Proposal for Reclassification of

Claratyne® Tablets

Loratadine 10 mg

General Sales Medicine Size Increase to 10 Days' Supply

January 2016

INDEX

SUMMARY

The current classification of loratadine in New Zealand 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 5 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 5 days' supply.

Prescription
Except for oral use.

This submission to the Medicines Classification Committee proposes changing this current classification to:-

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 for oral use.

Allergic rhinitis is a symptomatic disorder of the nose induced by inflammation mediated by immunoglobulin E (IgE) in the membrane lining the nose after allergen exposure, with symptoms of nasal drainage, nasal congestion, sneezing and/or nasal itching. Allergic rhinitis affects 20% or more of New Zealanders and Australians, impacting their work, study and quality of life and causing significant economic burden. Allergic rhinitis can be seasonal or perennial. Seasonal allergic rhinitis is caused by a reaction to seasonal aeroallergens such as pollens. This reaction has symptoms such as sneezing and nasal congestion and is readily able to be identified by consumers. Most adults now self-medicate for allergic rhinitis. An April 2015 Bayer Australia loratadine/Claratyne consumer study shows that only 5% - 12% of loratadine purchases originated from a recommendation by a doctor, regardless whether they obtained the medicine from pharmacy or non-pharmacy retailers.

Loratadine is an effective first line treatment for the symptoms of seasonal allergic rhinitis, and has been available as a general sale medicine since 2012 in small packs of 5 to help manage this minor self-limiting condition without the intervention of a healthcare professional. This broader access to the 5 pack general sales medicine has proved uneventful. According to Australian Aztec grocery scan data, 101,800 units of the loratadine general sales pack (5 dosage units) were purchased in supermarkets in Australia in 2012 and the number has increased to 622,900 units in the first half of 2015, a more than 6 fold level of growth in the last 3 years. The data suggests that in Australia there is a very strong demand for this medicine outside of pharmacies for the self-treatment of seasonal allergic rhinitis – although more limited data is available for New Zealand, what is available indicates the same trends are likely for New Zealand.

An April 2015 a Bayer Australia loratadine/Claratyne consumer study involving 880 consumers showed that: consumers planned their allergy medication purchases in advance, 1 in 4 pharmacy shoppers also purchase allergy medication in grocery, consumers purchased general sales loratadine as part of their 'weekly shop' (38%), 'top up shop' (36%), 'ran out of allergy' (12%) or 'stock up on allergy' (5%). This indicates that consumers are knowledgeable about their seasonal allergic rhinitis condition and are comfortable with self-treatment. The data also suggests that consumers want the convenience of purchasing more than 5 day's supply to avoid running out of medication to effectively control their seasonal allergic rhinitis.

The symptoms of seasonal allergic rhinitis typically appear during the hay fever season in which aeroallergens are abundant in the air. The length of seasonal exposure to these aeroallergens is dependent on geographic location and climatic conditions and can last for several months each year. The flexibility of loratadine used on an 'as needed' basis provides convenient self-medication during the hay fever season, especially for those with episodic or intermittent

symptoms which may be triggered by aeroallergens at any time during the season and lasting some weeks. In New Zealand, the 'as needed' analgesic medications paracetamol and ibuprofen are available in large packs as general sales medicines, for which consumers may only need a few doses for their pain/fever control during an episode. Loratadine's safety profile is comparable to these analgesics, and it is considered an ideal candidate as a general sales medicine in a larger pack for episodic symptom relief during the hay fever season.

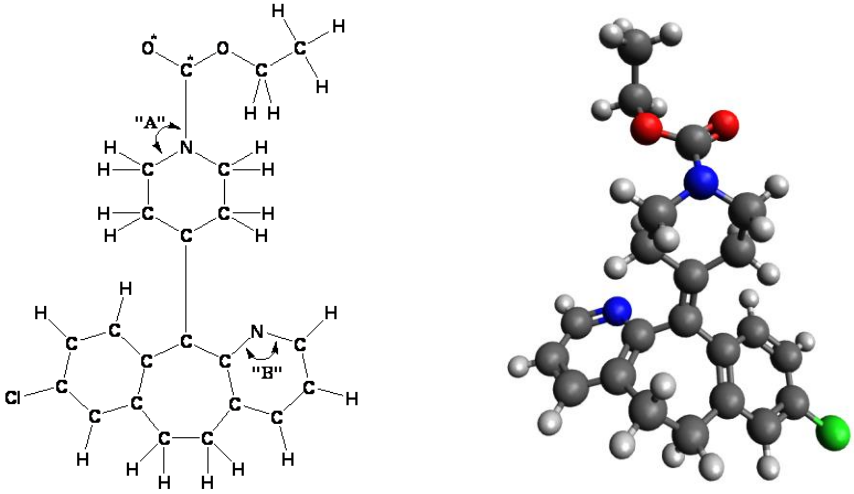
The symptoms of seasonal allergic rhinitis can be intermittent or persistent. Intermittent symptoms present for less than 4 days per week or less than 4 weeks in a year, while persistent symptoms are more than 4 days per week and last for more than 4 weeks in a year. During a season, the symptoms of seasonal allergic rhinitis can last for weeks or months; even intermittent symptoms can last for a few weeks. Therefore, from a therapeutic point of view, while safety is not compromised it makes sense to have a larger pack available (10 dosage units) corresponding with the nature of the condition which typically requires more than 5 days control during the hay fever season.

The proposed 10 pack size is consistent with current consumer behaviour of accessing more than 5 days' supply of a medicine at one time from a non-pharmacy outlet. From an accessibility and economic point of view, it is more convenient and cost effective for a consumer to purchase a larger pack for symptomatic control of the condition during hay fever season. This is reflected in the April 2015 Bayer Australia loratadine/Claratyne consumer study where the majority of consumers were open to obtaining the product from general sales retailers and considered pack size and price savings to be key factors.

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®. In other countries the brand name Claritin® is also used.

This proposal is specifically related to divided solid oral dosage forms such as tablets, chewable tablets and capsules.

A2. Name of the Company

This submission is made by:-

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Contact: Ms. Gillian Alexander
REGULATORY CONSULTANT

Bayer currently markets Losec tablets 10 mg as a Pharmacy Only Medicine in New Zealand in packs of 7 and 14 tablets.

A3. Dose Forms, Strengths and Pack Sizes

As stated above, 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 5 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 5 days' supply.
>
> Prescription
> Except for oral use.

Medsafe further restricts the sale of loratadine as a General Sales medicine, through the label statements database, to adults and children aged 12 years and over[1].

Bayer New Zealand Limited currently markets Claratyne 10 mg tablets (packs of 10, 30 and 60 tablets), Children's Claratyne 5 mg tablets (packs of 10 and 30 tablets) and Children's Claratyne 1 mg/mL syrup (bottles of 100 mL) within the Pharmacy Only Medicine classification available. Within this Claratyne range, other presentations, flavours and pack sizes are either registered or planned, but not marketed. Additionally, Claratyne 10 mg tablets (packs of 5 tablets) are currently marketed as a General Sales Medicine.

In terms of dose form, strength and pack size, the proposed reclassification can be summarised as proposing that the allowed General Sales pack size be increased from 5 to 10 day's supply. In effect, the Children's Claratyne products will not be included in the proposal due to the Medsafe restriction to adults and children aged 12 years and over[1]. Claratyne tablets, which are marketed, would be affected, and Claratyne Liqui-Gels soft gelatin capsules (registered but not marketed) and Claratyne Reditabs orodispersible tablets (submitted to Medsafe but not registered at the time of submission of this application) could potentially be affected. All of these presentations contain 10 mg loratadine per oral dose form.

A4. Indications

The current approved indication for Claratyne, as per the current data sheet[2], is:-

For the relief of:-

- symptoms associated with seasonal and perennial allergic rhinitis, such as sneezing, nasal discharge and itching, and ocular itching and burning
- symptoms and signs of chronic urticaria and other allergic dermatological disorders.

Labelling for the Pharmacy Only Claratyne tablets (see Section A7) reflect this approved indication, reworded into more consumer-friendly language to become:-

Who can use this product
Children 12 years and over Adults

Use this product for
Rapid 24 hour relief from the symptoms of hayfever, year round allergies and chronic urticaria (hives), without causing drowsiness. Once daily dose provides relief from:

- Sneezing
- Watery, itchy eyes
- Runny nose
- Itchy rash

Labelling for the General Sales Claratyne 10 mg 5 pack presentation (see Section A7) is restricted to allergic rhinitis and does not include chronic urticaria. The carton label states:-

> **Who can use this product**
> Children 12 years and over Adults
>
> **Use this product for**
> Rapid 24 hour relief from the symptoms of hayfever allergy, without causing drowsiness. Once daily dose provides relief from:
> - 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

A4.1 Dosage Recommendation

The current dosage instructions on the carton label for all Claratyne tablets, approved by Medsafe (see section A7) are:-

> How to use this product
>
> Age: Adults and children 12 years and over
> How much: 1 tablet
> How often: once daily as necessary

This dosage recommendation is already approved for Claratyne tablets as a General Sales medicine, and this proposal includes retaining these dosage instructions.

A5. Classification

The current classification of loratadine, taken from the Medsafe Web site on 25 January 2016, is:-

Loratadine, except for oral use	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 5 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 5 days' supply	General Sales

The classification sought for loratadine is:-

Loratadine, except for oral use	***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***

Essentially, this submission supports and embraces all of the current restrictions for the general sale of loratadine, including restriction to adults and children 12 years and over and providing advice through labelling that the product should not be used for more than 5 days at a time, with the only proposed change being that the pack size restriction on the General Sales medicine be increased from 5 to 10 tablets.

In New Zealand loratadine was considered by the MCC several times between 1986 and 1997[3], with a recommendation for the product taken orally to be a

Pharmacy Only medicine in 1990 and subsequent consideration 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 only five days' supply and when used for seasonal allergic rhinitis. This recommendation was subsequently adopted and remains the situation today.

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[4]. Two countries (Italy and the Czech Republic) have a pack size limit of 7 days' supply while in others there are pack size limits of 10, 14, 30, 70 or unlimited[4].

The general sale classification details in comparable overseas countries are listed in the table below.

Loratadine OTC/General Sale classification in other markets

Country	General Sale Classification Year	General Sale Classification details
Australia	2012	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.
Canada	2002	General sale approval for seasonal allergic rhinitis, perennial allergic rhinitis and chronic urticaria in children 12 years and over. No pack size limit.
UK	2002 (Initial 7 packs) 2012 (30 packs)	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. Maximum pack size 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 30kg: 10 mg; maximum daily dose in children weighing 30 kg or less: 5 mg. Maximum pack size 70 mg.
USA	2002	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.
	2006	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.

In Australia, at the May 1992 National Drugs and Poisons Scheduling Committee (NDPSC) meeting, loratadine was first included in in the SUSPD as a Prescription medicine (Schedule 4). In April 1994, the NDPSC rescheduled loratadine solid oral preparations containing 10 mg or less in packs of 10 dosage units to Pharmacist Only medicines (Schedule 3). The Schedule 3 pack size restriction on solid dose forms (10 dosage units) of loratadine was removed by the NDPSC in August 1996. At its November 1995 meeting, the NDPSC rescheduled loratadine liquid preparations to Schedule 3.

In Australia, an equivalent proposal as in this submission was made to amend the Poisons Standard. It was submitted on 12 October 2015, and is expected to be considered by the ACMS at their March 2016 meeting. The MCC will be kept informed of any outcomes from this proposal in Australia.

In November 1999, the NDPSC confirmed its decision of February 1999 to reschedule from Schedule 3 to Pharmacy Only medicines (Schedule 2) "loratadine in preparations for oral use". After discussions at the Advisory Committee on Medicines Scheduling (ACMS) meeting in February 2012, loratadine 10 mg or less in divided oral preparations in packs of no more than 5 dosage units was exempted from Schedule 2, and so effectively became a General Sales medicine, when used for the treatment of seasonal allergic rhinitis in adults and children 12 years and over.

Globally, loratadine-containing products are marketed in over 110 countries as a safe and effective non-sedating antihistamine for the treatment of allergic rhinitis and allergic skin disorders in adults and children[5].

Since 2002, loratadine tablets have been available in the UK as a general sales medicine 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 general sales 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.

In the US, loratadine was first approved for OTC use (equivalent to general sale in New Zealand) in 2002 for hay fever or other upper respiratory allergies for tablets, orally disintegrating tablets and syrups (syrups are for children 2 years and over), with no pack size restriction. In 2006, loratadine was further approved as chewable tablets and orally disintegrating tablets (5 mg) when used in children 2 years and over for the symptoms of hay fever or other upper respiratory allergies without a pack size limit.

In Canada, loratadine and its salts and preparations have been unclassified since 2002 when marketed for the symptomatic relief of seasonal allergic rhinitis, perennial allergic rhinitis and chronic urticaria in adults and children 12 years and over. There is no pack size limit for the unscheduled products.

A6. Extent of Usage

A6.1 New Zealand

Loratadine is a widely used product in New Zealand. As Bayer has only been the sponsor of this product for a short time, an extensive sales history is not available. However, 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 05/01/14	193,475	28,714	164,761
	MAT To 04/01/15	193,045	28,177	164,868
	MAT To 03/01/16	186,845	28,089	158,756

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 $45,000 in 2014 (Oct – Dec), and $150,000 for the whole of 2015. Clearly, availability of the product in grocery has been a popular development with consumers who are rapidly adopting this new retail outlet for the product.

A6.2 Australia

According to Australian Aztec scan data (see Table below) in the last 5.5 years (Jan 2010 - June 2015) about 13.8 million units of loratadine products were sold in Australia, comprising 12.1 million units sold in pharmacies and 1.7 million units sold through non-pharmacy outlets. Of the total 13.8 million units, about 11.3 million units were adult loratadine products, comprising 9.6 million units sold in pharmacies and 1.7 million units sold through non-pharmacy outlets.

General sales loratadine was first made available in Australia in late 2012 and there has been 1.7 million units sold in less than 3 years. The data shows a strong demand for loratadine medication outside of pharmacies with a greater than 6 fold increase in sales in the last 3 years. It appears that trends in Australia and New Zealand are similar in this respect.

Since the general sales product is only approved for the control of seasonal allergic rhinitis, this data shows that Australians are comfortable with purchasing products in non-pharmacy channels for the symptomatic control of seasonal allergic rhinitis without healthcare professional intervention, and this trend is increasing.

Total loratadine usage in Australia from 2010 to 2015 (Aztec scan sales)

		Total Loratadine (Adult)			Total Loratadine (Adult &Child)		
		Grocery & Pharmacy	Pharmacy	Grocery*	Grocery & Pharmacy	Pharmacy	Grocery*
Units (000s)	2010	1559.3	1559.3	0.0	1851.1	1851.1	0.0
	2011	1659.2	1659.2	0.0	2010.1	2010.1	0.0
	2012	1756.0	1654.2	101.8	2175.3	2073.5	101.8
	2013	2042.8	1647.6	395.2	2537.9	2142.7	395.2
	2014	2108.1	1527.3	580.8	2606.3	2025.5	580.8
	MAT to June15	2147.6	1524.7	622.9	2652.1	2029.2	622.9
	Total	11273.0	9572.3	1700.7	13832.7	12132.0	1700.7

*Weighted calculation

A6.3 World-Wide

Worldwide patient exposure for loratadine oral formulations for the PSUR reporting period 02 Feb 2012 through 01 Aug 2012 was estimated from unit sales data provided by IMS Health MIDAS market research database[5].

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 Loratadine from 2 Feb 2012 to 1 Aug 2012

Formulations	**Units Sold**	**Patient-Treatment Days**	**Patient-Treatment Years***
Tablets	164,707,389	164,707,389	450,944
Syrup	168,048,253	33,609,651	92,018
Reditabs	27,221,397	27,221,397	74,528
Oral Drops	2,337,820	467,564	1,280
Total**		**226,006,000**	**618,771**

* Patient-treatment years = patient-treatment days / 365.25.
** "Total" Patient-treatment days and patient-treatment years may not match summed reported formulation "Patient-treatment Days" and "Patient-treatment Years".

Total worldwide patient exposure for all loratadine oral formulations for the reporting period was estimated to be 226,006,000 patient-treatments days or 618,771 patient-treatment years. This represents an approximate usage of over one 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

Unless an over-the-counter product is classified Pharmacist Only Medicine, labelling is the key tool to guide consumers in the appropriate selection and safe usage of medical products. Particularly for General Sales medicines, it is critical to provide this information in a format that is accessible, legible and understandable. Good information design and clear wording contribute to improved useability for over-the-counter medicine labels[6]. Consumers value highly the information labelling and pack inserts provide regarding indications, directions for use and side effects before they start using an OTC medicine[6], and it is important that this information be delivered to them in an appropriate way. Features of good labelling are[6]:-

- Not overly demanding in terms of reading level
- Bullet points and clear headings aid comprehension
- Larger font size
- Shorter sentences
- Avoid use of all upper case lettering
- Optimal spacing between lettering
- Appropriate ordering of information
- Use of “plain” English and reduction of medical jargon

A study of women’s comprehension of the labelling for an emergency contra-ceptive pill in the USA[7], in which the labelling adhered to the standardised format required by the FDA and so largely adhered to the principles detailed above, found that most women understood the information well enough to use the product safely and effectively. It appears labelling that meets these requirements is likely to be well understood and appropriately acted upon by consumers.

On the following page is the currently approved labelling (5 tablet pack) for Claratyne 10 mg tablets. A more manipulable copy of this carton is provided as a reference for ease of reading[8]. These labels meet all of the requirements for loratadine 10 mg as a General Sales Medicine.

The current carton label for Claratyne as a General Sales medicine (5 tablet pack) is:-

The existing 5 pack general sale product carton label is considered satisfactory for the product to be sold without healthcare professional input – the pack communicates well and no additional warnings are thought to be necessary. Consequently, the 10 pack general sales product is proposed to comprise essentially the same carton label, with only the number of tablets it contains to be changed.

As for the current General Sales labels, the proposed packaging is designed to reduce any risk of inappropriate dosing or use that is not in accordance with the product registration. Safety information incorporated into the product labelling since the general sales loratadine product launch 2 years ago has proved effective at assisting consumers to achieve good health outcomes without the need for healthcare professional intervention. The existing labelling information including safety and medical information (detailed below) will be retained for the increased pack size to ensure there is sufficient information for consumers.

Outer Carton

As for the existing 5 tablet pack, the statements below will be included on the proposed general sales 10 packs:

- This product should not be used when pregnant or breast feeding except when advised by your doctor or pharmacist
- Do not use this product for children under 12 years of age
- Do not use this product more than the recommended dose
- Do not use this product with other antihistamines
- Consult your doctor before use if you have liver disease
- Consult your doctor or pharmacist if symptoms persist after 5 days
- 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

Although the proposed general sales product contains up to 10 days medication, the warning statement 'Consult your doctor or pharmacist if symptoms persist after 5 days' will be retained to ensure consumers are aware that continuous use of the product for more than 5 days at a time is not to be taken without appropriate healthcare professional advice. This proposed labelling situation is similar to other general sales products such as analgesics like paracetamol and ibuprofen, which are also used on an 'as needed' basis but are sold in much larger pack sizes. For example, Panadol OptiSorb tablets general sales 20 pack suggests to consumers 'not to use the product for more than a few days (adults) or 48 hours (children 7-17 years) except on medical advice[9].

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 also included on the current, and therefore the proposed, carton label. However, at the time of writing Bayer has made 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 proposal is expected to be considered at the planned MARC meeting in March 2016, and 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 is available to the MCC on request.

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 25 January 2014):-

Medicine/Group/ Class	**Conditions**	**Statements or requirements**
Antihistamines, non-sedating Includes: Cetirizine* Desloratadine Fexofenadine* Levocetirizine Loratadine* Rupatadine	For oral use	• 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. • Consult a healthcare professional before using in children aged six years and over. • Do not use with other antihistamines. • Do not use with other medicines intended to treat the symptoms of the common cold. [or] 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. • 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.

Clearly, several additional label warnings/restrictions have been placed on the product to ensure appropriate use when the product is sold as a General Sales medicine, and these are considered reasonable and appropriate. The proposed increase in pack size for General Sales availability is not considered to change the requirements, especially as the advice to not use the product for more than 5 days at a time without consulting a healthcare professional (should symptoms persist) is retained (see discussion above).

Unlike the Pharmacy Medicine presentations, the current New Zealand Claratyne presentation for General Sales availability contains a pack insert[10], which provides the consumer with a lot of information about their disease, the medicine they have purchased to treat it and when it would be appropriate to consult with a healthcare professional.

All the current safety and medical information appearing in the consumer information leaflet of the existing 5 pack general sales product will be retained for the proposed 10 pack including information which directs consumers to seek professional advice if they are experiencing non-hay fever symptoms.

Consult your doctor or pharmacist if you have any of the following symptoms:

- ear pain or discomfort
- pain in your face
- loss of smell
- taste disturbances or loss of taste
- fever
- chest discomfort, cough
- blocked nose without any other symptoms
- symptoms on only one side of your nose
- thick, green or yellow discharge from your nose
- repeated nosebleeds
- a drip down the back of your throat with thick mucus and/or runny nose

These symptoms are not usually found in hay fever.

As their primary source of information, the current carton label and pack insert for the Claratyne General Sales presentation provides complete and balanced information regarding the medicine the consumer has chosen, and there is no perceived need to adjust this information for the proposed larger pack size.

A9. Other Products

In addition to Claratyne 10 mg tablets that are the subject of this submission, there are a number of other loratadine only products registered to be sold and classified as available in the New Zealand market as Pharmacy Only Medicines at the time of this submission (taken from the Medsafe Web site on 26 January 2016). These are:-

Brand Name	Strength and Pack Size	Sponsor Company
Allertyne	Tablets 10mg Packs - 10, 30, 100	Actavis New Zealand Limited
Apo-Loratadine	Tablets 10mg Packs - 15, 30, 100	Apotex NZ Limited
Loraclear Hayfever Relief	Tablets 10mg Packs - 10, 30, 60, 90, 100	AFT Pharmaceuticals Ltd
Lorafix	Tablets 10mg Packs - 10, 30, 100	Actavis New Zealand Limited
Lora-tabs	Film-coated Tablets 10mg Packs - 10, 30, 60	Mylan New Zealand Limited
Lora-tabs Allergy & Hayfever	Tablets 10mg Packs - 10, 30, 60, 90, 100, 1000	Mylan New Zealand Limited
Loratyne	Tablets 10mg Packs - 10, 30, 100	Actavis New Zealand Limited
Lorfast	Tablets 10mg Packs - 10, 30, 100	Multichem NZ Ltd
Your Pharmacy Loratadine Tablets	Tablets 10mg Packs - 30, 60	Orion Laboratories (NZ) Ltd

Clearly, most of the products currently have a 10 tablet pack size available although it is not known if all of them are marketed. The proposed increase to 10 days' supply for the General Sales medicine has the potential to affect all of those products with a 10 tablet pack size, depending on whether the companies concerned chose to restrict their indications to seasonal allergic rhinitis. The proposed change has the potential to offer consumers more choice in this distribution channel, and to offer more companies the option to participate in this market segment should they choose to do so.

However, the proposed change is unlikely to force change on any products currently in the market, since it is likely that the sponsor of most or all of them have chosen to label with broader indications (perennial allergic rhinitis and urticarial) and so would remain Pharmacy Medicines.

PART B

B1. SUBSTANCE SUMMARY

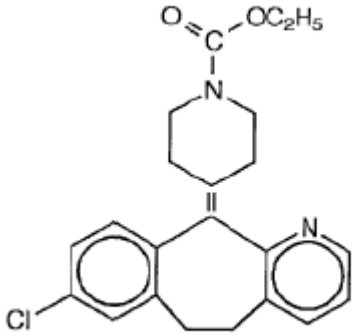
Loratadine is ethyl 4-(8-chloro-5,6-dihydro-11H-benzo [5,6]-cyclohepta [1,2-b] pyridin-11-ylidene)-1-piperidinecarboxylate[11].

Loratadine appears as a white to off-white crystalline powder. It is freely soluble in methanol, ethanol and chloroform, soluble in ether and practically insoluble in water[11].

Its chemistry information is below:

Name: Loratadine

Chemical Structure:



Molecular Formula: $C_{22}H_{23}ClN_2O_2$
Molecular Weight: 382.88
CAS Registry Number: 79794-75-5

Loratadine is a potent, long-acting tricyclic antihistamine with selective peripheral H_1-receptor antagonistic activity[11-12]. 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 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[11-12]. 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[11-12].

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[11].

Loratadine is not associated with cardiovascular toxicity[13].

No regulatory action has been taken world-wide since loratadine's launch due to safety concerns[5]. Safety data contained in company Periodic Safety Update Reports (PSURs) demonstrates that the overall benefit-risk balance for loratadine continues to be positive[5,14].

Loratadine has a rapid onset of action after oral administration, usually within one hour[15].

Loratadine 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[15-16]. Renal impairment has no significant effect on loratadine clearance[16].

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)

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 is one of the most common chronic respiratory conditions - affecting about 20% of the Australian population[18-19], 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[18-19]. 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 is readily self-diagnosed by consumers. 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[17,19]. Seasonal allergic rhinitis is typically easy to recognise as it coincides with the arrival of the relevant allergens in the environment with obvious symptoms[20-21].

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[17,20]. 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. 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[18]. This is confirmed by new data from the April 2015 Bayer Australia loratadine/Claratyne consumer study which showed that only 5 - 12% of loratadine purchases resulted from a recommendation by a doctor regardless of whether they obtained their medication via pharmacy or non-pharmacy retailers[22]. 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.

Once a day administration of 10 mg of loratadine provides effective treatment for the symptoms of seasonal allergic rhinitis and has been available as general sales medicines in small packs (maximum 5 dosage units) for control of the condition without the need for professional intervention. Since the product launch in 2014, the growth of loratadine supply in non-pharmacy retailers has

been significant, suggesting there is a strong demand for the medicine in non-pharmacy channels for self-medication of seasonal allergic rhinitis. The April 2015 Bayer Australia loratadine/Claratyne consumer study[22] involving 880 consumers showed that:

- consumers planned their allergy medication purchases in advance;
- 1 in 4 pharmacy shoppers also purchase allergy medication in grocery; and
- consumers purchased general sales loratadine as part of their 'weekly shop' (38%), 'top up shop' (36%), 'ran out of allergy' (12%) or 'stock up on allergy' (5%)

The symptoms of seasonal allergic rhinitis typically appear during the season in which aeroallergens are abundant in the air. The length of seasonal exposure to these aeroallergens is dependent on geographic location and climatic conditions and can last for several months each year[18-19]. The flexibility of antihistamine treatment[19] such as loratadine, used on an 'as needed' basis provides convenient self-medication during the hay fever season, especially for those with episodic or intermittent symptoms, which may be triggered by aeroallergens at any time of the season and lasting for weeks[15-17,20].

The symptoms of seasonal allergic rhinitis can be intermittent or persistent. Intermittent symptoms are defined as being present for less than 4 days per week or less than 4 weeks in a year, while persistent symptoms are defined as more than 4 days per week and last for more than 4 weeks in a year[17-18]. During a season the symptoms of seasonal allergic rhinitis can last for weeks or months, even intermittent symptoms can last for several weeks[16]. There is clinical evidence that suggests continuous treatment for allergic rhinitis is more effective than the use of second generation antihistamines on an intermittent basis[15,17,20]. The current general sales 5 pack of loratadine is not consistent with the treatment time typically required by many patients due to the recurrence of symptoms. A larger pack containing 10 dosage units will more conveniently provide treatment for purchasers wishing to obtain recurring intermittent symptomatic relief for the duration of their symptoms. From a therapeutic point of view, as long as safety is not compromised, it makes sense to have a larger pack available as this corresponds to the nature of the condition, which typically requires more than 5 days control during a season.

When a substance safety profile is very positive, it is more convenient for consumers to self-select the medication from retailers outside pharmacies, particularly if a pharmacy is not locally available or operates with limited trading hours. As previously discussed, consumer have already enthusiastically embraced the availability of loratadine 10 mg in packs of 5 tablets as a General Sales medicine. The proposed 10 tablet pack will facilitate this consumer behaviour by allowing them to access more than 5 days' supply in one pack

from a convenient outlet. From an accessibility and economic point of view, it will be more convenient and economical for a consumer to obtain a larger pack to allow for ongoing intermittent symptomatic control of the condition during the season.

The symptoms of seasonal allergic rhinitis are easily recognised because of the rapid and reproducible onset and offset of symptoms in association with pollen exposure[21], and these symptoms are unlikely to be indicative of a more serious underlying disease. 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 from Pharmacy Medicine to General Sale in 2012 has shown that the risks of misdiagnosis or masking of underlying diseases are minimal. The proposed 10 pack general sales product will retain the same labelling as the existing general sales 5 pack to ensure ongoing safe use of the medication.

Loratadine is potent, long lasting and has a rapid onset of action[11-12]. Its efficacy as a first line treatment for the symptomatic treatment of allergic rhinitis has long been established, with more than 20 years' user experience in New Zealand and globally. Once daily dosing of loratadine is simple and effective. With the flexibility of its use on an 'as needed' basis, loratadine is an ideal option for self-medication for the symptomatic control of seasonal allergic rhinitis.

Loratadine is considered to be a ‘second generation non-sedating antihistamine’ with an excellent safety profile. The toxicity and safety of loratadine have been well established over more than 20 years of product use in Australia and internationally.

Loratadine exhibits greater affinity for peripheral H_1-receptors than for central H_1-receptors and loratadine and its metabolites do not readily cross the blood-brain barrier[11-12]. These properties account for its lack of sedation effect compared to first generation antihistamines, and reinforces its position as an ideal option for treatment.

Loratadine has a safety profile similar to that of placebo - it does not potentiate the 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[11-12].

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 were administered without any untoward effects[11]. 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[13].

Loratadine has no known potential of abuse or dependency1[2]. The lack of CNS effects exhibited by loratadine means it has little potential for deliberate overdose or misuse. Relatively few cases of accidental overdose have been reported in the PSURs despite the high levels of usage and accessibility to loratadine. There has been no evidence of misuse/abuse of the product as a pharmacy or general sales medicine, and there is no potential for conversion of loratadine into illicit, prohibited or controlled substances.

Post marketing surveillance data for loratadine indicates a continuing favourable benefit/risk ratio[5, 14]. 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.
Review of Australian adverse event data since the product was introduced into Australia indicates that the number of loratadine adverse events in Australia is very low[23]. The introduction of the general sales 5 pack in Australia in 2012 did not result in any increased safety concerns, providing confidence that consumers can use this medicine safely and effectively without healthcare professional supervision. These observations also suggest that quality use of loratadine in a pack containing 10 dosage units in the general sales channel can be achieved using the same product information (labelling and pack insert).

Given that overdose (intentional or accidental) is rare, availability of a 10 tablet pack as a General Sales medicine is not expected to result in any changes to loratadine's safety profile. Bayer believes a general sales pack of loratadine containing 10 dosage units presents no increased risk to consumers compared to the currently available 5 pack. The convenience of improved accessibility either for those individuals whose symptomatic episodes tend to repeat during the hay fever season, or for those using the product on an 'as needed' basis, is worthwhile.

A change of classification to extend general sales loratadine from the current 5 pack to a 10 pack for use in adults and children 12 years and over will provide the convenience of improved accessibility and economic benefits to allow self-medication for during hay fever season, without compromising its benefit/risk ratio.

B3. TOXICITY AND SAFETY OF LORATADINE

The toxicity and safety of loratadine has been well established with over 20 years of product usage in the marketplace, much of which has been as an over-the-counter medicine.

The post marketing safety profile of loratadine is summarised in company PSURs. The latest available PSUR covering the period 02 Feb 2012 to 01 Aug 2012 is attached[5]. Additionally, a safety update covering 2 years of global experience from 02 Feb 2009 to 01 Feb 2011 is provided to support this proposal[14].

During the report period of 02 Feb 2012 to 01 Aug 2012, there was one safety update added to the company core data sheet (CCDS). In May 2012, 'dizziness' was added as a spontaneous adverse event in the CCDS[5]. Other than this, a review of the PSURs of loratadine oral use worldwide[5,14] shows there have been no relevant changes to either the overall frequency of adverse event reports, or the nature of the reported events. No new signals have been identified, and the safety information included in the Reference Safety Information and in the CCDS for loratadine products adequately reflects the information known at this time. The previously established favourable benefit-risk profile for loratadine for the relief of symptoms associated with seasonal allergic rhinitis, perennial allergic rhinitis and allergic skin disorders have been reconfirmed by the efficacy and safety data collected over many years[5].

Safety in Use

Diagnosis

Easy recognition of the familiar symptoms of seasonal allergic rhinitis and its seasonal nature lead to appropriate self-medication with loratadine containing medications[21]. The scope for misdiagnosis is limited.

Initial diagnosis is commonly made by, or at least confirmed by, a healthcare professional but once known the symptoms allergic rhinitis are well-recognised and self-medicated by consumers. 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].

Due to its very favourable safety profile, the ready diagnosis of seasonal allergic rhinitis and the need for greater access, loratadine was reclassified and made

available in non-pharmacy retailers in New Zealand in 2012. The strong demand of the general sales product as shown in the sales data (see section A6.1) with no change in safety profile[5,14, 23], suggests that the 2012 rescheduling of the 5 tablet pack loratadine 10 mg as a general sales medicine was beneficial to public health.

The proposed 10 tablet pack general sales product will include the same labelling as the current 5 pack general sales product[8,10] . A consumer information leaflet similar to that included in the current general sales product will be enclosed in the pack. This leaflet contains important symptom information to help consumers differentiate typical hay fever symptoms others that are not indicative of allergic rhinitis. The labelling will also refer consumers to a healthcare professional if symptoms persist for more than 5 days - this further minimises the risk of delaying any correct diagnosis, if applicable. Given that seasonal allergic rhinitis has a cyclical nature with easily recognised symptoms, together with the proven safety experience of the general sales presentation, it can be expected that the extension of the general sales loratadine pack size from 5 dosage units to 10 dosage units presents no increased risk of misdiagnosis, masking of underlying disease or delay in correct diagnosis.

Side Effects

Loratadine has an excellent safety profile. In clinical trials of loratadine at the recommended daily dose, adverse reactions incidence was reported as comparable to that of placebo[11]. The most frequently reported events included headache, somnolence, fatigue, dry mouth, rash and gastrointestinal disorders[11-12]. Rarely, abnormal hepatic function, alopecia, anaphylaxis, tachycardia, palpitations, dizziness and convulsion have also been reported[11-12]. Hypersensitivity to loratadine or the excipients in Claratyne have been reported on rare occasions. Studies of loratadine taken at the recommended dose have not revealed clinically significant levels of sedation in subjects[25-26].

In New Zealand, some information regarding adverse event incidence is available from the Suspected Medicine Adverse Reaction database. This data has a number of limitations and the reader is advised to visit www.medsafe.govt.nz/Projects/B1/ADRDisclaimer to be fully informed as to the exact nature of these limitations. This database shows 109 adverse events were reported (58 reports) from all loratadine containing products from 1 Jan 2000 up until 31 December 2015. No deaths were reported. The table below lists the top 10 adverse events reported in New Zealand over that time that were suspected to be causally related to loratadine:-

MedDRA Reaction Term	Number of Cases in New Zealand 2000 - 2015
Therapeutic response decreased	12
Somnolence	7
Dyspnoea	7
Dizziness	5
Diarrhoea	4
Headache	4
Rash	4
Urticaria	3
Pruritis	3
Palpitations	3

These adverse events are consistent with those reported internationally. Although incidence cannot be estimated from the SMARS database, it is clear from the figures above that it is low.

The Australian incidence of adverse events is similar to those observed in New Zealand and globally. The TGA Database of Adverse Event Notifications (DAEN) shows 807 adverse events were reported from all loratadine containing products from 1 Jan 1990 (prior to when the product was introduced into Australia) up until 20 May 2015, a period of more than 20 years[23]. Although the TGA reports may not necessarily 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 adverse events is very low and supports an excellent safety profile. The table below lists the top 10 adverse events reported to the TGA since loratadine was introduced into Australia - there are no notable differences identified when compared to the international experience with the product.

Top 10 adverse events reported in Australia since loratadine first marketed

MedDRA Reaction Term	Number of Cases
Somnolence	86
Drug Ineffective	84
Accidental exposure to product by child	84
Accidental Overdose	63
Palpitations	46
Dizziness	45
Insomnia	43
Headache	40
Nausea	37
Vomiting	24

To summarize, the adverse events associated with loratadine are well-known and their incidence is low. Local data from New Zealand and Australia is consistent with international data, providing confidence that there are no local effects to be aware of. Loratadine was considered suitable for reclassification to a general sales medicine in limited pack sizes in 2011, indicating that the Medicines Classification Committee was satisfied with the favorable safety profile of the product at that time. While this submission proposes an increase in the allowed general sales medicine supply of a maximum of 10 days usage from non-pharmacy outlets, this is still a short-term supply of the product that suitably limits potential risks, if any.

Contraindications

As with all medicines, loratadine is contraindicated in those individuals known to be hypersensitive to the active ingredient or excipients in the medication[2,12]. There are no other contraindications for loratadine.

Drug 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[12-13]. Concomitant administration with alcohol demonstrated no potentiating effect[11].

Special Populations

Children

While children are not the subject of this proposal, consideration of the safety in children adds a further dimension to the overall safety of loratadine.

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]. 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 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 and the condition that the subjects were being treated for in the studies. Also, in general, 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.

Elderly

The pharmacokinetic profile of loratadine does not change with increasing age and no dose adjustment is required.

Renal Impairment

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[28] 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 patients with normal renal function[12]. The elimination half-life for both the drug and the metabolite however, was not affected and haemodialysis also did not affect the pharmacokinetics of loratadine or desloratadine[12].

No dose adjustment is therefore required if there is a degree of renal insufficiency.

Severe Liver Impairment

Because loratadine is subject to first pass metabolism, it should be used with caution in patients with severe liver impairment[11]. The product labelling and consumer information leaflet included in the current, and proposed, product[8,10] indicate that patients should consult their healthcare professional before taking Claratyne/loratadine if they have liver disease.

Pregnancy and Breastfeeding

The use of loratadine in pregnancy is not recommended[2,12]. Loratadine is excreted in breast milk and its use should be avoided while breast-feeding[2,12].

The consumer information leaflet and product labelling states that Claratyne/ loratadine should not be taken without medical advice if pregnant or breast-feeding, and the statement is prominently emphasized with a pregnancy stop sign[8].

B4. POTENTIAL FOR MISUSE OR ABUSE OF LORATADINE

Loratadine has no known potential for abuse or dependency[12].

Loratadine does not readily cross the blood-brain barrier and therefore does not interact appreciably with H_1–receptors within the CNS, therefore limiting the incidence of sedation and drowsiness associated with first generation antihistamines.

Loratadine has been readily available as an OTC medicine for many years in New Zealand and internationally, including the 5 pack general sales product. There are very low numbers of reports of loratadine abuse or misuse globally. Literature searches have not revealed any reports of abuse or misuse with products containing loratadine. In the post-marketing surveillance reports, there were 2 cases reported during the 2 year period between 02 Feb 2009 to 01 Feb 2011[14], and none for the 6 months from 02 Feb 2012 to 01 Aug 2012[5]. To Bayer's knowledge there has been no evidence of misuse/abuse of the product as a pharmacy medicine, or general sales medicine in New Zealand or Australia[23].

Somnolence, headache and tachycardia have been reported with overdose[11-12], however relatively few cases of accidental overdose have been reported despite the high level of accessibility to loratadine[5,14]. During the 2 year period of 02 Feb 2009 to 01 Feb 2011, there were 38 overdose cases reported globally including 21 cases reported from a clinical study where loratadine >10 mg/ day was used as rescue therapy[14]. Of the reported overdose cases, the majority were of modest overdose and not associated with significant adverse events. During the 6 month period from Feb 2012 to Aug 2012, there were 7 healthcare professional confirmed overdose cases world-wide, of which one was considered serious[5].

In New Zealand, a search of the Suspected Medicine Adverse Reaction database does not report any cases of overdose, although it is not clear if the database would capture this detail. In Australia, a search of the TGA online adverse event database for all loratadine records since the product was first introduced found a low incidence of overdose cases during more than 20 years of product use (accidental exposure to product by children, 84 cases; accidental overdose, 63 cases; overdose, 10 cases)[23]. Available information from the Australian Poisons Information Centre annual reports[29-31] and Monash University Accident Research

Centre report[32] suggests that loratadine is not a substance subject to a high frequency of individual calls in Australia. This local information further supports the strong safety record for loratadine world-wide.

The maximum loratadine supply with the proposed new general sale pack is limited to 10 days. The labelling will advise users not to exceed the stated dose, not to use the product with other antihistamines, and to seek advice if symptoms persist for more than 5 days. Individuals are not likely to continue to self-medicate unnecessarily 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[11]. 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[13].

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

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