AFT pharmaceuticals

A New Force in Pharmaceuticals

Reclassification of Cetirizine Hydrochloride 10 mg tablets (Histaclear) 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]. The 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 most commonly used antihistamines is cetirizine hydrochloride which is characterised as a long acting, non-sedating antihistamine. Cetirizine hydrochloride exhibits a high affinity for peripheral H1-receptors and is effective for the symptomatic relief of allergic conditions, including SAR[4]. Cetirizine hydrochloride 10 mg tablets are readily available worldwide and have a well-established safety and efficacy profile. In New Zealand, cetirizine hydrochloride 10 mg tablets first gained marketing approval in New Zealand in February 1993. The current classification of cetirizine hydrochloride in New Zealand is Pharmacy Only Medicine (Schedule 2 medicine).

This application seeks the reclassification of cetirizine hydrochloride 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 on-going medical supervision[5, 6, 7]. Furthermore, SAR is typically simple to self-diagnose as it coincides with the arrival of the relevant allergen in the environment[8].

- Pharmacy operating hours are generally short compared to operating hours of supermarkets[9]. This can limit the access of SAR patients to required medication. The reclassification of cetirizine hydrochloride 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, cetirizine hydrochloride 10 mg tablets are classified as over-the-counter (OTC) medications; equivalent to unscheduled in New Zealand. In the United Kingdom, cetirizine hydrochloride 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 a packaging configuration which provides a therapeutic duration of a maximum of 5 days. Various studies acknowledged that cetirizine has an excellent safety record that is comparable to fexofenadine and other well tolerated antihistamines[10, 11, 12, 13]. In addition, research as shown that cetirizine at recommended doses has a longer duration of therapeutic effect in reducing SAR symptoms compared to fexofenadine 120 mg or 180 mg[14, 15].

- Cetirizine hydrochloride 10 mg tablets have been readily available as OTC medications in various countries for several years. In the United States, it has been classified as an OTC medication for SAR since 2007 and has a well-established safety and efficacy OTC record. Fexofenadine remained a prescription drug in the United States until 2011[16, 17].

- 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 cetirizine hydrochloride 10 mg (5 tablet pack) to a General Sale Medicine will also provide SAR patients an alternative medication to fexofenadine[18].

- No cases of drug abuse or dependence have been reported with cetirizine hydrochloride to date[10]. The reclassification of cetirizine hydrochloride10 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 cetirizine 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 associated with its misuse or abuse by consumers.

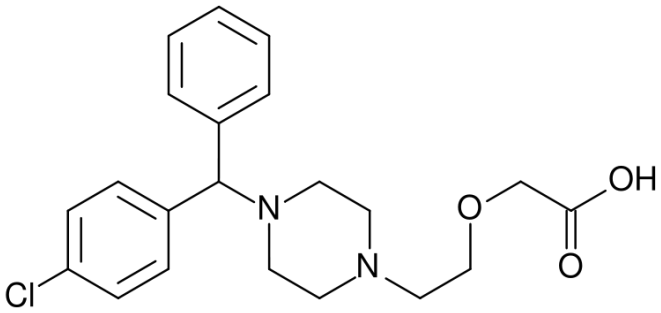
Cetirizine hydrochloride is a safe and effective non-sedating antihistamine that has been available as a general sales medicine in the United States and United Kingdom for a number of years. Due to its strong safety and efficacy profile AFT Pharmaceuticals believe that the reclassification of cetirizine hydrochloride 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: Cetirizine hydrochloride

Chemical Structure:



Molecular Formula: $C_{21}H_{25}ClN_2O_3 2(HCl)$

Molecular Weight: 461.81

CAS Registry Number: 83881-52-1

2. Proprietary name(s)

Histaclear

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: Cetirizine hydrochloride 10 mg

5. Pack size and other qualifications

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

Table 1: Histaclear pack size configurations

Medsafe File reference:	Pack Configuration	Pack sizes:	Current Classification:	Marketing Status
TT50-7312	Blister pack Al-PVC blisters in a carton	30 Tablets	Pharmacy only	Marketed
	Blister pack Al-PVC blisters in a carton	90 Tablets	Pharmacy only	Marketed
	Blister pack Al-PVC blisters in a carton	100 Tablets	Pharmacy only	Not marketed

6. Indications for which change is sought

Indication: Relief from symptoms of hay fever (seasonal allergic rhinitis) such as runny 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 Histaclear package configurations are classified as a Pharmacy Only Medicine (also known as Schedule 2 medicine).

8. Classification sought

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

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

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

Table 2: Classification status of cetirizine hydrochloride 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

Cetirizine hydrochloride 10 mg tablets were first marketed in Belgium in 1987 by UCB. It is now available in most markets worldwide. Cetirizine hydrochloride 10 mg tablets first gained marketing approval in New Zealand on the 25th of February 1993 under the trade

name Zyrtec by Pharmabroker Sales Ltd. Histaclear 10 mg was given consent by Medsafe on the 5th of July 2007 to be marketed and distributed in New Zealand.

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

Table 3(a): Net sales of cetirizine hydrochloride 10 mg products in New Zealand

Product	Annual Sales to April 2009	Annual Sales to April 2010	Annual Sales to April 2011
AFT Histaclear	$40,300	$142,700	$220,100
AFT Histaclear Tabs 10 mg (30s)	$40,300	$142,700	$178,000
AFT Histaclear Tabs 10 mg (90s)	~	~	$42,100
Allerid C	$17,300	$36,000	$39,300
Allerid CTabs 10 mg (10s)	$4,000	$15,200	$13,200
Allerid CTabs 10 mg (30s)	$13,300	$20,800	$26,100
Apo-Cetirizine	$89,600	$34,300	$30,700
Apo-Cetirizine Tabs 10 mg (15s)	$28,200	$14,400	$10,900
Apo-Cetirizine Tabs 10 mg (30s)	$61,400	$19,900	$19,900
Razene	$702,500	$972,300	$896,500
Razene Tabs 10 mg (30s)	$692,700	$656,100	$631,200
Razene Tabs 10 mg (90s)	$310,300	$316,200	$265,300
Arrow-Zetop	$111,100	$319,300	$387,900
Arrow-Zetop Tabs 10 mg (10s)	~	$2,700	$11,900
Arrow-Zetop Tabs 10 mg (30s)	~	$7,800	$21,800
Arrow-Zetop Tabs 10 mg (100s)	$111,100	$308,900	$354,300
Zyrtec	$1,224,000	$1,117,600	$1,032,300
Zyrtec Tabs 10 mg (10s)	$615,000	$589,200	$623,700
Zyrtec Tabs 10 mg (30s)	$609,000	$528,400	$408,700
Total	**$2,184,800**	**$2,622,200**	**$2,606,800**

Source: IMS

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

Product	Annual volumes to April 2009	Annual volumes to April 2010	Annual volumes to April 2011
AFT Histaclear	5,400	21,000	30,300
AFT Histaclear Tabs 10 mg (30s)	5,400	21,000	28,300
AFT Histaclear Tabs 10 mg (90s)	~	~	2,100
Allerid C	3,500	7,700	7,200
Allerid CTabs 10 mg (10s)	1,000	3,900	2,800
Allerid CTabs 10 mg (30s)	2,400	3,800	4,400
Apo-Cetirizine	12,200	5,100	4,400
Apo-Cetirizine Tabs 10 mg (15s)	4,700	2,400	1,800
Apo-Cetirizine Tabs 10 mg (30s)	7,500	2,700	2,600
Razene	110,200	109,500	101,100
Razene Tabs 10 mg (30s)	109,600	91,800	86,300
Razene Tabs 10 mg (90s)	91,100	17,700	14,800
Arrow-Zetop	50,500	141,800	165,800
Arrow-Zetop Tabs 10 mg (10s)	~	500	2,200
Arrow-Zetop Tabs 10 mg (30s)	~	900	2,600
Arrow-Zetop Tabs 10 mg (100s)	50,500	140,400	161,000
Zyrtec	87,700	82,100	81,300
Zyrtec Tabs 10 mg (10s)	65,500	62,700	66,400
Zyrtec Tabs 10 mg (30s)	22,300	19,300	14,900
Total	**269,500**	**367,200**	**390,100**

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 direct consumers. A copy of the proposed labelling is available in Appendix 1.

12. Proposed warning statements if applicable

The following warning statements (or equivalent) will be presented on the carton label for Histaclear:

- 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 problems, 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 of the Medsafe Therapeutic Database identified the following currently registered products containing cetirizine hydrochloride 10 mg- Table 4.

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

Product	Company	Medsafe Approval Date
Allerid C Tablets, 10 mg (Pharmacyonly)	Multichem NZ Limited	3/4/2003
Apo-Cetirizine Tablets, 10 mg (Pharmacy only)	Apotex NZ Ltd	26/4/2002

Razene Tablets, 10 mg (Pharmacy only)	Mylan New Zealand Ltd	4/10/2001
Arrow-Zetop Tablets, 10 mg (Pharmacy only)	Arrow Pharmaceuticals (NZ) Limited	3/4/2003
Zyrtec Tablets, 10 mg (Pharmacy only)	UCB Pharma/Pharmabroker Sales	25/2/1993
Arrow - Cetirizine (Pharmacy only)	Arrow Pharmaceuticals (NZ)	5/4/2007
Cetirizine (Pharmacy only)	REX Medical Ltd	21/2/2008

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 cetirizine hydrochloride 10 mg tablets provides effective symptomatic relief of seasonal allergic rhinitis (SAR) [10]. Histaclear 10 mg tablets contain the active ingredient, cetirizine hydrochloride, which is a long-acting non-sedating antihistamine with some mast-cell stabilising activity. It appears to have a low potential for drowsiness at usual doses and is virtually free of antimuscarinic activity. It is used for the symptomatic relief of allergic conditions, including SAR[4]. Cetirizine is characterised by infrequent-dose related adverse reactions, minimal clinically significant drug interactions and no contradictions other than hypersensitivity or idiosyncrasy to cetirizine[4,10]. Furthermore, cetirizine exhibits greater affinity for peripheral H1-receptors than for central H1-receptors as it doesn't readily cross the blood brain barrier. These properties account for the reduced sedative effects compared to first generation antihistamines[4].

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 the 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 tend not to seek medical advice regarding treatment. A study conducted in the US has found that only 12.4% of patients with allergic rhinitis (AR) consulted a physician, choosing instead to self-treat with home remedies and over-the-counter (OTC) medications[6, 19].

Currently, cetirizine hydrochloride 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[9]. This can limit the access of SAR patients to required medication. This application seeks the reclassification of cetirizine hydrochloride 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 patients.

The only current second generation antihistamine classified as a General Sale Medicine in New Zealand is fexofenadine in packaging configuration providing a therapeutic duration of a maximum of 5 days. Although the sedative effect of cetirizine at high doses is greater than that of fexofenadine, various studies have found that cetirizine at the recommended dose has an excellent safety record that is comparable to fexofenadine[11, 12]. Furthermore, it has been recognised that cetirizine has a longer duration of therapeutic effect in reducing SAR symptoms when compared to fexofenadine[14, 15]. It has also been highlighted that some SAR patients may not respond to a particular antihistamine medication but they can be treated successfully with a second antihistamine medication. Therefore, the reclassification of cetirizine hydrochloride 10 mg (5 tablet pack) to a General Sale Medicine will also provide SAR patients an alternative to fexofenadine[18].

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

Allergic rhinitis 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[20].

AR may be seasonal or perennial. Individuals with seasonal allergic rhinitis (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 on 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 it isn't characterised by continual exposure as in the case of PAR[8, 19, 21].

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[8]. 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 on-going 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[5]. In the US, it was recognised that most AR patients prefer to self-medicate and only 12.4% of patients consulted a physician[6]. 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[7].

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[8]. 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 Histaclear.

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 affects associated with first generation antihistamines; which are characterised with sedative and antimuscarinic effects[1, 11, 22]. 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[23].

Various studies have compared the safety and efficacy profiles of second generation antihistamines. Although some studies have highlighted that the sedative effect of cetirizine is greater than that of fexofenadine or loratadine, it remains much lower than the first generation antihistamines[11]. Various studies have acknowledged that cetirizine has an excellent safety record that is comparable to the other well tolerated antihistamines such as fexofenadine and loratadine[11, 12]. The cardiovascular safety of cetirizine 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. Similarly to fexofenadine, the ECG effects of cetirizine have been studied in normal subjects and it was established that doses up to six times the usual recommended dose did not prolong the QT interval and thus, it is safe from cardiac arrhythmia via the IKr channel[10,13].

A number of studies have shown that both cetirizine and fexofenadine are effective in the symptomatic relief of SAR, however, many have recognised that the administration of cetirizine at concentrations of 10 mg has a longer duration of therapeutic effect in reducing SAR symptoms when compared to the administration of 120 to 180 mg of fexofenadine. One study recognised that cetirizine produced greater relief of SAR symptoms than fexofenadine at 12 hours post dose and over the 5 to 12 hour post dose periods[15]. While another study also recognised that the reduction of SAR symptoms by cetirizine was significantly better than fexofenadine at 22 hours post dose[14].

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 be an important influence on the high prevalence of rhinitis and other allergic diseases found in these developed countries[1, 14].

5. Interactions with other medicines

Concomitant administration of cetirizine hydrochloride with drugs known to inhibit cytochrome P-450 microsomal enzymes (e.g., azithromycin, erythromycin, ketoconazole) has not been associated with clinically important interactions. The extent to which cetirizine is metabolised in the liver is not known but is believed to be minimal. It is excreted mainly unchanged in urine, thus, the drug may have a low potential for adverse drug interactions associated with metabolic enzyme systemshttp://www.medicinescomplete.com.ezproxy.auckland.ac.nz/mc/ahfs/current/a398026.htm - r3980262[10].

No interactions were observed in pharmacokinetic interaction studies when cetirizine was used concomitantly with pseudoephedrine or antipyrine. A 16% decrease in the clearance of cetirizine was observed in a multiple-dose study when theophylline (400 mg given once daily for 3 days) was administered with cetirizine hydrochloride (20 mg given once daily for 3 days); the disposition of theophylline was not altered by the concomitant administration with cetirizine[10].

6. Contraindications

Cetirizine is contraindicated in patients who are hypersensitive to cetirizine, hydroxyzine, or any ingredient in the formulation[10].

7. Possible resistance

Not applicable

8. Adverse events - nature, frequency etc.

Cetirizine hydrochloride is generally well tolerated. In placebo-controlled trials, adverse effects were mild to moderate and the rate of discontinuance of therapy secondary to adverse effects associated with the drug was similar to that reported with placebo[10].

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

Table 5: Percentage of patients experiencing adverse effects following loratadine administration

Adverse effect	% patients
Somnolence	14
Fatigue	6
Headache	>2
Dry mouth	5
pharyngitis	2
dizziness	2
Gastrointestinal distress	<2

Source: Reference 3 and reference 27

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. Current clinical evidence suggests that at recommended therapeutic dosages, cetirizine is without significant CNS activity. Although cetirizine can cross the brain barrier and binds to approximately 30% of the H_1 receptors in

the cerebral cortex, numerous studies using objective assessments of the CNS effects of cetirizine have demonstrated that the drug, at the standard 10 mg/day dosage, generally did not impair CNS function[24].

In placebo-controlled trials, the most commonly reported adverse effects associated with cetirizine hydrochloride are somnolence, fatigue and dizziness, occurring in 14%, 6% and 2% of patients, respectively[10, 24]. Overdose of cetirizine (>4 times the maximum recommended dosage) did not produce clinically significant CNS effects [24].

At therapeutic doses, cetirizine was associated with no or mild impairment of driving and psychometric test performance; these effects were not generally considered to have a significant impact on driver's ability. Although somnolence has been reported in some clinical trials, various studies have determined that the sedative properties of cetirizine are low when compared to other first- and second-generation antihistamine agents, and it is unlikely to be associated with significant sedative effects[24].

Overall, studies evaluating the CNS effects of cetirizine 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.

Unlike terfenadine and astemizole (which have been withdrawn from the US and other markets), cetirizine has not been associated with adverse cardiac effects when administered either as monotherapy or in combination with agents that are metabolised by the cytochrome P450 (CYP) system. In healthy adult volunteers cetirizine had no clinically relevant effect on the QT or QTc interval, even at dosages up to 6-fold higher than those recommended (e.g. 60 mg/day for 7 days in adults). Cetirizine shows no significant or

clinically relevant inhibition of cardiac potassium channels that regulate the duration of the action potential and as a consequence the duration of the QT interval[10, 24].

9. Precautions

The incidence of adverse effects associated with cetirizine generally appears to be less than that associated with the use of first generation (prototypical, sedating) antihistamines, although evidence from some clinical studies indicates that the incidence of somnolence associated with cetirizine may be higher than that associated with other second generation antihistamines (e.g., loratadine). Pharmacologic studies indicate that cetirizine does not have appreciable anticholinergic effects, although dry mouth has been reported in clinical studies more frequently with the drug than with placebo[10].

Somnolence

Because somnolence has been reported in some individuals in clinical studies, patients should be warned that the drug may impair their ability to perform hazardous activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle). The package label of Histaclear warns consumers about the possibility that this medication may affect their affect your ability to drive or operate machinery.

Hepatic or renal insufficiency

Patients with chronic hepatic impairment, patients with moderate renal impairment (creatinine clearance of 11–31 mL/minute), patients undergoing haemodialysis, and geriatric patients have decreased clearance of the drug. In patients with hepatic impairment, US licensed product information recommends that the dosage of cetirizine may need to be reduced to half the usual oral daily dose. Similarly in patients with renal impairment, both UK and US product information recommends a dosage reduction to half the usual daily dose[4, 10]. Cautions on the package label of Histaclear instructs patients with liver or renal diseases to check with medical practitioners or pharmacists before commencing treatment. Patients are also instructed to take the drug only as needed and not to exceed the recommended dosage.

Use during pregnancy and breast feeding

There are no adequate and controlled studies to date using cetirizine in pregnant women and animal studies are not always predictive of human response, cetirizine hydrochloride should be used during pregnancy only when clearly needed. The package label of Histaclear instructs breast feeding or pregnant woman to not commence treatment unless advised by their medical practitioner or pharmacist[10]. However, there have been no reports of foetal harm as a result of treatment with cetirizine. Reproduction studies in mice, rats, and rabbits using oral cetirizine hydrochloride dosages up to 96, 225, and 135 mg/kg daily, respectively (approximately 40, 180, and 220 times, respectively, the maximum recommended daily oral dosage in adults on a mg/m^2 basis), have not revealed evidence of teratogenicity[10].

In lactating beagles, about 3% of a cetirizine dose was distributed in milk. In mice, cetirizine caused reduced pup weight gain during lactation when dams were receiving a cetirizine hydrochloride dosage of 96 mg/kg daily (about 40 times the maximum recommended daily dosage in adults on a mg/m^2 basis). In rats, cetirizine hydrochloride and pseudoephedrine hydrochloride caused reduced pup weight gain and decreased viability during lactation when administered orally to dams in fixed combination at a dosage of 6/154 mg/kg (approximately 5 times the maximum recommended adult dosage on a mg/m^2 basis) but not when administered at a dosage of 1.6/38 mg/kg (approximately the maximum recommended adult dosage on a mg/m^2 basis). Cetirizine is also distributed into human milk. http://www.medicinescomplete.com.ezproxy.auckland.ac.nz/mc/ahfs/current/a398026.htm -r3980261Therefore, the use of cetirizine hydrochloride in nursing women is not recommended. The package label of Histaclear instructs breast feeding woman to not commence treatment unless advised by their medical practitioner or pharmacist[10].

10. Potential for abuse or misuse.

Cetirizine hydrochloride has no known potential for abuse. No cases of drug abuse or dependence have been reported with cetirizine hydrochloride to date[10]. Cetirizine has been readily available in many countries for several years as an OTC product. 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 cetirizine hydrochloride.

Furthermore, the reclassification of Histaclear 5 pack to a General Sale Medicine is not expected to increase the potential for abuse or misuse. Histclear's pack size of 5 tablets is smaller than the pack size of any product containing cetirizine hydrochloride in New Zealand pharmacies and this only permits short therapy duration of maximum 5 days. Therefore, this limits the use of this product and any potential misuse or abuse by consumers.

References

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