Reclassification of Cetirizine Hydrochloride 10 mg in packs containing no more than 10 dosage units

Present classification:	Pharmacy Only
Proposed classification:	General Sale

AFT Pharmaceuticals Limited

Level 1, Nielsen Building
129 Hurstmere Rd
Takapuna, Auckland, 0622
PO Box 33-203, Takapuna, Auckland

Objective:

This application seeks reclassification of cetirizine hydrochloride in divided solid dosage forms for oral use containing 10 milligrams or less per dose form when sold in the manufacturer's original pack containing not more than 10 dosage units.

PART A

1. **International Non-Proprietary Name of the Medicine**

   Cetirizine hydrochloride

2. **Proprietary name(s)**

   Histaclear
   (cetirizine hydrochloride 10 mg per tablet)

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

   AFT Pharmaceuticals Ltd
   129 Hurstmere Road
   Takapuna 0622
   Auckland
   New Zealand

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

   Dose form: Tablets
   Strength: 10 mg of cetirizine hydrochloride per tablet
   Pack size: Packs of 10 tablets or less (100 mg of cetirizine hydrochloride per pack total).

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

   Proposed pack size: In packs containing 100 mg of cetirizine hydrochloride or less (i.e. In packs of 10 tablets or less where each tablet contains cetirizine hydrochloride 10 mg)
   Storage conditions: Store below 30 °C.

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

   Indication: for the treatment of seasonal allergic rhinitis such as runny nose, nasal and sinus congestion, itchy nose and eyes and sneezing

7. **Present classification of the medicine**

Conditions	Classification
except for oral use	Prescription
for oral use **except** in divided solid dosage forms for oral use containing 10 milligrams or less of cetirizine hydrochloride per dose form for the treatment of seasonal allergic rhinitis when sold in the manufacturer's original pack containing not more than 5 days' supply	Pharmacy Only
in divided solid dosage forms for oral use containing 10 milligrams or less of cetirizine hydrochloride per dose form for the treatment of seasonal allergic rhinitis when sold in the manufacturer's original pack containing not more than 5 days' supply	General Sale

8. Classification sought

General sale - in divided solid dosage forms for oral use containing 10 milligrams or less of cetirizine hydrochloride per dose form for the treatment of seasonal allergic rhinitis when sold in the manufacturer's original pack containing not more than 10 dosage units.

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

AUSTRALIA:	General sale, Pharmacy, Prescription Only preparations containing 10 days' supply of Cetirizine 10 mg are classified as General sale
UNITED KINGDOM:	GSL, Pharmacy, Prescription Only preparations containing 30 tablets of cetirizine 10 mg are classified as GSL
UNITED STATES:	OTC, Prescription
CANADA:	OTC, Prescription

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

Sales data in New Zealand (IMS accessed on 07 January 2020)

Product	Units sales to Dec 16	Units sales to Dec 17	Units sales to Dec 18	USD sales to Dec 16	USD sales to Dec 17	USD sales to Dec 18
Film-coated tablets						
Tablets						

Sales data in Australia (IMS accessed on 07 January 2020)

Product	Units sales to Dec 16	Units sales to Dec 17	Units sales to Dec 18	USD sales to Dec 16	USD sales to Dec 17	USD sales to Dec 18
Film-coated tablets						

Product	Units sales to Dec 16	Units sales to Dec 17	Units sales to Dec 18	USD sales to Dec 16	USD sales to Dec 17	USD sales to Dec 18
PHARMACARE						
Capsules						
Tablets						

Product	Units sales to Dec 16	Units sales to Dec 17	Units sales to Dec 18	USD sales to Dec 16	USD sales to Dec 17	USD sales to Dec 18

USD: United States Dollar

Product approval dates in New Zealand

Product	**Approval date**
Apo-Cetirizine Tablet, 10 mg	26/04/2002
Arrow - Cetirizine Film coated tablet, 10 mg	5/04/2007
Cetirizine Hayfever & Allergy Relief Film coated tablet, 10 mg, Pharmacy Health	29/08/2019
Cetirizine tablets 10mg Tablet, 10 mg, Ipca	15/05/2014
Hayfever Relief Film coated tablet, 10 mg, Ethics	13/09/2012
Hayzone Film coated tablet, 10 mg	7/03/2019
Histaclear Tablet, 10 mg (Pharmacy Only)	5/07/2007
Histaclear Tablet, 10 mg (General sale)	24/05/2012
Medreich Cetirizine Hayfever & Allergy Relief Film coated tablet, 10 mg	29/08/2019
Razene Film coated tablet, 10 mg	4/10/2001
Razene Allergy & Hayfever Film coated tablet, 10 mg	2/07/2009
Your Pharmacy Cetirizine Tablets Tablet, 10 mg	17/01/2013
Zanlan Film coated tablet, 10 mg	7/02/2002
Zetop Film coated tablet, 10 mg	3/04/2003
ZISTA Tablet, 10 mg	15/05/2014
Zodac Film coated tablet, 10 mg	12/07/2001
Zyrtec Film coated tablet, 10 mg	25/02/1993

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

There is mounting evidence of a rise in the prevalence of allergic diseases, including rhinitis, over recent decades. It is estimated that approximately 20 per cent of the New Zealand population suffers from allergic rhinitis.[1] Hence, increasing the availability of the medicine as “General Sale” will greatly benefit New Zealanders.

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

Please refer to Appendix A.

13. Proposed warning statements (if applicable)

- Do not use in children under 12 years old.
- Do not use for more than 10 days at a time.
- Do not use with other antihistamines.
- Do not use if you are pregnant or breastfeeding except on the advice of a healthcare professional.
- Do not use if you have impaired kidney function
- 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

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

Apo-Cetirizine Tablet, 10 mg

Arrow - Cetirizine Film coated tablet, 10 mg

Cetirizine Hayfever & Allergy Relief Film coated tablet, 10 mg, Pharmacy Health

Cetirizine tablets 10mg Tablet, 10 mg, Ipca

Hayfever Relief Film coated tablet, 10 mg, Ethics

Hayzone Film coated tablet, 10 mg

Medreich Cetirizine Hayfever & Allergy Relief Film coated tablet, 10 mg

Razene Film coated tablet, 10 mg

Razene Allergy & Hayfever Film coated tablet, 10 mg

Your Pharmacy Cetirizine Tablets Tablet, 10 mg

Zanlan Film coated tablet, 10 mg

Zetop Film coated tablet, 10 mg

ZISTA Tablet, 10 mg

Zodac Film coated tablet, 10 mg

Zyrtec Film coated tablet, 10 mg

PART B

1) Indications and dose

- **What is the medicine indicated for, and for which indication(s) is the reclassification application for?**

  The medicine is used for the relief of symptoms of hayfever (seasonal and perennial allergic rhinitis) such as runny nose, nasal and sinus congestion, itchy nose and eyes and sneezing, it may also be used in skin allergies to relieve itching and rashes.

  The reclassification application is intended for the following indication:

  "for the treatment of seasonal allergic rhinitis such as runny nose, nasal and sinus congestion, itchy nose and eyes and sneezing"

- **What is the evidence that the proposed indication is an OTC indication (ie, that the diagnosis and treatment can be understood by the consumer; that the risks of inappropriate treatment can be minimised)?**

  Cetirizine (for oral use) is classified as a non-prescription (OTC) medicine in Medsafe Classification database. It is already available as a General sale medicine in packs containing no more than 5 tablets. The medicine is intended for treatment of an allergic condition, symptoms of which are clearly mentioned on the label of the medicine. The patient can match his/her symptoms/ condition with those on the medicine label and can easily and correctly take the medicine.

- **What is the treatment population for the indication (ie, age, gender, etc.)?**

  The treatment population for the indication is:
  Adults and Children (12 years and over)

- **What is the dose and dose frequency of the medicine for this indication?**

  The dose and dose frequency of the medicine for this indication is:
  Adults and Children (12 years and over): 1 tablet daily

2) Presentation

- **What is the proposed dose from and strength of the medicine to be reclassified? Is this the same for all indications?**

  The proposed dose form is tablets. The strength of the medicine is 10 mg. This is same for all indications.

- **What disposal considerations need to be made for the medicine?**

  No special disposal considerations are required for this medicine.

- **How practical and easy to use is the proposed presentation?**

The proposed presentation is patient-friendly and convenient to use. The tablets are packed in a blister. Each tablet can be easily pulled out of the blister without affecting the integrity of the other tablets in the blister.

This presentation is effectively already available for supply in grocery outlets and this change effectively increases the pack size from 5 tablets to 10 tablets.

3) Consumer benefit

- **What is the history of this medicine's use for the proposed indication(s) (ie, number of users, number of countries used in)?**

  Cetirizine is a widely used medicine all over the globe. It was patented in 1981 and came into medical use in 1987. It is currently available as a single ingredient preparation in Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Indonesia, Israel, Ireland, Italy, Japan, Malaysia, Mexico, Netherland, Norway, New Zealand, Philippines, Poland, Portugal, Russia, South Africa, Singapore, Sweden, Switzerland, Thailand, Turkey, UAE, UK, Ukraine, USA and Venezuela. Its available as multi-ingredient preparations in Argentina, Belgium, Brazil, Canada, Chile, China, Finland, France, Germany, Hong Kong, Hungary, India, Indonesia, Italy, Malaysia, Mexico, Philippines, Poland, Singapore, Spain, Thailand, Turkey, Ukraine, USA and Venezuela.[2] In 2017, cetirizine was the 66th most prescribed medication in United States, with more than 11 million prescriptions.[3]

  Cetirizine tablets are available in New Zealand as General sale medicine since May 2012.

- **To what extent is this medicine used for the proposed indication(s) (ie, duration of use, frequency of use)?**

  The recommended dose of cetirizine is 2.5 to 10 mg depending on age and symptom severity.[2] The time of administration can be varied to suit individual patient needs.

- **What is the evidence that improved access is beneficial for the individual?**

  Currently, cetirizine hydrochloride 10 mg tablets (except packs of 5 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.[4] This can limit the access of SAR patients to required medication. Increasing the number of tablets per pack from 5 to 10 will provide patients easier and more convenient access to therapy.

  A similar antihistamine agent, loratadine, are already available in packs of 10's as General sale medicine and this proposed change would align availability for cetirizine.

- **What is the evidence of improved consumer involvement in their health?**

With better access to the medication, consumers will be able to take care of their allergic symptoms in a more efficient way. 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 12.3% of patients with allergic rhinitis (AR) consulted a physician, choosing instead to self-treat with home remedies and over-the-counter (OTC) medications.[5, 6] Increasing the availability of this medicine in general sales will improve the consumer involvement in their health.

- **What are the benefits from a consumer viewpoint?**

  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.[7] Hence, easy availability of this medicine in general sales will enable the patients to start the medicine as soon as the symptoms get noticed and increasing available pack sizes to also offer packs of 10s would lessen the requirement for the patient to revisit the purchase point.

4) Contraindication and precautions

- **What are the contraindications for the medicine and how easy are they to identify and prevent?**

  Cetirizine is contraindicated in patients who are hypersensitive to cetirizine or hydroxyzine.[8]

- **What are the precautions for this medicine and how easy are these to understand?**

  There are a few precautions to be undertaken and all of these are very easy to understand. The precautions are listed below[8] (Precautions for single drug formulations of cetirizine are described, precautions for fixed dose combinations of cetirizine with other drugs are not discussed):

  The incidence of adverse effects associated with cetirizine use 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). In addition, effects similar to those occurring in patients receiving first generation antihistamines have been reported, and the potential for typical adverse effects induced by these antihistamines should be considered during cetirizine therapy. 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. 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). In addition, patients should be warned that additive CNS depression may occur when cetirizine is administered concomitantly with other CNS depressants, including alcohol.

a. Paediatric precautions: The paediatric precautions are related to dosing in children of less than 12 years of age. Since the proposed medicine is indicated for adults and children (12 years and above), the paediatric precautions are not discussed.
b. Geriatric precautions: Safety and efficacy of cetirizine in geriatric patients have not been specifically studied to date; however, in clinical trials of cetirizine for the treatment of seasonal allergic rhinitis, perennial allergic rhinitis, or chronic urticaria involving over 3900 patients, 186 patients were 65 years and older, and 39 patients were 75 years and older. Although no overall differences were observed between geriatric and younger patients in the type or frequency of adverse effects in clinical trials, the possibility that some older patients may exhibit increased sensitivity to the drug cannot be ruled out. With regard to efficacy, clinical trials of cetirizine for each studied indication did not include sufficient numbers of patients 65 years and older to determine whether they respond differently than younger adults.

   Because geriatric patients frequently have decreased renal function, cetirizine hydrochloride dosage should be selected with caution, and it may be useful to monitor renal function in these patients. The elimination half-life of cetirizine was prolonged and total body clearance decreased in one study in a limited number of geriatric adults (mean age: 77 years) compared with those in younger adults (mean age: 53 years).
c. Pregnancy, fertility and lactation: 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. Because 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.

   In a fertility and general reproductive performance study in mice, oral cetirizine hydrochloride did not impair fertility at dosages of 64 mg/kg daily (about 25 times the maximum recommended daily dosage in adults on a mg/m^2 basis).
   Cetirizine is distributed in human milk. Therefore, use of cetirizine hydrochloride is not recommended in nursing women.

- **Does the medicine have a low therapeutic index?**

  Specific data about the therapeutic index of cetirizine is not available.

- **What class effects need to be considered and what are the risks?**

  Cetirizine is a long-acting antihistamine. The drug has been characterized as a selective, peripheral H_1-receptor antagonist. The pharmacology of cetirizine resembles that of other currently available antihistamines. Cetirizine is the

carboxylic acid metabolite of hydroxyzine. The increased polarity of cetirizine (compared with hydroxyzine) may decrease distribution of the drug into the CNS, resulting in reduced potential for adverse CNS effects compared with some first-generation antihistamines (e.g., diphenhydramine, hydroxyzine).

a. Antihistaminic effects: In animals and humans, the antihistaminic effect of cetirizine (as measured by suppression of the wheal and flare response induced by intradermal injection of histamine) is comparable to that of astemizole (no longer commercially available in the US), clemastine, chlorpheniramine, diphenhydramine, hydroxyzine, loratadine, pyrilamine, and terfenadine (no longer commercially available in the US). Experimental evidence indicates that the drug exhibits a specific and selective antagonism of histamine H_1-receptors. Results from several experimental models indicate that cetirizine has inhibitory effects on the acute early phase of immediate hypersensitivity response mediated by the action of H_1-receptors. Results of in vitro studies indicate that cetirizine has no measurable affinity for receptors other than histamine H_1-receptors, including calcium-channel blocking receptors, α_1-adrenergic receptors, or dopamine D_2 receptors. Unlike many other currently available antihistamines, cetirizine does not possess appreciable anticholinergic or antiserotonergic effects, although the incidence of dry mouth in clinical trials was higher in patients receiving cetirizine than in those receiving placebo.

   Whereas decreased efficacy (subsensitivity, tolerance), including decreased inhibition in skin reactivity to allergen or histamine, may occur within days or weeks of initiation of therapy with first generation antihistamines, tolerance to the effects of cetirizine usually does not occur. In a 5-week study in children with allergic rhinitis, tolerance to the effects of cetirizine involving histamine skin tests was not reported, and tolerance also did not occur in patients with physical urticarias who were receiving cetirizine for 8-110 weeks. However, in a limited number of patients, the PC_{20} value (the concentration of histamine required to produce a 20% decrease in forced expiratory volume in 1 second [FEV_1]) declined from 118 mmol/L after a single 15-mg dose of cetirizine hydrochloride to 53 mmol/L after administration of 15 mg of cetirizine hydrochloride twice daily for 1 week, although PC_{20} values after 1 week of therapy with cetirizine in such patients remained substantially greater than in patients receiving placebo.

b. Respiratory effects: In animals, cetirizine inhibits histamine-induced nasal airway resistance, and such inhibition appears to be comparable to that of chlorpheniramine. Results of a double-blind, randomized, comparative study in patients with allergic rhinitis indicate that response to nasally inhaled histamine was reduced substantially more by cetirizine than by placebo. In addition, 1.5 and 4 hours after oral administration of the drugs, 10-mg doses of cetirizine hydrochloride were at least as effective as 10-mg doses of loratadine in inhibiting histamine-induced nasal airway resistance. In patients with mild asthma, cetirizine hydrochloride doses of 5-20 mg had a protective effect against nebulized histamine-induced bronchospasm; oral cetirizine may attenuate substantially histamine-induced decreases in FEV_1. Cetirizine also had a protective effect against allergen-induced bronchospasm in patients with allergic asthma; however, such effect was observed only against the late allergic reaction and not against the early allergic reaction.

c. Nervous system effects: In vitro, cetirizine exhibits an affinity for histamine H_1-receptors from brain to peripheral tissues similar to that of terfenadine; however, in vivo, unlike prototypical (first generation) antihistamines, cetirizine (probably because of the polarity of the drug) does not readily cross the blood-brain barrier and, therefore, does not appear to interact appreciably with H_1-receptors within the CNS at usual doses. In some clinical trials, the incidence of certain CNS effects (e.g., somnolence) was higher in patients receiving cetirizine than in those receiving placebo. In addition, some data indicate that the incidence of other CNS effects (e.g., EEG disturbances, impaired psychomotor performance) may be higher in patients receiving cetirizine than in those receiving other second-generation antihistamines (e.g., loratadine).

   In part, adverse CNS effects of cetirizine reported in these studies may have resulted from use of higher than recommended dosages, indicating a correlation between dose of cetirizine hydrochloride and its description as a non-sedating antihistamine. In several other studies, the CNS effects of cetirizine did not differ from those of placebo or other second-generation antihistamines (e.g., astemizole) or, alternatively, no adverse CNS effects were reported with the drug. However, in controlled clinical trials in patients receiving 5- or 10-mg daily dosages of the drug or placebo, the overall incidence of somnolence was 13.7 or 6.3% in patients receiving cetirizine or placebo, respectively.

d. Cardiac effects: Although serious cardiac effects, including ventricular fibrillation and death associated with prolonged QT interval and atypical ventricular arrhythmia (torsades de pointes), have been reported in patients receiving certain other second generation antihistamines (e.g., astemizole, terfenadine), administration of cetirizine hydrochloride alone to healthy adult men at dosages of up to 60 mg daily (6 times the maximum daily dosage) for 1 week has not been associated with clinically important prolongation of the QT interval corrected for rate (QTc). In animals, cetirizine dosages up to 500 times the recommended clinically effective dosage were not associated with important changes in ECG parameters (e.g., QTc intervals).

e. Other effects: Cetirizine may inhibit mediators other than histamine, including those that release histamine. In one study, cetirizine inhibited cold-induced urticaria in cold-challenged patients.

Cetirizine appears to have some activity against allergic inflammation mediators. In studies conducted for up to 12 hours following cutaneous antigen challenge, the late phase recruitment of eosinophils, neutrophils, and basophils (components of allergic inflammatory response) was inhibited by 20-mg doses of cetirizine hydrochloride.[8]

- **What are the risks of the medicine being used in OTC environment?**

  The medicine is already available as an OTC medicine in New Zealand, hence there is no risk.

  The relative risk is for changing the pack size from the 5 tablets already available to 10 tablets. In Pharmacy packs up to 90 tablets are already available so the overall risk profile is not expected to change by increasing the pack size to 10 tablets from 5 tablets presently.
  The successful reclassification of the 5's pack size of cetirizine from Pharmacy Medicine to General sale in 2012 has demonstrated that the risks of misdiagnosis or

masking of underlying diseases are minimal. The proposed 10's pack will also retain all the warning statements required for cetirizine to be sold as a General sale medicine.

In addition, it should be noted that loratadine is already available in larger packs of 10's without any problems being evident. The risk:benefit ratio is not significantly different for loratadine in comparison with cetirizine.

- **What other drug interactions need to be considered?**

  Because cetirizine is metabolized only minimally in the liver and is excreted mainly unchanged in urine, the drug has a low potential for adverse drug interactions associated with metabolic enzyme systems.[8]

  a. Drugs affecting hepatic microsomal enzymes: 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 changes in ECG parameters (e.g., QT, intervals), and no clinically important interactions have been reported in patients receiving cetirizine concomitantly with azithromycin, erythromycin, or ketoconazole. Although concomitant administration of cetirizine hydrochloride (20 mg daily) with ketoconazole (400 mg daily) has been associated with prolongation of the QT, interval (with an increase of 17.4 msec), such increase is not considered clinically important. It is not known whether cetirizine is metabolized in the liver by the cytochrome P-450 microsomal enzyme system
  b. Other drugs: 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); disposition of theophylline was not altered by the concomitant administration with cetirizine.

- **What food and/or drink interactions need to be considered?**

  Although food may decrease peak plasma concentrations of cetirizine and lengthen the time to achievement of peak plasma concentrations, cetirizine may be administered without regard to food because food does not affect the extent of absorption of the drug when administered as conventional tablets.[8]

- **Are there any other restrictions when taking the medicine (ie, driving restrictions or operating machinery)?**

  As described above, since 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). This statement is present on the label under "warnings".

- **Are there any special populations where exposure to the medicine needs to be restricted?**

Patients 12 years of age or older who have impaired renal function (e.g., creatinine clearance of 11-31 mL/minute) or hepatic impairment and are undergoing haemodialysis (creatinine clearance of less than 7 mL/minute), should receive a cetirizine hydrochloride dosage of 5 mg daily.[8] These warnings are also included in the label under “warnings”

5) Undesirable effects

- **What are the known undesirable effects and the frequencies of these? Do these vary for special populations? Are these reversible or treatable?**

  During controlled and uncontrolled clinical trials in patients 12 years of age and older receiving oral cetirizine hydrochloride dosages of 5-20 mg daily for 1 week to 6 months (mean duration: 30 days), 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. Discontinuance of therapy because of adverse events was reported in 2.9% of patients receiving cetirizine compared with 2.4% of those receiving placebo. The incidence of adverse effects was not affected by race, age, gender, or body weight.[8]

  Adverse effects reported in 2% or more of patients 12 years of age and older who received cetirizine hydrochloride (as conventional tablets) at dosages up to 10 mg daily included somnolence, fatigue, dry mouth, pharyngitis, and dizziness.

  a. Nervous system effects: The most frequent adverse effect in patients 12 years of age and older reported during cetirizine therapy is somnolence, occurring in 11, 14, or 6% of patients receiving 5-mg doses, 10-mg doses, or placebo, respectively. Overall, somnolence has been reported in 13.7 or 6.3% of patients receiving cetirizine or placebo, respectively. In addition, in clinical trials in patients 6-11 years of age, somnolence occurred in 1.9, 4.2, or 1.3% of patients receiving 5-mg doses, 10-mg doses, or placebo, respectively. Discontinuance of therapy because of somnolence has been reported in 1 or 0.6% of patients receiving cetirizine or placebo, respectively. In patients 6-24 months of age, somnolence occurred with essentially the same frequency in those who received cetirizine versus placebo. Fatigue or dizziness occurred in 5.9 or 2%, respectively, of patients 12 years of age and older receiving cetirizine, whereas these effects occurred in 2.6 or 1.2%, respectively, of patients receiving placebo. Headache was reported in more than 2% of patients 12 years of age and older receiving the drug; however, headache occurred more frequently in patients receiving placebo. In clinical trials in patients 6-11 years of age, headache occurred in 11, 14, or 12.3% of patients receiving 5-mg doses, 10-mg doses, or placebo, respectively. Abnormal coordination, ataxia, confusion, abnormal thinking, agitation, amnesia, anxiety, depersonalization, depression, emotional lability, euphoria, impaired concentration, insomnia, sleep disorders, nervousness, paroniria, dysphonia, asthenia, malaise, pain, hyperesthesia, hypoesthesia, hyperkinesia, hypertonia, migraine headache, myelitis, paralysis, paraesthesia, ptosis, syncope, tremor, twitching, and vertigo have been reported in less than 2% of patients 12 years of age and older and children 6-11 years of age receiving cetirizine hydrochloride; however, a causal relationship to the drug has not been established. Aggressive reaction, seizures, hallucinations, suicidal ideation, and suicide have been reported rarely during post-marketing surveillance.

b. Oronasopharyngeal and pulmonary effects: Dry mouth or pharyngitis occurred in 5 or 2%, respectively, of those receiving cetirizine, whereas these effects occurred in 2.3 or 1.9%, respectively, of those receiving placebo.

   Bronchitis, dyspnea, hyperventilation, increased sputum, pneumonia, respiratory disorder, rhinitis, nasal polyp, sinusitis, upper respiratory tract infection, increased salivation, discoloration and/or edema of the tongue, and aggravated dental caries have been reported in less than 2% of patients 12 years of age and older and children 6-11 years of age receiving cetirizine hydrochloride; however, a causal relationship to the drug has not been established. Orofacial dyskinesia also has been reported.

c. GI effects: Nausea was reported in more than 2% of patients 12 years of age and older receiving cetirizine; however, nausea occurred more frequently in patients receiving placebo.

   Anorexia, increased appetite, taste loss, taste perversion, dyspepsia, gastritis, stomatitis (including ulcerative stomatitis), enlarged abdomen, eructation, flatulence, constipation, melena, rectal haemorrhage, and haemorrhoids have been reported in less than 2% of patients 12 years of age and older and children 6- 11 years of age receiving cetirizine hydrochloride; however, a causal relationship to the drug has not been established.

d. Cardiovascular effects: Palpitation, tachycardia, hypertension, chest pain, facial edema, generalized edema, leg edema, peripheral edema, hot flashes, or cardiac failure has been reported in less than 2% of patients 12 years of age and older and children 6-11 years of age receiving cetirizine hydrochloride; however, a causal relationship to the drug has not been established.

   Although serious cardiac effects, including ventricular fibrillation and death associated with prolonged QT interval and atypical ventricular tachyarrhythmia (torsades de pointes), have been reported in patients receiving certain other second-generation antihistamines (e.g., astemizole and terfenadine), administration of cetirizine hydrochloride alone to healthy adult men at dosages of 60 mg daily (6 times the maximum recommended daily dosage) for 1 week has not been associated with significant prolongation of the QT interval corrected for rate (QTc).

   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 changes in ECG parameters (e.g., QTc intervals) and that no clinically important interactions have been reported in patients receiving cetirizine concomitantly with azithromycin, erythromycin, or ketoconazole.

e. Genitourinary and renal effects: Cystitis, dysuria, haematuria, micturition frequency, polyuria, urinary incontinence, urinary retention, urinary tract infection, dysmenorrhea, intermenstrual bleeding, leukorrhea, menorrhagia, decreased libido, or vaginitis has been reported in less than 2% of patients 12 years of age and older and children 6-11 years of age receiving cetirizine hydrochloride; however, a causal relationship to the drug has not been established. Glomerulonephritis also has been reported.

f. Dermatologic and sensitivity reactions: Acne, dermatitis, dry skin, eczema, rash (which may be erythematous), urticaria, skin disorder, skin nodules, purpura, bullous eruption, furunculosis, hyperkeratosis, hypertrichosis, alopecia, seborrhea,

pruritus, purpura, photosensitivity reactions (which may be toxic), or angioedema has been reported in less than 2% of patients 12 years of age and older and children 6-11 years of age receiving cetirizine hydrochloride; however, a causal relationship to the drug has not been established. Anaphylaxis also has been reported.

g. Ocular and otic effects: Visual field defect, blindness, conjunctivitis, ocular pain, glaucoma, loss of ocular accommodation, ocular haemorrhage, periorbital edema, xerophthalmia, deafness, otalgia, ototoxicity, or tinnitus has been reported in less than 2% of patients 12 years of age and older and children 6-11 years of age receiving cetirizine hydrochloride; however, a causal relationship to the drug has not been established.

h. Hepatic effects: Transient, reversible elevations of hepatic aminotransferases (transaminases) occurred during cetirizine therapy. In addition, hepatitis with substantial elevations of aminotransferases and bilirubin has been associated with the use of cetirizine.

i. Other adverse effects: Accidental injury, back pain, fever, increased weight, cholestasis, pallor, rigors, lymphadenopathy, hemolytic anemia, thrombocytopenia, breast pain in women, or parosmia has been reported in less than 2% of patients 12 years of age and older and children 6-11 years of age receiving cetirizine hydrochloride; however, a causal relationship to the drug has not been established.[8]

- **What are risks and consequences of known undesirable effects?**

  As described above, majority of the adverse effects are mild and do not pose any serious risk. These again are not seen to be significantly different from loratadine which is already available in packs of 10’s from grocery outlets.

- **Are there any significant safety concerns for the medicine under review?**

  No, there are no significant safety concerns for the medicine under review.

- **Have there ever been any withdrawals of the medicine or other regulatory actions taken for safety reasons (during a time period or in a specific jurisdiction)?**

  To the best of our knowledge, there were no withdrawals or regulatory actions of the medicine for safety reasons.

- **Are there any withdrawal effects following cessation of use of the medicine?**

  Pruritus and/or urticaria may occur when cetirizine is stopped, even if those symptoms were not present before treatment initiation. In some cases, the symptoms may be intense and may require treatment to be restarted. The symptoms should resolve when the treatment is restarted.[9]

6) Overdose

- **Is there a potential for overdose of the medicine?**

Since each tablet is individually packed in a blister pocket, the chances of accidental overdose are negligible (as opposed to multi dose containers like bottles where two or three tablets can slip into the patient's hand while dosing). Further, the dosing instructions are clearly mentioned on the pack.

Packs of 90's are already available from Pharmacy so packs of 10's would be expected to result in less risk than from these larger packs.

- **What are the consequences of overdose of the medicine?**

  Somnolence was reported in one adult who ingested 150 mg of cetirizine hydrochloride; no other adverse effects, including clinical manifestations, abnormal blood chemistry, or abnormal hematology, occurred in this individual. Restlessness and irritability followed by drowsiness were reported in an 18-month old child who ingested about 180 mg of cetirizine hydrochloride.[8]

- **Are there any reports of overdose of the medicine?**

  Few reports are available for the overdosing of cetirizine in children. The symptoms were mostly drowsiness and sedation but no other side effects.[10] However, AFT has not received any report of overdose of Histaclear.

7) Medication errors and abuse/ misuse potential

- **Would reclassification affect the risk of unnecessary use?**

  The 5's pack of this medicine is already available as "General sale" medicine. Including the 10's pack as "General sale" medicine would just allow better access of patients to the medicine without increasing the risk of unnecessary use.

- **Will the medicine be provided with necessary tools to allow correct dosing (eg, liquids supplied with a measuring device)?**

  No measuring devices are required for this medicine as it is a tablet dose form.

- **What are reported medication errors post-market?**

  As mentioned above, since the medicine is supplied as a unit-dose blister pack, the chances of medication error are negligible and increasing pack size from 5's to 10's would be unlikely to change this.

- **What are the reported cases of abuse/ misuse/ accidental overdose?**

  There are no reports of abuse/misuse. The cases of accidental overdose have been discussed above. Accidental overdose is more likely in paediatric patients taking liquid formulations of cetirizine.

- **How would reclassification affect import considerations?**

Reclassification would not affect import considerations.

- **What is the addiction potential of this medicine?**

  Cases of abuse or dependence have not been reported.[8]

8) Communal harm and/ or benefit

- **What are the possibilities of community harm resulting from wider use of the medicine in question (eg, the development of antibiotic resistance in bacteria)?**

  There is no possibility of community harm from wider use of the medicine.

- **What are the possibilities of community benefit resulting from wider use of the medicine in question (eg, greater herd immunity as a result of improved access to a communicable disease vaccine or increased rates of immunisation)?**

  Wider access to this medicine will lead to better control of allergic rhinitis and improved patients access as less visits to purchase the medicine would be required i.e. 10 days' supply (10 tablets) could be purchased as opposed to the current 5 days' supply (5 tablets).

9) Integrated benefit-risk statement

- **A summary of reclassification benefits**

  SAR can have a detrimental effect on patients' quality of life. The symptoms of SAR include sneezing, itching, watery rhinorrhoea, 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. 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 12.3% of patients with allergic rhinitis (AR) consulted a physician, choosing instead to self-treat with home remedies and over-the-counter (OTC) medications.[5, 6]

  Currently, cetirizine hydrochloride 10 mg tablets (in packs of more than 5 tablets) are available as a Pharmacy Only Medicine 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.[4] This can limit the access of SAR patients to required medication and/or additionally decrease access by requiring more frequent trips to purchase medicine. This application seeks the reclassification of cetirizine hydrochloride 10 mg - in packs of no more than 10 tablets - to a General Sale Medicine. This will provide patients easier and more convenient access to an effective and safe short-term therapy. It is further noted that this is entirely consistent with the other common antihistamine, loratadine which has been in place for some time now.

- **A summary of reclassification harm.**

  No harm to the consumer/ patient is expected as a result of this reclassification.

- **A summary of the need for the medicine at the classification proposed.**

  There is mounting evidence of a rise in the prevalence of allergic diseases, including rhinitis, over recent decades. It is estimated that approximately 20 per cent of the New Zealand population suffers from allergic rhinitis.[1] The Best Practice Advocacy Centre 'bpacnz' approximates that SAR may affect up to 30% of adults and 40% of children.[11] 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.

  This scenario, coupled with the fact that most consumers tend to self-treat the condition rather than consulting a physician, sets the increased need of the medicine to be available as a "General sale" medicine and in packs for 10 days' supply (10 tablets) vs only 5 days' supply (5 tablets).

- **Precedent – how are other medicines in the same class classified?**

  Cetirizine is a second-generation antihistamine. The classification of other second-generation antihistamines in New Zealand is described below:

Medicine	**Classification**
Loratadine	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)
Levocetirizine	Pharmacy Only (For oral use)
Desloratadine	Pharmacy Only (For oral use)
Fexofenadine	General Sale (for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when in capsules containing 60 milligrams or less of fexofenadine hydrochloride or in tablets containing 120 milligrams or less of fexofenadine hydrochloride with a maximum daily dose of 120 milligrams when sold in the manufacturer's original pack containing 10 dosage units or less and not more than 5 days' supply)

Medicine	Classification
	Pharmacy Only (for oral use except for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when in capsules containing 60 milligrams or less of fexofenadine hydrochloride or in tablets containing 120 milligrams or less of fexofenadine hydrochloride with a maximum daily dose of 120 milligrams when sold in the manufacturer's original pack containing 10 dosage units or less and not more than 5 days' supply)

10) Risk mitigation strategies

- **Are there any risk mitigation strategies required? If so, what risk mitigation strategies are required (eg, healthcare professional education, integration of care, consumer information to be provided, etc.)?**

  No risk mitigation strategies are required for this reclassification since the product is already available without problem in packs of 5's in grocery and this change increases the pack size to allow for 10 days' supply (10 tablets).

- **What is the evidence that these proposed risk mitigation strategies would be effective?**

  Not applicable.

- **What post-market surveillance activities would be carried out?**

  No specific post-marketing surveillance activities would be carried out as a result of this reclassification.

- **Is the proposed reclassification supported by professional bodies?**

  Not applicable.

References

1. Hay fever (allergic rhinitis). Southern Cross Medical Library. Accessed 09 January 2020. Available from: https://www.southerncross.co.nz/group/medical-library/hay-fever-allergic-rhinitis.
2. Martindale The Complete Drug Reference. 39th ed., London, UK: Pharmaceutical Press.
3. The Top 300 of 2020. Provided by the ClinCalc DrugStats Database. Accessed on 09 January 2020. Available from: https://clincalc.com/DrugStats/Top300Drugs.aspx.
4. Chemist shops have the shortest opening hours. NZ Retailers Assoc. Accessed on 09 January 2020. Available from: https://www.scoop.co.nz/stories/BU0303/S00025.htm.
5. Malone, D.C., Lawson, K.A., Smith, D.H., Arrighi, H.M., and Battista, C., A cost of illness study of allergic rhinitis in the United States. J Allergy Clin Immunol., 1997. 99(1 Pt 1): p. 22-7. doi: 10.1016/s0091-6749(97)70296-3.

6. Schoenwetter, W.F., Dupclay, L., Jr., Appajosyula, S., Botteman, M.F., and Pashos, C.L., Economic impact and quality-of-life burden of allergic rhinitis. Curr Med Res Opin., 2004. 20(3): p. 305-17. doi: 10.1185/030079903125003053.
7. Thompson, A.K., Juniper, E., and Meltzer, E.O., Quality of life in patients with allergic rhinitis. Ann Allergy Asthma Immunol., 2000. 85(5): p. 338-47; quiz 347-8. doi: 10.1016/S1081-1206(10)62543-4.
8. AHFS Drug Information 2007. Bethesda, MD 20814, USA: American Society of Health-System Pharmacists.
9. Zirtek Allergy Relief 10 mg film-coated Tablets. SmPC. UCB Pharma Limited. Accessed on 09 January 2020. Available from: https://www.medicines.org.uk/emc/product/175/smpc.
10. Hansen, J.J. and Feilberg Jorgensen, N.H., [Accidental cetirizine poisoning in a four-year-old boy]. Ugeskr Laeger., 1998. 160(41): p. 5946-7.
11. Seasonal allergic rhinitis. BPAC Best Practice Journal. 2009. BPJ: 24. Accessed on 09 January 2020. Available from: https://bpac.org.nz/BPJ/2009/November/hayfever.aspx.

2D Barcode along with Batch Details
Such as GTIN, B., Exp., Sr. No.

Histaclear Tablets Carton (10's) Cutter Die
Size : 115(L) x 19(W) x 60(H) mm
Date : 6 Jan 2020
Rajesh Kadam

Job Ref:	Client/Date:	Proof No.	BC Info.	CMYK	Die Line/Varnish FREE AREA
2620	15-01-20	2	SUPPLIED Magnification	C M Y K	Does Not Print die / Does Not Print NO VARNISH

UTOPIA CREATIVE
0212 050947
BRANDING | PACKAGING | DESIGN

Important : Barcode verification is the responsibility of the client. **DO NOT SCALE ANY PORTION OF THE BARCODE**