SUBMISSION FOR RECLASSIFICATION OF MEDICINE

ZADITEN
(KETOTIFEN 0.025% for Ophthalmic Use)
TT50-7009, TT50-7009/1

June 2008

PART A

1. International non-proprietary name
Ketotifen

2. Proprietary name
Zaditen (TT50-7009 and TT50-7009/1)

3. Company requesting reclassification
Novartis New Zealand Limited
6 – 8 MacKelvie Street, Grey Lynn, AUCKLAND

4. Dose forms and strengths for which a reclassification is sought
Eye drops, solution, 0.25mg/mL, preserved formulation TT50-7009

Eye drops, solution, 0.25mg/mL, unpreserved formulation TT50-7009/1

5. Pack size and other qualifications
2.5mL multidose bottle
5mL multidose bottle
0.4mL preservative-free single dose units (packs of 5 and 20)

6. Indications for which change is sought
Treatment and prevention of signs and symptoms of seasonal allergic conjunctivitis. (No changes to the currently approved indications)

7. Present classification of medicine
Restricted medicine

8. Classification sought
Pharmacy medicine

9. Classification status in other countries:

Table 1 Registration and OTC status in selected countries

Country	Approval date	Launch details	Date of OTC Status
USA	02.07.99	01.09.99	19.10.2006
Sweden	30.06.00	29.11.00	22.03.2004
Denmark	30.11.00	16.04.01	25.08.2003
Norway	13.12.00	01.04.01	22.03.2004
Iceland	20.12.00	-	02.10.2003
Australia	19.07.04	09.09.04	09.2006

10. Extent of usage in NZ and elsewhere:

Table 2 - NZ sales details

Presentation	Launch date	Total no. packs sold to May 2008
5mL multi-dose bottles, single pack	March 2005	11,604

2.5mL multi-dose bottles, single pack	March 2005	5,040
0.4mL single dose units, packs of 20	September 2007	1,062
0.4mL single dose units, packs of 5	April 2008	300

Full details of the worldwide regulatory status of Zaditen eye drops are provided in Appendix 1

11. Labelling for the proposed new presentation(s)

Labelling of the proposed new presentations are provides in Appendix 2

12. Proposed warning statements

- Label – "Keep out of reach of children" (which is on the current label).
- Data sheet: Current warnings remain.

13. Other products affected

None

PART B - Reasons for requesting classification change

1. Benefits to the consumer and to the public expected from the proposed change

Seasonal allergic conjunctivitis (SAC) is the most common form of ocular allergy with a prevalence of 10 to 20% in the overall population. The self-limiting symptoms are readily recognised by seasonal allergic conjunctivitis sufferers e.g. swelling, excessive lacrimation and mucous discharge. Although not a life-threatening disease and even though serious sequelae due to corneal involvement are very rare, the extreme discomfort caused by distressing signs and symptoms may strongly affect the sufferer's quality of life.

People who are diagnosed with SAC and suffer a recurrence of symptoms each season often rely on self medication which is available OTC. They usually have an urgent need to obtain relief from the symptoms of SAC but do not need to consult a doctor or ophthalmologist. 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.

Pharmacological treatment of SAC – mainly with antihistamines and mast cell stabilisers – is a most effective way of managing the seasonal exacerbation of symptoms. Ketotifen 0.025% eye drops combine the pharmacological actions of an antihistamine, a mast cell stabiliser and a direct eosinophil inhibitor. They have a rapid onset of action, occurring within minutes, and provide almost immediate symptom relief. Unlike most of the eye drops currently available OTC for this condition that require dosing three to four times a day, ketotifen 0.025% eye drops have a simple twice daily dosage regimen The simplified dosing regimen leads to better patient compliance and reduces the exposure of the consumer to the substance.

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

Seasonal allergic conjunctivitis (SAC), the most common ocular allergy, 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. 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. Once a patient has been diagnosed with SAC and responded to treatment, he/she can readily recognise the recurrence of symptoms when the new pollen season starts. Usually, the signs and symptoms of SAC do not warrant a visit to the doctor. The ready 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 that product use without direct supervision by a pharmacist is safe.

3. Relevant comparative data for like compounds

Apart from prescription only medicines, a range of OTC products is currently available including topical and systemic antihistamines (H_1-receptor antagonists), topical mast cell stabilisers and topical sympathomimetic vasoconstrictors frequently used in fixed combinations with topical antihistamines.

Comparative mechanism of action and classification of other substances for ophthalmic use

Ketotifen combines the pharmacological actions of an antihistamine (H_1-receptor antagonist), mast cell stabiliser and direct inhibitor of eosionphils. Olopatadine hydrochloride is a selective H_1-receptor antagonist and mast cell stabiliser. Other H_1-receptor antagonists used to treat allergic conjunctivitis include levocabastine hydrochloride, antazoline salts and pheniramine maleate and azelastine hydrochloride. 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. A comparison of the mechanisms of action of ketotifen with other products used for allergic eye conditions is given in Table 3:

Table 3 Mechanisms of action of Zaditen compared to other ophthalmic products

	Antihistamine	Mast cell stabiliser	Direct inhibitor of eosinophils
Ketotifen (Zaditen)	✓	✓	✓
Olopatadine hydrochloride	✓	✓	
Lodoxamide		✓	✓
Sodium cromoglycate		✓	
Levocabastine	✓		
Antazoline	✓		
Pheniramine	✓		
Azelastine hydrochloride	✓		

The majority of these substances are included in Pharmacy medicine when used in ophthalmic preparations and they have enjoyed Pharmacy medicine status since 1999-2000. Two exceptions are olopatadine hydrochloride, which included in Prescription medicine and indicated for treatment of SAC for up to 14 weeks, and azelastine hydrochloride which is included in Pharmacist only medicine in topical eye preparations. An eye drop formulation containing azelastine hydrochloride has not yet been marketed in New Zealand. Refer Table 4:

Table 4 Current classification of other products with similar benefits:

Ingredient	Conditions (if any)	Classification
Antazoline	in eye drops	Pharmacy only
Azelastine HCl	in eye drops	Restricted (not marketed)
Levocabastine	in topical eye or nasal preparations	Pharmacy only
Lodoxamide	in eye drops	Pharmacy only
Naphazoline	in eye drops	Pharmacy only
Olopatadine HCl	in eye drops	Prescription
Pheniramine	in eye drops	Pharmacy only
Sodium cromoglycate	in preparations for nasal or ophthalmic use	Pharmacy only

Comparative efficacy versus other OTC anti-allergy products

Comparative clinical studies have demonstrated that Zaditen 0.025% is at least as effective as, or more effective than, currently available OTC treatments for SAC. In a pivotal registration study conducted in an environmental setting in Australia , ketotifen 0.025% eye drops were found to produce a significantly better outcome than levocabastine 0.05% eye drops for the relief of symptoms of SAC. This randomised, double masked, parallel group, multi-centre study involved 320 investigators, primarily general practitioners. A total of 519 patients (172 on Zaditen, 173 on vehicle placebo, and 174 on levocabastine) with moderate to severe signs and symptoms of SAC were treated twice a day for 4 weeks. The key efficacy assessment was performed after 5 to 8 days of treatment, allowing for the short duration of acute allergic episodes. Efficacy variables included global efficacy, signs and symptoms of SAC and symptom-free days. Patients receiving Zaditen experienced more symptom-free days than patients on either vehicle placebo or levocabastine and the difference of approximately 30% between placebo and Zaditen was statistically significant *(Appendix 5: Kidd M, McKenzie SH, Steven I, et al., 2003).*
A comparative study using ketotifen 0.025% and sodium cromoglycate 4% in the conjunctival allergen-challenge model confirmed that a single dose of ketotifen was superior to a 2-week regimen of cromoglycate four times daily in alleviating symptoms of allergic conjunctivitis. *(Appendix 6: Greiner JV, Michaelson C, McWhirther CL et al., 2002)*.

4. Local data or special considerations relating to NZ

There is now considerable experience with the availability of Zaditen® eye drops containing 0.025% ketotifen as an OTC medicine. The product has been available in New Zealand since March 2005. New Zealand consumers, pharmacists and pharmacy staff should now be familiar with the use of the product following its local availability as a Pharmacist Only Medicine for some 26 months. During this time a comprehensive education and advertising campaign has been undertaken by Novartis Pharmaceuticals to provide information on seasonal allergic conjunctivitis (SAC) and the differences between various products used in its treatment.

The Novartis affiliate in Australia has submitted a rescheduling application for ketotifen for ophthalmic use from a Pharmacist only medicine to a Pharmacy Medicine in May 2008, therefore the Australian label can be used, without the need for overlabelling, supply of the product to the New Zealand market will be simpler, faster and more efficient. Should there ever be a shortage of supply in New Zealand, Novartis New Zealand will be able to obtain immediate supply from Novartis Australia.

5. Interactions with other medicines

Topical ocular formulations of ketotifen fumarate have shown little systemic drug exposure. In a pharmacokinetic study conducted in 18 healthy volunteers with Zaditen (ketotifen 0.025%) eye drops, plasma levels of ketotifen after ocular administration for 14 days were in most cases below the limit of quantitation (20 pg/mL). Despite the very sensitive analytical method, there is 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 Zaditen eye drops.

After oral administration, ketotifen is eliminated biphasically, with an initial half-life of 3 to 5 hours and a terminal half-life of 21 hours. About 1% of the substance is excreted unchanged in the urine within 48 hours and 60 to 70% as metabolites. The main metabolite is the practically inactive ketotifen-N-glucuronide.

There is no evidence of interference with the metabolism of other drugs due to the inhibition or induction of drug metabolising enzymes by ketotifen. No interactions with food are expected. Clinical experience over the last 30 years has not revealed any potential for serious adverse reactions or interactions when ketotifen is co-administered with commonly used medicines.

Potential for masking or compromising medical management of a disease

Unlike the majority of other antihistamine eye drops used to treat allergic conjunctivitis, Zaditen (ketotifen 0.025% eye drops) contains no vasoconstrictor. Its potential for masking a serious disease is therefore lower than many Pharmacy medicine products for this indication.

The signs and symptoms common to all forms of conjunctivitis are non-specific and generally include various degrees of ocular discomfort, redness, chemosis, tearing and discharge. The constellation and intensity of clinical findings may vary. The most common causes of conjunctivitis are allergy and infection. History and clinical presentation usually allow differentiation between allergic and infective aetiology, particularly in the case of SAC, which is a bilateral, acute and recurrent condition triggered by onset of the pollen season.

SAC may occur alone or be associated with other symptoms of hay fever such as rhinitis. Ocular itching, although not specific to ocular allergy, strongly points to this diagnosis. Foreign body sensation or grittiness may also be reported by patients suffering from SAC. Other clinical signs which may be present include tearing, watery or mucous discharge, variable degree of chemosis and ocular hyperaemia.

Common conditions such as dry eye or chronic blepharitis may mimic SAC or coexist with SAC. The symptoms tend to be more persistent and generally not

associated with intense ocular itching if dry eye or blepharitis occur alone. However, patients with tear film defects may be more prone to allergic conjunctivitis because of their inability to wash away allergens from the conjunctival sac. Treatment with ketotifen eye drops is unlikely to mask these conditions, delay diagnosis or have a major impact on subsequent treatments with artificial tears, topical anti-inflammatory drugs, or antibiotics.

Chronic forms of ocular allergy such as vernal keratoconjunctivitis (VKC), giant papillary conjunctivitis (GPC) and atopic keratoconjunctivitis (AKC) are unlikely to be confused with SAC. It is also unlikely that use of topical ketotifen would delay the diagnosis, mask these diseases or have a negative effect on subsequent treatment since topical antihistamines and mast cell stabilisers are often considered as a treatment option.

Conjunctivitis due to bacterial, chlamydial or viral infections may, initially, have a presentation similar to SAC. However, a consistent feature of acute papillary conjunctivitis caused by infection is conjunctival discharge, typically mucopurulent or purulent in nature. Morning crusting, difficulty in opening eyelids in the morning, ocular discharge and discomfort, usually described as stinging or burning, conjunctival redness, often described as “beefy-red” conjunctiva, prompt patients to seek medical advice. Treatment with topical ketotifen is not likely to mask infection, accelerate its spread, significantly delay diagnosis or have adverse effects on the subsequent antimicrobial treatment. Herpetic blepharoconjunctivitis or keratitis may lead to rapid progression if treated with topical steroids, but it is unlikely that ketotifen eye drops will aggravate the disease. Keratitis associated with herpetic infection is usually unilateral and is characterised by pain and foreign body sensation. Patients who suffer from recurrent ocular herpetic disease are often aware when a relapse takes place and are unlikely to confuse it with SAC.

Conjunctivitis may occur as an isolated infection or in conjunction with lid or corneal disease and lead to blepharoconjunctivitis or keratoconjunctivitis. Involvement of ocular tissues other than conjunctiva will elicit tissue-specific signs and symptoms and may also affect vision, particularly if the central cornea is involved. Topical treatment with ketotifen is not likely to mask the symptomatology or prevent patients seeking medical advice in such cases.

Vision threatening conditions associated with conjunctival irritation, commonly referred to as a “red eye”, include chemical burns and other forms of trauma, episcleritis/scleritis, orbital cellulitis, uveitis and acute angle closure glaucoma. Apart from ocular hyperaemia and conjunctival irritation, these conditions, are associated with pain, visual disturbances or ocular motility problems and have specific history. Although acute allergic conjunctivitis may be a coexisting finding in some of these conditions, it is highly unlikely that they will be confused with SAC. Topical treatment with ketotifen may reduce the initial itching or redness but is not likely to change the natural course, aggravate or suppress the condition, or delay the need to seek urgent medical help.

Conjunctivitis may be a manifestation of systemic disease such as infectious mononucleosis or sarcoidosis. It may also be a concomitant finding in patients who have urogenital chlamydial infection. Although topical treatment with ketotifen may reduce ocular itching and conjunctival injection in these conditions, it will not have an impact on systemic symptoms and is unlikely to delay diagnosis or jeopardise subsequent treatments.

Ketotifen 0.025% eye drops reduce itching but do not have analgesic properties and will not suppress the perception of pain. Ketotifen eye drops will have a limited impact on symptomatology of bacterial, viral or fungal conjunctivitis or keratoconjunctivitis and are unlikely to suppress manifestation of these diseases, postpone the need to seek medical advice, or delay correct diagnosis and appropriate treatment.

6. Contraindications

Known hypersensitivity to ketotifen or to any of the excipients.

7. Possible resistance

Not applicable

8. Adverse events - nature, frequency etc.

The post-marketing safety of Zaditen 0.025% and 0.05% eye drops has been monitored and evaluated in multiple Periodic Safety Update Reports (PSURs). The most recent PSUR (PSUR 7) and an Addendum Report (to 31 January 2008) can be found in Appendices 3 and 4 respectively. No change has been observed in the safety profile of ketotifen eye drops and no new safety findings have been identified to-date. The majority of reported adverse events were related to signs and symptoms of ocular irritation such as itching, burning, increased tearing and conjunctival oedema. Some of these events are at least partially associated with the underlying condition.

Estimates of patient exposure since ketotifen was first approved in the US on 2 July 1999 are presented in Table 5. An overview of the number of adverse reaction reports by PSUR review period is presented in Table 6 Adverse reaction reports received from 2 July 1999 to 30 June 2006.

Table 5 Estimate of patient exposure from 2 July 1999 to 30 June 2006

	Patient exposure MD (Patient-years)	**Patient exposure SDU (Patient-years)**	**Total**
PSUR 1	250,000	500	250,500
PSUR 2	173,000	1,300	174,300
PSUR 3	243,000	4,600	247,600
PSUR 4	417,000	8,600	425,600
PSUR 5	355,000	14,000	369,000
PSUR 6	564,000	16,000	580,000
PSUR 7	420,000	19,000	439,000
Total	**2,422,000**	**64,000**	**2,486,000**

Table 6 Adverse reaction reports received from 2 July 1999 to 30 June 2006

	Serious Unlisted	Serious Listed	Non-serious Unlisted	Non-serious Listed	Total
PSUR 1	0	0	10	2	12
PSUR 2	0	0	8	13	21
PSUR 3	1	0	6	14	21
PSUR 4	2	0	15	35	52
PSUR 5	2	0	22	28	52
PSUR 6	0	2	17	50	69
PSUR 7	2	1	12	40	55
Total	**7**	**3**	**90**	**182**	**282**

It should also be noted that no safety issue has ever been identified with ketotifen 0.05% eye drops that have been marketed in Japan for more than 16 years, even though the recommended dose of 1 drop **4 times a day** corresponds to a 4 times higher daily dose than that recommended for Zaditen 0.025% eye drops administered **twice daily.**

The excellent safety profile of Zaditen is further supported by nearly 30 years experience with oral formulations of ketotifen used in many countries at daily doses which are more than 60 times higher than the recommended daily dose of the 0.025% eye drops.

9. Potential for abuse or misuse

Information on how to use ketotifen 0.025% eye drops is listed in the Consumer Medicine Information (CMI). If ketotifen 0.025% eye drops are approved for inclusion as a Pharmacy medicine, the CMI will continue to be supplied as a pack insert for consumers and electronically for pharmacists. The additional information provided in this document, such as instructions not to use the product if you are allergic to the medicine or any of its ingredients and to remove soft contact lenses before use, helps to ensure a very low risk of adverse events arising from incorrect use of ketotifen.

Doses higher than those recommended do not appear to involve significant risks. After more than 16 years of market experience with ketotifen 0.05% eye drops administered 4 times a day in Japan (i.e., 4 times the recommended daily dose of ketotifen 0.025% eye drops administered twice a day), no significant differences in the safety profiles of the two strengths and regimens were found. Similarly, administration of ketotifen 0.025% eye drops 4 times instead of twice a day for 6 weeks to healthy subjects including children (age 3 and older) resulted in a safety profile similar to that of the vehicle placebo control.

Preserved formulations of Zaditen eye drops contain 0.01% (0.1mg/mL) benzalkonium chloride (BAC), which is one of the most commonly used antimicrobial preservatives in topical multidose ophthalmic preparations. It is known that preservatives, including BAC, can disrupt the precorneal tear film and lead to inflammatory changes of the ocular surface when used in long term treatment. Toxicity of preservatives is of lesser concern in short term treatment of seasonal allergic conjunctivitis. Nevertheless, there is no evidence that use of ketotifen eye drops over longer periods of time increases the risk of adverse effects. Of the 6184 patients included in the six-year safety report on ketotifen 0.05% eye drops submitted to the Japanese health authority, 1566 were treated

for more than 3 months, and 715 for more than 6 months. With 0.26% and 0.84%, respectively, the incidence of adverse effects was lower in these subgroups than in the total population studied (2.17%).

There is practically no risk of significant adverse effects due to accidental oral ingestion since the contents of a 5mL bottle of ketotifen 0.025% eye drops would be equivalent to 1.25mg of ketotifen. Thus is substantially lower than the recommended daily dose for oral formulations of ketotifen (2mg).

Overdose

Clinical results have shown no serious signs or symptoms after oral ingestion of up to 20mg of ketotifen. Serious symptoms, including loss of consciousness or convulsions, were observed in 3 adults ingesting higher doses. All patients, even those taking up to 120mg, made a full recovery. There was no evidence that ventricular tachycardia may occur after ketotifen overdose.

There is practically no risk of adverse effects due to accidental oral ingestion of ketotifen eye drops. Oral ingestion of the contents of a 5mL bottle would be equivalent to 1.25mg of ketotifen (recommended daily oral dose is 2mg). No case of overdose has been reported with ocular presentations of ketotifen worldwide.

Supporting Data Details:

Appendix 1 Marketing Authorisation Status
Appendix 2 NZ Proposed Labelling
Appendix 3 PSUR 7
Appendix 4 PSUR AR 01Jul2006-31Jan2008
Appendix 5 Reference - Kidd M, McKenzie SH, Steven I, et al. Efficacy and safety of ketotifen eye drops in the treatment of seasonal allergic conjunctivitis. *Br J Ophthalmol* 2003;87:1206-1211.
Appendix 6 Reference - Greiner JV, Michaelson C, McWhirther CL et al. Single dose of ketotifen fumarate 0.025% vs 2 weeks of cromolyn sodium 4% for allergic conjunctivitis. *Advances in Therapy*. 2002;19:185-193.

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