providing important symptom information to help consumers differentiate typical hayfever symptoms from others. A list of symptoms not usually associated with allergic rhinitis (e.g. ear or face pain, loss of smell or taste, fever, chest discomfort, cough, blocked nose, thick green or yellow discharge, nosebleed) is provided.

The symptoms of seasonal allergic rhinitis can easily be identified because of the rapid and reproducible onset and offset of symptoms in association with pollen exposure[19], and these are unlikely to be indicative of a more serious underlying diagnosis. The seasonal nature of the symptoms leads to easy recognition by sufferers, largely negating the need for professional advice. The successful reclassification of the 5 pack size of loratadine from Pharmacy Medicine to unscheduled in 2014 has demonstrated that the risks of misdiagnosis or masking of underlying diseases are minimal. The proposed unscheduled loratadine product for children 6 - 12 years of age will retain the same labelling statements as the existing unscheduled pack to ensure ongoing safe use of the medication. To further minimise any potential risk of misdiagnosis or delay in diagnosis in this particular age group, Bayer proposes an additional label statement[2]:

> 'Do not use this product when experiencing first-time hayfever symptoms without advice from a healthcare professional'.

The labelling will also refer consumers to a healthcare professional if symptoms persist for more than 5 days, thus further minimising the risk of delaying any incorrect diagnosis, if applicable.

Given that seasonal allergic rhinitis has a cyclical nature with easily recognised symptoms, together with the proven safety experience of the unscheduled medication, it can be reasonably expected that the inclusion of children in the age group of 6 to 12 years presents no increased risk of misdiagnosis, masking of underlying diseases or delay in correct diagnosis.

## *B2.2 Loratadine*

### *B2.2.1 Contraindications*

As with all medicines, loratadine is contraindicated in those individuals known to be hypersensitive to the active ingredient or excipients within the medication[13]. No other contraindications are noted for this medication, confirming its excellent safety profile.

### *B2.2.2 Interactions*

An increase in plasma concentrations of loratadine has been reported with concomitant use of drugs which inhibit CYP3A4 or CYP2D6, with the potential to increase the incidence of adverse events. However, studies demonstrated that the increase in plasma concentrations of loratadine experienced with concomitant administration of ketoconazole, erythromycin and cimetidine resulted in no clinically significant changes, including no ECG changes[13]. Concomitant administration with alcohol demonstrated no potentiating effect[13].

### *B2.2.3 Adverse Effects*

Loratadine has an excellent safety profile. In clinical trials when the medicine was prescribed at the recommended daily dose, adverse reactions were reported comparable to that of placebo[13]. Most frequently reported events included headache, somnolence, fatigue, dry mouth, rash and gastrointestinal disorders. Rarely, abnormal hepatic function, alopecia, anaphylaxis, tachycardia, palpitations, dizziness and convulsions have also been reported. Hypersensitivity to loratadine or excipients in Claratyne has been reported on rare occasions[13]. Studies of loratadine taken at the recommended dose have not revealed clinically significant levels of sedation in subjects[26,27].

The types and frequencies of the adverse events reported in paediatric and adolescent subjects were consistent with adverse events reported in adult subjects treated with loratadine[27]. Consequently the experience of children

taking loratadine is not expected to be different to that of adults taking the medication, and so it is appropriate that the two patient categories be able to access the medication in the same way i.e. through general sales outlets as well as pharmacy.

The Australian user experience is similar to the global situation. The TGA Database of Adverse Event Notifications (DAEN) shows 813 adverse events reported for all loratadine containing products from 1 Jan 1990 (prior to when the product was introduced in Australia) up until 18 May 2016, a period of more than 20 years[28]. Only 28 reports were related to Claratyne syrup which is specially formulated for use in children 1-12 years of age[29]. Although the TGA reports may not necessary include all adverse events, taking into account the long history of product use and the significant population exposure in Australia, the data shows that the number of the adverse events is very low and supports an excellent safety profile. In New Zealand, a search of the Suspected Medicine Adverse Reaction database has not been conducted as this detail is already available to MCC.

### *B2.2.4 Special Populations*

#### *Children*

A review of paediatric data on loratadine in accordance with EU Article 45 of Regulation no 1901/2006 (which requires submission of all paediatric trials to the Paediatric Committee for review with any changes in product labelling for paediatric indications) was completed[27] in 2010. The marketing authorisation holder submitted data from eight studies including a total of 1,501 subjects, of which 753 were paediatric subjects between 6 months and ≤11 years of age, 95 were adolescent subjects between 12 and ≤17 years of age, and 653 were adult subjects ≥18 years of age. The rapporteur concluded that the data from these studies revealed no concerns regarding the efficacy or safety of loratadine in any age group, when subjects are treated with appropriate doses. Loratadine was considered to be consistently well-tolerated. The incidence and types of adverse events reported in paediatric and adolescent subjects were similar to those seen in previously reported studies with loratadine. Also, in general, the type and frequency of the adverse events reported in paediatric and adolescent subjects were consistent with adverse events reported in adult subjects treated with loratadine.

In summary, loratadine is indicated in children from 12 months of age and is generally safe. The type and frequency of adverse events reported in children are consistent with those reported in adults. This proposal is to seek scheduling exemption for loratadine in solid dosage form for children between 6 - 12 years of age. The risk of loratadine as an unscheduled medicine for this age group

appears highly similar to that for adults (i.e. suitable for general sale), and any potential risk is further minimised by the proposed limited age group (6 - 12 years), dosage form (solid only, not syrups), pack size (maximum 10 days' supply) and appropriate product labelling.

*Renal Impairment*

The total body clearance and volume of distribution of loratadine did not differ significantly between volunteers with normal renal function, and those with chronic renal failure[30], although in patients with renal failure the AUC and the peak plasma concentration for both loratadine and desloratadine (the active metabolite), were found to be higher than in people with normal renal function[13]. The elimination half-life for both the medicine and the metabolite however, was not affected and haemodialysis also did not affect the pharmacokinetics of loratadine or desloratadine[13].

No dose adjustment is therefore required for patients with a degree of renal insufficiency, and so the medicine is suitable for self-medication in this group of patients.

*Severe Liver Impairment*

Because loratadine is subject to first pass metabolism, loratadine should be used with caution in people with severe liver impairment[13]. Both existing and proposed unscheduled product labelling including the consumer information leaflet[1,2,12,25] advise that a doctor should be consulted before use if suffering from liver disease.

*B2.2.5 Possible Resistance*

Resistance to loratadine (i.e. reduction in efficacy as usage continues) does not appear to be a recognised phenomenon with this medicine. There is one report of resistance to loratadine from the FDA, out of over 20,000 total side effect reports (https://www.ehealthme.com/ds/loratadine/drug-resistance/). Any possibility of resistance is minimised by the label advice to only use the medicine as needed and to consult a doctor if symptoms persist for more than 5 days.

Post marketing surveillance data for loratadine indicates a continuing favourable benefit/risk ratio[10,11]. Review of the PSURs for oral loratadine use worldwide shows there have been no relevant changes to either the overall frequency of adverse event reports or the nature of reported events. No regulatory action has been taken world-wide since launch due to reported adverse events.

## *B2.3 Potential Abuse or Misuse of Loratadine*

Loratadine has no known potential for abuse or dependency[13].

Loratadine has been readily available as an OTC medicine for many years in New Zealand and internationally, including the unscheduled products sold in New Zealand and Australia since 2012 for children 12 years and over. Despite this very wide availability, there are no reports of loratadine abuse or misuse globally. Literature searches have not revealed any reports of abuse or misuse with products containing loratadine. In post-marketing surveillance reports, there were 5 cases of drug abuse reported during the 3 year period between 2 February 2013 to 2 February 2016[10], and for the 12 months from 3 February 2016 to 2 February 2017 there were 3 reported cases of drug dependence and 1 of drug abuse[11].

Somnolence, headache and tachycardia have been reported with overdose[13], however, relatively few cases of overdose have been reported despite the high level of accessibility to loratadine. During the 3 year period between 2 February 2013 to 2 February 2016[10], there were 128 accidental overdose cases and 25 overdose cases reported globally – however, the report noted that these cases were considered to have been reported disproportionately due to changes in coding and late reporting of some events meaning that they should have rightly belonged in another reporting period. Despite this, the incidence of overdose is low when compared with total exposure to the medicine. During the 12 month period from 3 February 2016 to 2 February 2017, there were 2 accidental overdose cases only[11], confirming the view that the previous reporting period was unusual.

In Australia there has been no evidence of misuse or abuse of the product since the product was launched, including the time it has been available outside of pharmacies. Searches of the DAEN[28] demonstrates that loratadine is not associated with abuse or misuse. Search of the DAEN for all loratadine records since the product was first introduced found a low incidence of overdose cases (Table 3). Further limiting the search to children's products only (Claratyne syrups) found a very low number of overdose cases (Table 3). Loratadine products have been in the Australian market for more than 20 years with very broad exposure and the low incidence of overdose reports suggests a safe local user experience in both adults and young children. It is reasonable to assume that the situation would be the same in New Zealand.

**Table 8: Accidental exposure and overdose cases reported to the TGA since loratadine introduced into Australia in 1992[28,29].**

| MedDRA Reaction Term | Number of Cases (All Loratadine Products Including Claratyne Syrup) | Number of Cases (Claratyne Syrup) |
|---|---|---|
| Accidental Exposure to Product | 8 | 1 |
| Accidental Exposure to Product by Child | 84 | 16 |
| Accidental Overdose | 63 | 12 |
| Overdose | 11 | 3 |

The maximum supply proposed for unscheduled loratadine for children between 6 and 12 years is 10 days. The labelling advises users not to exceed the stated dose, not to use the product with other antihistamines, and to seek medical advice if symptoms persist for more than 5 days. Individuals will not continue to self-medicate unnecessarily unless symptoms are present and there is no evidence to suggest that individuals unnecessarily take antihistamines. The likelihood of an accidental or deliberate overdose is minimal.

In volunteer studies, single doses of loratadine up to 160 mg (16 times the recommended adult daily dose) did not show any untoward effects[13]. Even prolonged administration of four times the clinical dose of loratadine over a 90 day period demonstrated no clinically significant increase in the QT interval on ECG, suggesting the risk posed by accidental or deliberate overdose is minimal[31].

There is no potential for conversion of loratadine into illicit, prohibited or Controlled Drug substances.

Given that loratadine has a well-established safety profile, and the risk of misuse and inappropriate use is rare, an unscheduled classification for loratadine in a small pack size of 10 dosage units for children 6 - 12 years of age, presents minimal risk to children whilst providing an efficacious second generation non-sedating antihistamine. Any potential risks can be further minimised or managed by the labelling, packaging and pharmacovigilance reporting systems.

## *B2.4 Benefits of Reclassifying Loratadine for Children 6 – 12 years to General Sales Medicine*

To date, second generation non-sedating antihistamines are only available for adults and children 12 years and over outside of pharmacies in New Zealand. This leaves a whole class of efficacious and safe medications such as loratadine unavailable for purchase outside of pharmacies for children under 12 years of age in New Zealand. This is in contrast to countries with similar health care systems such as Australia, the UK and the USA where these medicines have been freely accessible outside of pharmacies for children 2 years and over for more than 10 years. Therefore, there is a gap in access for a safe and effective medication for children to treat a minor self-limiting condition.

As with previous reclassifications of loratadine for adults over the last few years, the benefits of the proposed rescheduling are:-

1. Greater convenience for the purchaser
   In this case it is known that the purchaser is usually not the patient, as most commonly it is the child's parents that are purchasing their medicine. The proposed switch offers these purchasers the opportunity to buy their children's medication at the same time they are possibly buying their own medication or in with their grocery shopping, thereby offering a significant convenience for these purchasers.

2. Greater availability for the purchaser
   The possibility of Children's Claratyne being available for general sales retail outlets offers purchaser's more places at which they can purchase the required medicine, along with a greater range of opening hours. When ill, children often find the symptoms of the illness more distressing and may have less resilience that do adults – consequently, greater availability especially outside normal working hours offers significant benefit to families whose children suffer from allergic rhinitis.

3. More economical pricing
   It is likely that the price of the equivalent product will be less at general sales outlets – an important consideration for families with children as this demographic is recognised as often being financially stressed.

As previously discussed, adults have already enthusiastically embraced the availability of loratadine 10 mg in packs of 5 and 10 tablets as a General Sales medicine. The proposed Children's Claratyne products will facilitate this trend by allowing consumers to access medicine for their children from a convenient outlet. From an accessibility and economic point of view, it will be more convenient and economical for a consumer to obtain medication allowing for ongoing intermittent symptomatic control of the condition during the season.

Bayer concludes that a change of classification to extend unscheduled supply to include children 6 - 12 years of age will provide children and their carers with easier and more convenient access to an efficacious and safe medication for the short term control of seasonal allergic rhinitis during hayfever season, without compromising its benefit/risk ratio.

# B3. CONCLUSION

This proposed reclassification application seeks scheduling exemption of loratadine 10 mg or less in divided preparations for oral use in packs containing not more than 10 dosage units when used for the treatment of seasonal allergic rhinitis in children 6 - 12 years of age.

The proposed Children's Claratyne products can with reasonable safety be supplied outside of pharmacies taking into consideration the hazard to health, the risk of misuse and inappropriate use. This is supported on the basis that the benefit/risk ratio is favourable and demand for treatments during hayfever season is strong. The convenience of increased access to a safe and effective medication for children between 6 - 12 years is clear. There is no evidence to suggest that pharmacist or pharmacy involvement in the sale of loratadine divided oral preparations in small quantities is critical.

Allergic rhinitis affects significant numbers of New Zealand children and the prevalence is increasing, impacting quality of life, learning and school performance. Second generation non-sedating antihistamines are efficacious and a safe first line treatment for the control of seasonal allergic rhinitis. They have been used in children 12 months of age and over for more than 20 years in New Zealand and globally. Currently, no medications in this class are available outside of pharmacies for children under 12 years of age, and with limited locations and opening hours the need for an effective and safe allergy treatment outside of pharmacies for younger children is significant.

Available safety data, including drug interactions and potential for misuse and overdose, have been reviewed and the benefit/risk ratio is clearly in favour of improving the accessibility to consumers and their children without healthcare professional involvement.

The symptoms of seasonal allergic rhinitis are easily recognised, and not likely to be indicative of a more serious underlying condition. The seasonal nature of the symptoms leads to easy recognition by sufferers, largely negating the need for professional advice.

The proposed labelling has been based on current unscheduled loratadine packaging with additional statements proposed to provide clear medical and safety information for self-medication, and to adequately minimise any potential risks in the proposed age group of 6 - 12 years.

Overseas experience in countries similar to New Zealand such as Australia, the UK and USA demonstrate that unscheduled supply of loratadine in the proposed small pack size for children in this group is effective, safe and beneficial for the control of the symptoms of allergic rhinitis.

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