AFT pharmaceuticals

A New Force in Pharmaceuticals

Reclassification of Loratadine 10 mg tablets (Loraclear Hayfever Relief) in packs containing no more than 5 days supply.

Present Classification:	Pharmacy Only Medicine
Sought Classification:	General Sale Medicine

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Executive Summary

The prevalence of seasonal allergic rhinitis (SAR) has been increasing over recent decades, particularly in developed countries[1]. Best Practice Advocacy Centre 'bpac^{nz}' approximates that SAR may affect up to 30% of adults and 40% of children in New Zealand[2]. SAR can have a detrimental effect on patients' quality of life. The symptoms of SAR include sneezing, itching, watery rhinorrhea, and nasal blockage. These can lead to sleep disturbance, limitations in activity, and both practical and emotional problems for patients[3].

Second generation antihistamines are widely regarded as an effective and safe treatment option for SAR. One of the principal second generation antihistamines is loratadine. Loratadine is a long-acting, non-sedating antihistamine that selectively antagonises peripheral H1-receptor activity to provide symptomatic relief of seasonal allergic rhinitis (SAR) [4, 5]. Loratadine 10 mg tablets are readily available worldwide and have a well established safety and efficacy profile. In New Zealand, loratadine 10 mg tablets first gained marketing approval in 1988. The current classification of loratadine in New Zealand is Pharmacy Only Medicine (Schedule 2 medicine).

This application seeks the reclassification of loratadine 10 mg tablets - in packs of no more than 5 dosage units - to a General Sale Medicine. Packs of no more than 5 dosage units provide a maximum duration of therapy of 5 days for adults and children 12 years and over.

Supporting arguments for this proposal include:

- Allergic Rhinitis (AR) is readily self-diagnosed by patients. Various studies in the United States, United Kingdom and Australia have suggested that a significant portion of AR patients do not visit their medical practitioners for diagnosis and/or ongoing medical supervision[6, 7, 8]. Furthermore, SAR is typically simple to self-diagnose as it coincides with the arrival of the relevant allergen in the environment[9].

- Pharmacy operating hours are generally short compared to operating hours of supermarkets[10]. This can limit the access of SAR patients to required medication. The reclassification of loratadine 10 mg to a General Sale Medicine will allow patients easier and more convenient access to an effective and safe short term therapy for SAR.

- In the United States, loratadine 10 mg tablets are classified as over-the-counter (OTC) medications; equivalent to unscheduled in New Zealand. In the United Kingdom, loratadine 10 mg tablets are classified as General Sales List (GSL); also equivalent to unscheduled in New Zealand.

- The only current second generation antihistamine classified as a General Sale Medicine in New Zealand is fexofenadine in packaging configuration which provides a duration of therapy of a maximum of 5 days. Loratadine has a similar safety profile to fexofenadine but is more effective at reducing SAR symptoms, particularly at the early stages of therapy[11, 12, 13].

- Loratadine 10 mg tablets have been readily available as OTC medications in various countries for several years. In the United States, loratadine 10 mg tablets have been classified as an OTC medication for SAR since 2003 and have a well established safety and efficacy OTC record. Fexofenadine remained a prescription drug in the United States until 2011[14, 15].

- Some SAR patients may not respond to a particular antihistamine medication but can be treated successfully with a different antihistamine medication. Therefore, the reclassification of loratadine 10 mg (5 tablet pack) to a General Sale Medicine will provide SAR patients an alternative medication to fexofenadine[13].

- Loratadine has no known potential for abuse or misuse. The reclassification of loratadine 10 mg - 5 pack - to a General Sale Medicine is not expected to increase the potential for

abuse or misuse. A pack size of 5 tablets is smaller than the pack size of any product containing loratadine in New Zealand pharmacies or hospitals and it only permits short term therapy (maximum 5 days). This limits the use of this product and any potential misuse or abuse by consumers.

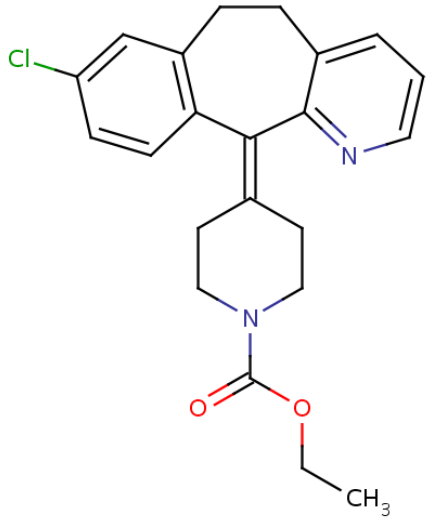
Loratadine is a safe and effective non-sedating antihistamine that has been available as a general sales medicine in the United States and United Kingdom for a number of years. Due to its strong safety and efficacy profile AFT Pharmaceuticals believe that the reclassification of loratadine 10 mg tablets with the appropriate indication, duration of treatment and dose restrictions to a General Sale Medicine will provide a significant benefit to New Zealand patients afflicted with SAR without imposing any greater risk than its current classification.

Part A

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

Name: Loratadine

Chemical Structure:



Molecular Formula: $C_{22}H_{23}ClN_2O_2$

Molecular Weight: 382.883

CAS Registry Number: 79794-75-5

2. Proprietary name(s)

Loraclear Hayfever Relief

3. Name of company/organisation/individual requesting reclassification

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

Dose form: Tablet
Strength: Loratadine10 mg

5. Pack size and other qualifications

The current pack sizes and other qualifications for Loraclear are outlined in Table 1.

Table 1: Loraclear pack size configurations

Medsafe File reference	Pack Configuration	Pack sizes:	Current Classification:	Marketing Status
TT50-7312	Aluminium foil Aluminium-PVC blister strips in a carton	10 Tablets	Pharmacy only	Not marketed
	Aluminium foil Aluminium-PVC blister strips in a carton	30 Tablets	Pharmacy only	Marketed
	Aluminium foil Aluminium-PVC blister strips in a carton	100 Tablets	Pharmacy only	Marketed
	Aluminium foil Aluminium-PVC blister strips in a carton	60 Tablets	Pharmacy only	Marketed

6. Indications for which change is sought

Indication: For relief from the symptoms of hay fever (seasonal allergic rhinitis) such as nose, nasal and sinus congestion, itchy nose and eyes and sneezing.

Patient population: Adults and children 12 years and over.

7. Present classification of medicine

Currently, all Loraclear package configurations are classified as Pharmacy Only Medicines (also known as Schedule 2 medicines).

8. Classification sought

This application seeks to reclassify loratadine 10 mg oral tablets in packaging configurations of up to 5 tablets (maximum 5 day therapeutic duration) to a General Sale Medicine (also referred to as Unscheduled Medicine).

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

Loratadine 10 mg tablets are available over the counter in most countries. The classification of loratadine for the United States, Canada, Australia and the United Kingdom are shown in Table 2.

Table 2: Classification status of loratadine 10 mg tablets in selected countries.

Country of Registration	Classification
United States	OTC - equivalent to unscheduled in New Zealand
Canada	OTC - Pharmacy Only
Australia	OTC - Pharmacy Only
United Kingdom	GSL - equivalent to unscheduled in New Zealand

OTC – over-the-counter, GSL – General Sales List. Sources: Online Databases of US Food and Drug Administration (FDA), Health Canada, Australian Therapeutic Goods Administration (TGA), UK electronic Medicines Compendium (eMC)

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

Loratadine 10 mg tablets were first marketed in Belgium in February 1988 by Merck & Co's. Loratadine is now available in most markets worldwide. In New Zealand, loratadine 10 mg tablets first gained marketing approval in New Zealand on the 12th of May 1988 under the trade name Claratyne, by Schering-Plough (NZ) Ltd. Loraclear 10 mg was given consent by Medsafe on 12 January 2006 to be marketed and distributed in New Zealand.

The sales and volume of loratadine 10 mg products in New Zealand for the past three years are shown in Table 3a and 3b.

Table 3 (a): Net Sales of Loratadine 10 mg products in New Zealand

Product	Annual sales to April 2009	Annual sales to April 2010	Annual sales to April 2011
AFT Loraclear	$602,400	$848,500	$829,500
AFT Loraclear Tabs 10 mg (30s)	$77,400	$241,700	$325,200
AFT Loraclear Tabs 10 mg (100s)	$525,000	$606,800	$438,700
AFT Loraclear Tabs 10 mg (60s)	~	~	$65,600
Apo-Loratadine	$287,000	$161,200	$124,600
Apo-Loratadine Tabs 10 mg (15s)	$71,400	$41,500	$31,600
Apo-Loratadine Tabs 10 mg (30s)	$215,600	$119,700	$93,000
Lorfast Tablets	~	$47,300	$52,900
Lorfast Tabs 10 mg (10s)	~	$18,600	$16,500
Lorfast Tabs 10 mg (30s)	~	$28,700	$36,400
Lora-Tabs	$529,100	$635,300	$585,100
Lora-Tabs10 mg (30s)	$529,100	$549,300	$466,500
Lora-Tabs10 mg (60s)	~	$85,900	$118,600
Claratyne	$972,500	$736,100	$625,100
Claratyne Tabs 10 mg (10s)	$516,400	$380,200	$311,200
Claratyne Tabs 10 mg (30s)	$456,100	$355,900	$313,900
Total	**$2,391,000**	**$2,428,400**	**$2,217,200**

Source: IMS

Table 3 (b): Volume sold (packs) of Loratadine 10 mg products in New Zealand

Product	Annual volumes to April 2009	Annual volumes to April 2010	Annual volumes to April 2011
AFT Loraclear	155,800	197,900	234,500
AFT Loraclear Tabs 10 mg (30s)	9,100	28,400	38,300
AFT Loraclear Tabs 10 mg (100s)	146,700	169,500	193,500
AFT Loraclear Tabs 10 mg (60s)	~	~	2,700
Apo-Loratadine	44,600	22,900	17,600
Apo-Loratadine Tabs 10 mg (15s)	13,900	6,900	5,200
Apo-Loratadine Tabs 10 mg (30s)	30,700	16,000	12,300
Lorfast Tablets	~	9,500	9,600
Lorfast Tabs 10 mg (10s)	~	4,500	3,500
Lorfast Tabs 10 mg (30s)	~	5,000	6,100
Lora-Tabs	59,500	55,300	47,900
Lora-Tabs10 mg (30s)	59,500	51,300	42,400
Lora-Tabs10 mg (60s)	~	4,000	5,500
Claratyne	62,000	46,400	38,700
Claratyne Tabs 10 mg (10s)	46,200	34,000	27,800
Claratyne Tabs 10 mg (30s)	15,900	12,400	10,900
Total	**321,900**	**332,000**	**348,300**

Source: IMS

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

The proposed carton labeling will be similar to that for the current Pharmacy Only Medicine but with additional restrictions on indications, duration of therapy and warning statements to further guide consumers. A copy of the proposed labelling can be found in Appendix 1.

12. Proposed warning statements

The following warning statements are presented on the carton label for Loraclear:

- Do not exceed the recommended dose.
- Do not use in children under 12 years unless advised to by your doctor or

pharmacist.

- Do not take for more than 5 days unless advised to by your doctor or pharmacist.
- Do not use with other antihistamines.
- Do not use when pregnant or when breast feeding except when advised by your doctor or pharmacist.
- If you have liver or kidney disease, check with your doctor or pharmacist before starting this medicine.
- 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.

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

A search on the Medsafe Therapeutic Database identified the following currently registered products containing loratadine 10 mg - Table 4.

Table 4: Current New Zealand registered products containing loratadine 10 mg.

Product	Company	Medsafe Approval Date
Apo-Loratadine Tablets, 10 mg (Pharmacy only)	Apotex NZ Ltd	6/12/2001
Lorfast Tablets, 10 mg (Pharmacy only)	Multichem NZ Limited	14/7/2005
Lora-Tabs, 10 mg (Pharmacy only)	Mylan New Zealand Ltd	2/8/2001
Claratyne Tablets, 10 mg (Pharmacy only)	Merck Sharp and Dohme (NZ) Ltd	12/5/1988
Claratyne Liqui-Gels (Pharmacy only)	Merck Sharp and Dohme (NZ) Ltd	19/8/2010
Aridine (Pharmacy only)	Douglas Pharmaceuticals Ltd	14/6/2001

Part B

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

Once a day administration of Loraclear 10 mg tablets provides effective symptomatic relief of seasonal allergic rhinitis (SAR). Loraclear 10 mg tablets contain the active ingredient, loratadine, which is a potent, long-acting, non-sedating antihistamine. Loratadine selectively antagonises peripheral H1-receptor activity, providing effective treatment of allergic conditions, including SAR. Loratadine is the active ingredient of the non-prescription drug Claritin (a best-selling prescription drug until 2002 when it became available without a prescription) and is one of the principal antihistamines found in low-cost non-prescription generics in hospitals, pharmacies and other stores worldwide. Loratadine is characterised by infrequent-dose related adverse reactions, minimal clinically significant drug interactions and no contraindications other than hypersensitivity or idiosyncrasy to loratadine[4, 5]. Furthermore, loratadine does not readily cross the blood brain barrier, exhibiting greater affinity for peripheral H1-receptors than for central H1-receptors. These properties account for the lack of sedation compared to first generation antihistamines[5].

SAR can have a detrimental effect on patients' quality of life. The symptoms of SAR include sneezing, itching, watery rhinorrhea, and nasal blockage. These symptoms typically occur in seasonal episodes, primarily during spring and autumn and may lead to sleep disturbance, limitations in activity, and both practical and emotional problems. The cost of treating this condition and indirect costs related to loss of workplace productivity resulting from this disease are substantial. It is also a significant cause of lost work and school days for patients[3]. Despite severe symptoms, people with allergic rhinitis (AR) tend not to seek medical advice regarding treatment. A study conducted in the US has found that only 12.4% of patients with AR consulted a physician, choosing instead to self-treat with home remedies and over-the-counter (OTC) medications[7, 16].

Currently, loratadine 10 mg tablets are available as a Pharmacy Only Medication in New Zealand. Pharmacy operating hours are generally short compared to operating hours of supermarkets. A study in New Zealand by the NZ Retailers Association concluded that supermarkets were open for 101.5 hours per week on average and pharmacies were open 55.1 hours per week on average in same areas examined[10]. This can limit the access of SAR patients to required medication. This application seeks the reclassification of loratadine 10 mg - in packs of no more than 5 tablets - to a General Sale Medicine. Packs of no more than 5 tablets provide a maximum duration of therapy of 5 days for adults and children 12 years and over. This will provide patients easier and more convenient access to an effective and safe short term therapy for SAR.

The only current second generation antihistamine classified as a General Sale Medicine in New Zealand is fexofenadine in a packaging configuration providing a therapeutic duration of a maximum of 5 days. Loratadine has a similar safety profile to fexofenadine[11]. Furthermore, it is essential to stress that loratadine 10 mg tablets have been readily available as OTC general sales medications in various countries for several years. In the United States, loratadine 10 mg tablets have been classified as an OTC medication for SAR since 2003 and has a well established safety and efficacy profile while fexofenadine remained a prescription drug in the United States until 2011[14, 15].

A number of studies have indicated that loratadine is more effective at reducing SAR symptoms when compared to fexofenadine[12, 13]. It has also been highlighted that some SAR patients may not respond to a particular antihistamine medication and they can be treated successfully with a different antihistamine medication. Therefore, the reclassification of loratadine 10 mg (5 tablet pack) to a General Sale Medicine will provide SAR patients an alternative medication to fexofenadine[13].

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

AR is a hypersensitivity reaction involving the inflammation of the nasal airways. It occurs when an allergen, such as pollen or dust, is inhaled by an individual with a sensitised immune system[1]. Sensitised individuals exhibit an immunoglobulin E (IgE)–mediated immune response which triggers a complex interaction of inflammatory mediators that result in the recruitment of inflammatory cells to the nasal mucosa and a subsequent inflammation of the mucous membranes of the nose, eyes, eustachian tubes, middle ear, sinuses, and pharynx[17].

AR may be seasonal or perennial. Individuals with SAR have symptoms primarily in spring and autumn, during the pollinating season of the plants to which they are sensitive, such as grass, trees, or various weeds. Those with perennial allergic rhinitis (PAR) have symptoms year round to allergens that have no seasonal variation, such as house dust mites, mould spores, or animal dander. The initial symptoms of AR typically include nasal itching, sneezing, watery nasal discharge, and blocked nose. Additionally, conjunctival symptoms (allergic conjunctivitis), impaired smell and headache may occur in association. These symptoms are usually more severe in patients with SAR rather than PAR as allergic reactions in SAR are typically triggered by higher concentrations of allergens and isn't characterised by continual exposure as in the case of PAR[9, 16, 18].

AR is readily self-diagnosed by patients. Furthermore, SAR is typically simple to recognise as it coincides with the arrival of the relevant allergen in the environment[9]. Self care options for AR including the availability of medications and knowledge about the condition allows patients to manage their symptoms adequately without the need for ongoing medical supervision. Various studies worldwide have indicated that a significant portion of patients do not visit their medical practitioners for AR diagnosis. In the UK, a study identified that only 18% of subjects with AR had visited their general practitioner in regards to their hay fever, over a preceding 2 year period[6]. In the US, it was recognised that most AR patients prefer to self medicate and only 12.4% of patients consulted a physician[7]. Another survey in

Australia acknowledged that most Australian adults now self-medicate for AR and revealed that nearly two-thirds of respondents did not consult their physician about their current AR treatment[8].

Therefore, forward planning and the ease of accessibility to medication is likely to support SAR patients by reducing the number and severity of symptomatic episodes[9]. Where episodic symptoms are inadequately controlled, then a review of the diagnosis and treatment options is often required and this will be indicated on the packaging label of Loraclear.

3. Relevant comparative data for like compounds

The newer, second generation antihistamines are widely regarded as an effective and safe treatment option to ease the symptoms of hay fever, hives and other allergies. They do not readily cross the blood brain barrier and thus lack the sedative effects associated with first generation antihistamines[1, 11, 19]. Second generation antihistamines generally have a better safety profile than first generation antihistamines. A non-sedating, non-impairing second generation antihistamine is preferred for all SAR patients, particularly those with a higher risk for the development of adverse effects[20].

Various studies have compared the safety and efficacy profiles of second generation antihistamines. Loratadine at recommended doses has been repeatedly shown to be safe in SAR patients. Similar to fexofenadine (the only second generation antihistamine classified as a General Sale Medicine in New Zealand), loratadine at recommended doses is not associated with sedative properties or performance impairment in tasks requiring a high degree of alertness or concentration when compared to placebo[11]. The cardiovascular safety of loratadine has been demonstrated in drug-interaction studies, elevated-dose studies, and clinical trials. Cardiac toxicity via ventricular arrhythmias has been reported rarely with second generation antihistamines such as astemizole and terfenadine. Loratadine is recognised to be safe from cardiac arrhythmia via the IKr channel based on pre-clinical and clinical evidence (see section 8 – Cardiac effects)[21].

A number of studies have shown that both loratadine and fexofenadine are effective in the symptomatic relief of SAR, however, it has been repeatedly recognised that reduction of SAR symptoms occurs at a significantly earlier stage when patients are treated with loratadine compared to fexofenadine[10, 12, 13]. This is particularly relevant to the nature of this application as the sought reclassification of loratadine 10 mg tablets (5 tablet pack) is for a short duration of therapy (5 days). Another study comprising 659 patients illustrated that the mean reduction of SAR symptoms were significantly greater when treated with loratadine compared to fexofenadine over a 14 day treatment course. Furthermore, in an attempt to assess the crossover treatment of patients who did not respond to the first antihistamine prescribed, loratadine was shown to provide a significantly better response than fexofenadine for patients who failed to respond to the first antihistamine prescribed[13].

Loratadine has been widely accepted as an effective treatment option for AR. Loratadine 10 mg tablets have been selected as *Consumer Reports Health Best Buy Drugs* due to its dosing convenience, cost, effectiveness and safety compared to other widely used second generation antihistamines including azelastine, cetirizine, desloratadine, fexofenadine, levocetirizine and olopatadine[19].

4. Local data or special considerations relating to New Zealand

There is mounting evidence of a rise in the prevalence of allergic diseases, including rhinitis, over recent decades. Allergy New Zealand approximates 20 per cent of the New Zealand population suffers from rhinitis[1]. The Best Practice Advocacy Centre 'bpac^{nz}' approximates that SAR may affect up to 30% of adults and 40% of children[2]. Furthermore, AR prevalence is reported to be higher in westernised English-speaking countries, including New Zealand, Canada, Australia, the United States and the United Kingdom when compared to other countries such as those in Eastern Europe and South and Central Asia. Lifestyle factors may have an important influence on the high prevalence of rhinitis and other allergic diseases found in these developed countries[1].

5. Interactions with other medicines

Loratadine is metabolised by cytochrome P450 isoenzymes CYP3A4 and CYP2D6. Therefore use with other drugs that inhibit or are metabolised by these hepatic enzymes may result in changes in the plasma concentration of either drug[22]. In controlled clinical trials, increased plasma concentrations of loratadine have been reported after concomitant use with certain drugs (mentioned in more detail below) that inhibit hepatic microsomal enzymes. However, this increase in plasma concentration was not associated with any clinically significant adverse events[4, 5]. Although loratadine metabolism, like that of terfenadine, is inhibited by certain drugs affecting hepatic enzymes, unchanged loratadine does not appear to share the cardiotoxic potential of unchanged terfenadine[4].

Erythromycin can inhibit the metabolism of loratadine. Similarly, clarithromycin inhibited the metabolism of loratadine and its active metabolite desloratadine[22]. Ketoconazole also appears to be able to inhibit the metabolism of loratadine, and at therapeutic doses is approximately three times more inhibitory than erythromycin. However, the concentrations of ketoconazole required are reported to be much higher than those required to inhibit the metabolism of astemizole (a piperidine derivative related to loratadine) or terfenadine. Clearance of the active metabolite desloratadine is also reduced[22].

Cimetidine appears to have an inhibitory effect on the metabolism of loratadine and also attenuates the clearance of its active metabolite desloratadine although no clinically significant consequences have been reported[22].

When administered concomitantly with alcohol, loratadine has no potentiating effects as measured by psychomotor performance studies[5].

6. Contraindications

Loraclear is only contraindicated in patients who have shown hypersensitivity or idiosyncrasy to loratadine[4, 5].

7. Possible resistance

Not applicable.

8. Adverse events - nature, frequency etc.

Loratadine is generally well tolerated. In controlled trials the adverse effect profile of loratadine was similar to that of placebo[4]. Unwanted effects that occasionally arise are most often mild and transient[23].

The most prevalent adverse effects associated with loratadine in large-scale controlled trials are listed in Table 5, below.

Table 5: Percentage of patients experiencing adverse effects following loratadine administration (n=1926)

Adverse effect	% patients
Drowsiness/somnolence	8
Insomnia	<2
Headache	12
Fatigue	4
Dry mouth	3
Pharyngitis	<2
Dizziness	<2
Gastrointestinal distress	<2

Source: Reference 4

Nervous System

Histamine is a neurotransmitter that plays an important part in the control of vigilance during the waking state. Blockade of the neuronal effects of endogenous histamine in the central nervous system (CNS) leads to the pronounced sedative effects commonly seen with first generation antihistamines. While not devoid of CNS effects, loratadine does not significantly cross the blood-brain-barrier and is therefore not associated with this pronounced sedation[4].

The most commonly reported adverse effects associated with loratadine use are headache, occurring in approximately 12% of patients, and drowsiness, occurring in approximately 8% of patients. The incidence of drowsiness appears to be dose related: the incidence in patients receiving 10 mg of loratadine is no greater than that in patients receiving placebo, but sedation becomes more prominent with doses of 20-40 mg [4].

A number of studies have been carried out to assess the severity and magnitude of mental impairment associated with loratadine. The level of sedation associated with 10 mg of loratadine has been assessed using EEG changes and subjective somnolence scores as endpoints. Loratadine produced a slight change in the EEG but this was not significantly different to placebo. Somnolence, measured by a visual analogue scale (VAS) was increased compared to baseline, but not compared to placebo. Psychomotor function, assessed using driving impairment, was similar to that of placebo following a 10 mg dose of loratadine. However, at a higher dose of 20 mg, loratadine was associated with a mild impairment in driving ability. Cognitive function has also been measured using cognitive battery tests – reaction times, compensatory tracking, divided attention and mathematical processing. Loratadine 10 mg was not associated with any cognitive impairment, compared to baseline or placebo[23]. The lack of CNS effects of loratadine 10 mg has also been established compared to other AR targeting compounds such as fexofenadine, promethazine and terfenadine[24, 25].

Overall, studies evaluating the CNS effects of loratadine suggest that at recommended doses, the CNS effects closely resemble those of placebo.

Cardiac Effects

Second generation antihistamines (terfenadine and astemizole) have been associated with rare but serious adverse cardiac effects including ventricular arrhythmias and cardiac arrest. These adverse effects occurred through the concentration-dependent blockade of the rapid component of the outward delayed rectifier current (I_{Kr}) potassium channels of cardiac cells. I_{Kr} blockade causes delays in repolarisation in myocardiac and cardiac conducting cells and the prolongation of QT intervals on the ECG.

Considerable research has therefore been undertaken to evaluate the cardiac safety of loratadine. Animal tissue models suggest that loratadine does block I_{Kr} but only at concentrations that are unlikely to be attained clinically[23]. Studies in healthy volunteers and atopic children show that loratadine was not associated with prolongation of the QT interval[26, 27].

Research suggests that even when given in large doses loratadine does not appear to cause the cardiac conduction disorders associated with the non–sedating antihistamines astemizole and terfenadine[22].

Overall it has been concluded that although loratadine is not entirely free of cardiac risks in predisposed patients acute cardiac events in response to 10 mg loratadine are extremely rare[23].

9. Precautions

The incidence of adverse effects associated with loratadine use generally appears to be less than that associated with the use of first generation (prototypical, sedating) antihistamines. However, similar effects have been reported, and the potential for typical adverse effects have been considered during loratadine therapy. Pharmacologic studies indicate that loratadine does not have appreciable anticholinergic effects at doses exceeding those required

for antihistaminic activity, and anticholinergic-like effects (e.g., dryness of the nose) either did not occur, or occurred with a frequency similar to placebo in clinical studies [4].

Hepatic or renal insufficiency

Patients with hepatic impairment or renal insufficiency (e.g., glomerular filtration rate less than 30 mL/minute), including geriatric patients, have decreased clearance of the drug, and should be given a lower initial dose of loratadine. Cautions on the package labelling of Loraclear instructs patients with liver or renal diseases to check with medical practitioners or pharmacists before commencing treatment [4].

Concurrent antihistamine administration

The package labelling of Loraclear also instructed patients to take the drug only as needed and not to exceed the recommended dosage. Patients are also advised against concurrent use of loratadine with other OTC antihistamines [4].

Use during pregnancy and breast feeding

The package label of Loraclear instructs pregnant woman not to commence treatment unless advised by their medical practitioner or pharmacist. UK product information does not recommend the use of loratadine in pregnancy due to limitations of controlled studies to date using loratadine in pregnant women. Reproduction studies in rats and rabbits using loratadine dosages up to 75 and 150 times, respectively, the maximum daily human dosage on a mg/m^2 basis have not revealed evidence of harm to the foetus [4]. However, one study reported an increased incidence of hypospadias in male infants born to women who received loratadine during pregnancy[4, 28]. The US CDC has also analysed data from the National Birth Defects Prevention study; they found no increase in the risk of second- or third-degree hypospadias in the infants of women who used loratadine in early pregnancy.

In addition, in two small prospective cohort studies that surveyed pregnant women who contacted a teratology information service, use of loratadine during the first trimester of pregnancy was not associated with major congenital anomalies and did not influence the rate of live birth, gestational age at birth, and birth weight[4, 28, 29]. Despite these findings, it should be noted that interpretation of these results is limited by the statistical limitations of the studies. Thus, while these data may be useful, further studies are needed to completely rule out the teratogenic risk of loratadine. Because there are no adequate and controlled studies to date using loratadine in pregnant women, loratadine should be used during pregnancy only when the potential benefits justify the possible risks to the foetus[4, 22].

No adverse effects have been seen in breast fed infants whose mothers were receiving loratadine, and the American Academy of Paediatrics considers that it is usually compatible with breast feeding. However, UK licensed product information recommends that loratadine should not be used in breast-feeding mothers[22]. Loratadine and desloratadine distribute readily into breast milk, achieving concentrations that are equivalent to those in plasma (milk to plasma AUC ratio of 1.17 for loratadine and 0.85 for desloratadine). Therefore, it has been recommended that caution should be exercised when loratadine is administered to a nursing woman, and a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother[4]. The package label of Loraclear instructs breast feeding woman to not commence treatment unless advised by their medical practitioner or pharmacist.

10. Potential for abuse or misuse.

Loratadine has no known potential for abuse. It has been readily available as an OTC medication in the United States and United Kingdom for several years. Moreover, an extensive literature search conducted for this application has not been able to locate any reports of abuse or misuse associated with products containing loratadine.

Furthermore, loratadine is second generation antihistamine which does not readily cross the blood-brain barrier and therefore does not interact appreciably with H_1-receptors within the CNS, limiting the incidence of sedation and drowsiness associated with first generation antihistamines[4]. This further reinforces the unlikeliness of loratadine abuse.

The reclassification of Loraclear 5 pack to a General Sale Medicine is not expected to increase the potential for abuse or misuse. Loraclear's pack size of 5 tablets is smaller than the pack size of any product containing loratadine in New Zealand pharmacies or hospitals and it only permits short term therapy (maximum 5 days). This limits the use of this product and any potential misuse or abuse by consumers.

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