Submission to the Medicines Classification Committee for the Reclassification of Ketotifen from a Prescription Medicine to a Pharmacy Only Medicine with the Following Condition:

"for ophthalmic use"

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INTRODUCTION

This application contains data to support the reclassification of ketotifen from Prescription Medicine to Pharmacy Only Medicine with the inclusion of the Classification Condition "for ophthalmic use". The data available for over the counter (OTC) use of ophthalmic ketotifen support the Medicines Classification Committee definition, adopted for suitability for OTC sale:

Medical products which may be available without prescription shall show a substantial safety in use in the treatment of minor ailments or symptoms, usually capable of rapid and spontaneous relief, which are easily identifiable by users and do not justify a medical consultation.

This reclassification application presents data to support the OTC classification of 0.025% ketotifen for ophthalmic use in the indication "Seasonal Allergic Conjunctivitis" (SAC). SAC is considered by the medical profession and also by sufferers as a condition which is easy to self diagnose because of the typical clinical presentation and the seasonal recurrence. People who are diagnosed with SAC and suffer a recurrence of symptoms each season often rely upon self medication which is available OTC. They do not need to book an appointment with their doctor or an ophthalmologist which has to be done in advance, when they have urgent need to obtain relief from itchy eyes or other acute symptoms of hay fever. Self medication of SAC is considered to be a safe and cost effective way of controlling the annual exacerbation of allergy symptoms during the pollen season.

Cold compresses, irrigation with saline solution or artificial tears may suffice to relieve mild symptoms but pharmacologic treatment – mainly with antihistamines and mast cell stabilisers – is more effective in managing the seasonal exacerbation of symptoms. Apart from prescription only medication there is a range of products available OTC, including topical and systemic antihistamines (H_1-receptor antagonists), topical mast cell stabilisers, and topical sympathomimetic vasoconstriction agents frequently used in fixed combinations with topical antihistamines. Examples of anti-allergy products available OTC in New Zealand includes Livostin (levocabastine), Lomide (lodoxamide) and Opticrom (sodium cromoglycate), Albalon-A (naphazoline / antazoline) and Otrivine-Antistin (antazoline / xylometazoline).

Zaditen®, the product that has prompted this application, is an eye drop solution containing 0.025% ketotifen. Because ketotifen is currently a Prescription Medicine and there are no existing Classification Conditions, Zaditen® is automatically considered a Prescription Medicine.

Current and Proposed Classification and Conditions for ketotifen:

Current Ketotifen Classification Conditions	Proposed Ketotifen Classification Conditions	Current Classification	Proposed Classification
Nil conditions	***"except for ophthalmic use "***	Prescription Medicine	No change
Nil conditions	***"for ophthalmic use"***	Prescription Medicine	***Pharmacy Only Medicine***

The international history of both oral and ophthalmic ketotifen provides strong evidence for considering it as a Pharmacy Only Medicine. The Zaditen® formulation involves low systemic exposure to the active ingredient (0.025%). At the recommended dose, its safety profile is comparable to placebo and an unusually large clinical experience with systemic administration attests to this safety.

Introduction to the Product:

Ketotifen (Zaditen®) eye drops is a sterile solution containing 0.025% (0.25mg/mL) ketotifen, a histamine H_1-receptor antagonist and mast cell stabiliser which also inhibits eosinophil chemotaxis, activation and degranulation. Zaditen® was approved in 2000 through the Mutual Recognition Procedure (MRP) in all EU countries except Belgium for the symptomatic treatment of SAC. The formulation has also been registered in numerous other countries world-wide. The international registration status is presented in Appendix V.

Ketotifen was originally developed by Sandoz Pharma (now Novartis). Oral formulations of ketotifen have been marketed world-wide for more than 20 years for systemic treatment and prevention of asthma and various allergic disorders. In addition, an ophthalmic formulation containing 0.05% (0.50mg/mL) ketotifen was developed by Sankyo Co. Ltd and has been approved in Japan for the indication of allergic conjunctivitis since 1991.

More recently, Novartis Ophthalmics (formerly CIBA Vision) has marketed Zaditen®/Zaditor® eye drops (ketotifen 0.025%) in a number of countries including the USA, Sweden and Canada since they were first approved by the US FDA in 1999 (international registration status provided as *Appendix V*, also refer to *Part A.10*).

In New Zealand ketotifen tablets were approved in 1984, followed by syrup in 1985 and sustained release tablets in 1993. The tablets and syrup have been previously marketed in New Zealand but were discontinued between 1998 and 2000 due to decreasing sales.

A New Medicine Application for Zaditen® 0.25 mg/mL eye drops was submitted to Medsafe on November 28, 2002. The MAAC have recently recommended approval of this application for the "treatment and prevention of signs and symptoms of seasonal allergic conjunctivitis".

The application for Zaditen® 0.25 mg/mL eye drops has been submitted as a prescription only medication. However, the product fulfils the requirements to change the classification for its supply from subject to a medical prescription to not subject to a medical prescription.

Zaditen® 0.25 mg/mL eye drops are safe when used correctly. Preclinical studies, clinical and post-marketing experience indicate that the product has low general toxicity, low risk of type A and type B reactions and low risk of serious adverse reactions due to interactions with commonly used medicines.

Symptomatic treatment with Zaditen® 0.25 mg/mL eye drops is unlikely to mask an underlying condition, which requires urgent medical attention or supervision. Seasonal allergic conjunctivitis is considered to be a common condition, which is reliably self-diagnosed. This is supported by the fact that several anti-allergy drugs, antihistamines and mast cell stabilisers, are available without medical prescription. It is recommended that if Zaditen® 0.25 mg/mL eye drops do not provide the desired symptomatic relief within a few days or cause an undesired effect, the patient should consult a pharmacist or doctor.

There is no indication that Zaditen® 0.25 mg/mL eye drops are likely to be misused or cause serious risk to the patient if used incorrectly. Moreover, there are no specific safety issues associated with systemic administration of ketotifen, which has been in used for over 20 years.

Zaditen® 0.25 mg/mL eye drops have been shown to be effective and safe to use for the symptomatic treatment of seasonal allergic conjunctivitis in adults, elderly and children aged 3 and older. From a clinical point of view the product fulfils the criteria which justify a change of classification from "medicinal product subject to a medical prescription" to "medicinal product not subject to a medical prescription".

PART A

1. International Non-proprietary Name of the medicine

Ketotifen

2. Proprietary name(s)

Zaditen®

3. Name of company requesting reclassification

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

Dose form: Drops, eye, solution
Strength: 0.025%

5. Pack size and other qualifications

Pack size: 3mL and 5mL (LDPE bottle with LDPE dropper and HDPE cap)

6. Indications for which change is sought

Treatment and prevention of signs and symptoms of seasonal allergic conjunctivitis.

7. Present classification of medicine

Prescription Medicine: Nil conditions

8. Classification sought

Pharmacy Only Medicine: **"**for ophthalmic use"

9. Classification status in other countries

Classification of ketotifen:

Japan:	Prescription
USA / Canada:	Prescription
EU:	Prescription
Australia:	New Chemical Entity
Nordic countries:	Prescription (an OTC Switch application has recently been submitted). Please refer to *Appendix X*.

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

Country	Zaditen® approval date	Zaditen® launch details
USA	Approved 02.07.99	01.09.99
Japan	Approved 29.03.91	01.07.91 (Japan only markets a 0.05% product)
Sweden	Approved 30.06.00	29.11.00
Canada	Approved 29.05.00	01.08.00

International Market Experience (Refer to Appendix VII):
During the period of review in the PSUR (January 2002 to June 2002) approximately 3,273,000SDU (0.025%) units and 2,920,000 units of MDU (0.025% and 0.05%) were sold worldwide. A rough estimate of patient exposure was calculated as follows. If one assumes that each MDU will be discarded 4 weeks after first opening, then one bottle equals one patient month. Similarly, if one assumes that on average, two single dose units are used per patient per day, then 60 SDU equal one patient month.

As the duration of treatment among patients varies, an exact patient calculation is impossible to make.

Based on the number of units sold and the assumptions made above, we calculate that 2,920,000 bottles (MDU) equals 2,920,000 patient months or 243,000 patient years. Similarly, 3,273,000 SDU equals 54,550 patient months (3,273,000/ 60) or 4546 patient years.

Please note: There are no other ophthalmic ketotifen products on the New Zealand market. Consequently, we are unable to provide sales volumes in New Zealand.
Also refer to *Appendix V* - International Registration Status

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

- Primary dropper bottle label and secondary carton

Refer to *Appendix I* for the draft artwork submitted to Medsafe.

12. Proposed warning statements if applicable

Labelling (primary and secondary):

- KEEP OUT OF REACH OF CHILDREN
- Not to be used later than four weeks after bottle is first opened.
- Avoid touching the dropper tip of the bottle to any surface since this may contaminate the solution.
- For external use only.

Pack Insert (CMI):

- Do not use Zaditen® if you have an allergy to:
  - any medicine containing ketotifen
  - any of the ingredients listed at the end of this leaflet.
- Tell your doctor if you are pregnant or plan to become pregnant or are breast-feeding.
  Your doctor can discuss with you the risks and benefits involved.
- If you become pregnant while using Zaditen®, tell your doctor immediately.
- Tell your doctor if you wear soft contact lenses.
  You should remove soft contact lenses before using Zaditen®and not reinsert them until at least 15 minutes after use.
- If you are using any other eye drops at the same time as Zaditen® leave an interval of at least 5 minutes between each eye drop to stop the drops being washed out of the eye.
- Be careful driving or operating machinery until you know how Zaditen® affects you.

This medicine may cause blurred vision or tiredness in some people. If you have either of these symptoms, do not drive, operate machinery or do anything else that could be dangerous. Children should be careful when riding bicycles or climbing trees.

- Tell your doctor or pharmacist if you notice any of the following and they worry you:
  - Burning, stinging or blurring of vision immediately after using the drops.
  - Eye irritation or feeling of having something in your eye.
  - Swollen eyelid or other eyelid changes.
  - Unusual sensitivity of the eye to light.
  - Headache or tiredness.
  - Dry mouth.

  The above list includes the more common side effects of your medicine. They are usually mild and short-lived.
- Tell your doctor as soon as possible if you notice any of the following:
  - Tiny breaks in the skin covering the eye.
  - Runny or sticky discharge from the eye with itching of the eye and crusty eyelids.
  - Pain in the eye
  - Bleeding under the surface of the eye.
  - Skin rash.
  - Wheezing or difficulty breathing.

  The above list includes serious side effects which may require medical attention.

Refer to Part B.8. that provides the frequency of Adverse Events.

The CMI also contains all standard statements required in the CMI templates and guidelines.
Please refer to *Appendix IV* that contains the CMI submitted to Medsafe.

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

To our knowledge there are no other ophthalmic ketotifen products on the New Zealand market or in registration.

PART B

1. A statement of the benefits to both the consumer and to the public expected from the proposed change (Refer to *Appendix VII and X*)

The classification change from Prescription Medicine to Pharmacy Only Medicine for an ophthalmic 0.025% ketotifen eye drop solution, offers consumers suffering from seasonal allergic conjunctivitis, a safe and effective alternative for self medication.

Seasonal allergic conjunctivitis is the most common form of ocular allergy with a prevalence of 10 to 20% in the overall population. The self-limiting symptoms of seasonal allergic conjunctivitis are readily recognised by seasonal allergic conjunctivitis sufferers e.g. swelling, excessive lacrimation and mucous discharge. Although serious sequelae due to corneal involvement are very rare, the extreme discomfort caused by distressing signs and symptoms may strongly affect the sufferer's way of life.

Currently ketotifen is a Prescription Medicine; consequently Zaditen® eye drops are automatically a Prescription Medicine. This application presents data to support a classification change from Prescription Medicine to Pharmacy Only Medicine to enable consumers who suffer from seasonal allergic conjunctivitis, access to Zaditen® eye drops without the added time and expense of visiting their doctor for a prescription.

Benefits to the consumer of an OTC ketotifen eye drop include:

- a safe and effective alternative to the currently marketed medications e.g. antihistamines, vasoconstrictors, mast cell stabilisers, non-steroidal anti-inflammatory medicines and corticosteroids
- broader effect than other medications
- fast onset of action (within minutes)
- almost immediate symptom relief
- long duration of action (8 to 12 hours)
- Convenient and simple twice daily dosing
- well tolerated
- excellent and well established safety profile (comparable to placebo)
- low exposure to the active ingredient

2. Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated (Refer to *Appendix VII and X*)

The proposed indication for Zaditen® 0.25mg/mL eye drops is "treatment and prevention of signs and symptoms of seasonal allergic conjunctivitis".

Seasonal allergic conjunctivitis (SAC), the most common ocular allergy (Buckley 1998), is the ocular component of hay fever. It typically affects people between 10 and 40 years of age, many of whom have a history of atopy. It occurs seasonally, triggered by exposure of the eyes to pollen from grasses, trees, and/or weeds, and may be associated with other manifestations of hay fever such as rhinitis. The hallmark of SAC is intense itching of both eyes which may be associated with redness, chemosis and excessive lacrimation. The condition is characterised by recurrent episodes of acute attacks and spontaneous regression at the end of the pollen season. It is generally self-limiting over a period of several days to several months and is not life threatening. Although symptoms like itching and redness interfere with everyday life, the condition does not disturb corneal function or impair visual acuity.

Self-diagnosis of SAC is primarily based on typical history of SAC combined with its characteristic clinical presentation. Other forms of ocular allergy are not seasonal in their manifestation, and common forms of conjunctivitis associated with infection are characterised by noticeable ocular discharge apart from various forms of ocular discomfort. Episodes of keratitis are associated with pain rather than itching in addition to blurred vision if corneal lesions are in the visual axis.

Patients who were once diagnosed to suffer from SAC and responded to treatment can readily recognise the recurrence of symptoms when the new pollen season starts. Usually, the intensity of signs and symptoms of SAC does not warrant a visit to the doctor. The availability and frequent use of antihistamines and mast cell stabilisers as OTC products indicates that self-assessment of SAC by the patient is possible and product use without medical supervision is considered safe.

3. Relevant comparative data for like compounds

Ketotifen fumarate is a benzocycloheptathiophene derivative. There is no structural relationship between ketotifen fumarate and the active substances levocobastine hydrochloride or disodium cromoglycate.

Therapeutically, ketotifen is a histamine H_1-receptor antagonist and mast cell stabiliser. In addition, ketotifen inhibits eosinophil infiltration, activation and degranulation. Other H_1-receptor antagonists used to treat allergic conjunctivitis include levocobastine hydrochloride, antazoline salts and pheniramine maleate. Other mast cell stabilisers used to treat allergic conjunctivitis include sodium cromoglycate and lodoxamide. Lodoxamide also claims a direct inhibitory action on eosinophils and eosinophil infiltration is a secondary effect of all mast cell stabilisers due to inhibition of mediator release.

Eye drops containing antihistamines or mast cell stabilisers which are currently supplied in New Zealand and used in the management of allergic conjunctivitis, including eye drops with a direct or an indirect effect on eosinophils, are over-the-counter medications (refer to table below). This provides additional support that ketotifen for ophthalmic use together with the indication SAC is appropriate for OTC availability.

Classification and Conditions for like compounds:

Ingredient	Conditions (if any)	Classification
Antazoline		Pharmacy Only
Levocabastine	for nasal or ophthalmic use	Pharmacy Only
Levocabastine	except for nasal or ophthalmic use	Prescription
Lodoxamide	for ophthalmic use	Pharmacy Only
Naphazoline;	except for nasal use when sold at an airport	Pharmacy Only
Pheniramine		Pharmacy Only
Sodium cromoglycate	for nasal and ophthalmic use	Pharmacy Only
Sodium cromoglycate	except for nasal and ophthalmic use	Prescription
Xylometazoline	except for nasal use when sold at an airport	Pharmacy Only

Besides the identification and avoidance of the offending allergens, symptom control is the most practical method of providing relief to seasonal allergy sufferers. Symptom control may be obtained either with simple measures such as cold compresses, irrigation with saline solution or artificial tears, or with therapeutic agents including antihistamines, vasoconstrictors, mast cell stabilisers, non-steroidal anti-inflammatory drugs and corticosteroids. Except in severe cases, sufferers of seasonal allergic conjunctivitis generally self-medicate using over-the-counter medicines.

Antihistamines (H_1-receptor antagonists) are among the most frequent initial therapeutic approaches as histamine is one of the main chemical mediators triggering symptoms of ocular allergy. Ophthalmic formulations are targeted directly to the affected site and usually provide rapid symptom relief without significant systemic side effects.

Due to their slower onset of action, mast cell stabilisers are generally used for prophylactic treatment.

Topical NSAIDs may not alleviate all signs and symptoms associated with seasonal allergic conjunctivitis and corticosteroids are effective but long term use is associated with side effects.

Ketotifen 0.025% eye drops combine the pharmacological actions of antihistamines and mast cell stabilisers. In addition, ketotifen inhibits eosinophil infiltration, activation and degranulation. The rapid onset of action, occurring within minutes, provides almost immediate symptom relief, and the long duration of action of 8-12 hours offers the convenience of a twice daily dosing regimen.

Unless SAC is not already controlled by currently available OTC medications (in severe cases), it is almost exclusively a self-managed condition. Zaditen® 0.25mg/mL eye drops is considered at least as safe as currently available Pharmacy Only Medicine products used for this indication and probably safer than those currently available products containing a vasoconstrictor, due to ketotifen's reduced potential to mask a more serious disease.

4. Local data or special considerations relating to NZ

To our knowledge, there are currently no ophthalmic products containing ketotifen in New Zealand.

New Zealand has a high proportion of allergy sufferers.

5. Interactions with other medicines

The Zaditen® Toxico-pharmacological Expert Report (see *Appendix IX*) states that clinical experience does not indicate that pharmacokinetic drug-drug interactions with ketotifen are a problem. Due to marginal systemic exposure, drug-drug interactions are very unlikely.

There is no evidence of interference with the metabolism of other medicines due to the inhibition or induction of drug metabolising enzymes by ketotifen. Clinical experience during the last 20 years does not indicate that commonly used medicines can produce serious adverse reactions due to interaction when co-administered with systemic ketotifen.

The recommended daily dose of Zaditen® 0.25mg/mL eye drops is only 1.5% of the recommended daily oral dose. Systemic exposure after topical administration of ketotifen eye drops according to the recommended ocular dosing scheme was investigated in healthy volunteers. In most cases, plasma levels were below the limit of quantitation (20 pg/mL). Despite the very sensitive analytical method there was no evidence of significant systemic exposure, reducing the risk of systemic adverse effects and drug-drug interactions. To date, no interactions have been reported with the use of ketotifen eye drops.

6. Contraindications

Hypersensitivity to ketotifen or to any of the excipients.

7. Possible resistance

N/A

8. Adverse events - nature, frequency etc.

(Also refer to *Appendix III* – Data Sheet, *Appendix VI* - Six year safety report*, Appendix VII* – PSUR, *Appendix VIII* - Expert Report on the Clinical Documentation).

The safety profile of ketotifen oral formulations has been reviewed in the Written Summary on the Safety Zaditen® (systemic forms) (included in *Appendix VIII*). Oral formulations of ketotifen have been in use for more than 20 years for the prophylactic treatment of asthma and the treatment of other allergic conditions. The recommended daily dose of oral formulations is 2mg. It was concluded that orally adminstered ketotifen, with an exposure of approximately 15 million patient-years over a period of 2 decades, can be considered a well tolerated and safe treatment. Of particular importance is the strong evidence that ketotifen does not have the potential to cause QT prolongation known to occur during treatment with some classical H_1-receptor antagonists.

Studies conducted to support registration of Zaditen® include safety data for a total of 1256 subjects (see *Appendix VIII*). Ketotifen 0.25mg/mL eye drops were well tolerated and safe. At the recommended dose, the most frequent ocular adverse reaction was burning / stinging; the most frequent non-ocular adverse reactions were headache, skin rash and somnolence. All reactions except burning/stinging (1.7%) occurred in less than 1% of subjects treated.

At the recommended dose, the following adverse events have been reported (see *Appendix III*):

<u>Ocular side effects:</u>

- Between 1% and 2%: burning/stinging, punctuate corneal epithelial erosion.
- <1%: blurring of vision upon drug instillation, dry eyes, eyelid disorder, conjunctivitis, eye pain, photophobia, subconjunctival haemorrhage.

Systemic side effects:

- <1%: headache, somnolence, skin rash, eczema, urticaria, dry mouth and allergic reaction.

No case of overdose has been reported. Oral ingestion of the contents of a 5 mL bottle would be equivalent to 1.25 mg of ketotifen which is 60% of a recommended oral daily dose for a 3 year old child. Clinical results have shown no serious signs or symptoms after oral ingestion of up to 20 mg of ketotifen.

The tolerability and safety of Zaditen® 0.25mg/mL eye drops after market introduction has been monitored and evaluated in Periodic Safety Update Reports (PSURs) (see *Appendix VII*). No change in the safety profile has been observed and no new safety issue identified to date. A cumulative list of all published or unpublished spontaneous adverse event reports on Zaditen® 0.25mg/mL eye drops received to date is available upon request. The list includes information on 51 cases reporting 126 adverse events in total, none of them being serious. Fifty per cent of adverse events occurred in the eye, the most frequent ones being irritation (12), redness (10) and itching (8). Based on the sales figures, the corresponding medicine exposure is estimated to be approximately 400,000 patient-years.

An eye drop formulation of 0.5mg/mL ketotifen has been marketed in Japan since 1991 in the indication of allergic conjunctivitis. In the six-year safety report submitted to the Japanese health authority (*Appendix VI)* no serious adverse events and an excellent tolerability were reported in over 6,000 patients included in the survey. The report estimates that the total number of patients exposed to ketotifen eye drops in Japan over the 6 year period was 2,288,000. The safety profile of the 0.5mg/mL formulation is very similar to that of the 0.25mg/mL formulation, with stinging eyes and eye irritation being the most frequently reported adverse events (2.6%). It should be noted that these data relate to higher dosage of ketotifen (0.05% q.i.d.) than that recommended in this application (0.025% b.i.d.).

In consideration of all safety data it can be concluded that ketotifen is devoid of reproductive toxicity and genotoxic or carcinogenic properties. Zaditen® 0.25mg/mL eye drops pose low risk of serious Type A adverse reactions in the general population and very low risk of serious Type B reactions. No differences in the safety profile of ketotifen were found between different age groups or populations of different ethnic origin.

9. Potential for abuse or misuse

The possibility of abuse of Zaditen® is extremely low by virtue of its presentation in a 3mL or a 5mL bottle intended for up to 4 weeks treatment. These pack sizes make overuse for long periods unlikely.

The potential for harm from inappropriate use of Zaditen® is considered to be low as demonstrated by more than 10 years of market experience with the 0.5mg/mL formulation administered four times a day in Japan (i.e. four times the recommended daily dose of Zaditen® 0.25mg/mL eye drops administered twice a day), no significant differences in the safety profiles of the two strengths and regimens were found.

There is practically no risk of significant adverse effects due to accidental oral ingestion since a bottle of 5mL Zaditen® 0.25mg/mL eye drop solution contains an amount of ketotifen substantially lower than doses given in approved oral dosage forms. The content of a 5mL bottle would be equivalent to 1.25mg of ketotifen fumarate (note that the recommended daily dose for oral formulations of ketotifen is 2mg).

In addition, ketotifen does not rank amongst substances known to be toxic in overdose or to be addictive and has a large safety margin in acute overdose.