Section 21 Ophthalmological Preparations

Ketotifen - Addition

Application submitted by International Council of Ophthalmology
1. Summary statement of the proposal for inclusion, change or deletion

We propose the inclusion of ketotifen ophthalmic solution, a dual action anti-allergic topical medication that combines both mast cell stabilising and antihistaminic properties and has been shown to have good efficacy and safety in treating seasonal allergic conjunctivitis. Because of its dual action, ketotifen can “have the advantage as both a prophylactic to prevent mast cell degranulation and a therapeutic agent to bring about symptomatic relief following the onset of symptoms.”

The May 2005 approval of generic ketotifen by the U.S. Food and Drug Administration has reduced the cost associated with the use of this drug and has made it a very practical option for treating allergic conjunctivitis in the developing world.

2. Name of the focal point in WHO submitting or supporting the application (where relevant)

Ivo Kocur

3. Name of the organization(s) consulted and/or supporting the application

International Council of Ophthalmology

4. International Nonproprietary Name (INN, generic name) of the medicine

Ketotifen fumarate ophthalmic solution

5. Formulation proposed for inclusion; including adult and paediatric (if appropriate)

Ketotifen fumarate ophthalmic solution 0.025%

6. International availability - sources, if possible manufacturers and trade names

Ketotifen fumarate is available in the US, UK, India, Argentina, Australia, Austria, Bahrain, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Croatia, Czech Republic, Denmark, Ecuador, Egypt, Finland, France, Germany, Greece, Hong Kong, Hungary, Iceland, Indonesia, Iran, Iraq, Ireland, Italy, Japan, Jordan, Kuwait, Latvia, Lebanon, Lithuania, Malaysia, Malta, Netherlands, New Zealand, Norway, Oman, Philippines, Poland, Portugal, Qatar, Russian Federation, Saudi Arabia, Singapore, Slovakia, Slovenia, South Africa, South Korea, Spain, Sweden, Switzerland, Syria, Thailand, Turkey, United Arab Emirates, United Kingdom, Venezuela and several other countries.

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Individual medicine

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)
"Older population studies estimate a prevalence of 15–20% of allergic conjunctivitis, but more recent studies implicate rates as high as 40%. Ocular symptoms are common and contribute to the burden of allergic rhinitis and lower quality of life. Ocular allergies rank a very close second and at times may overcome the primary complaints of nasal congestion in rhinoconjunctivitis patients."\textsuperscript{2} Because of its dual action, ketotifen can "have the advantage as both a prophylactic to prevent mast cell degranulation and a therapeutic agent to bring about symptomatic relief following the onset of symptoms."\textsuperscript{1}

Seasonal allergic conjunctivitis is one of the most common types of allergic eye disease, "and the prevalence of allergy is expected to increase rapidly. Currently allergic eye disease is not well managed and the prevalence of ocular allergy may be underestimated. Despite seasonal allergic conjunctivitis being relatively mild, they can significantly affect the quality of life including economic impacts."\textsuperscript{1}

9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostics, treatment or monitoring facilities and skills)

Ketotifen fumarate 0.025% is an eye drop that needs to be administered twice daily, every 8-12 hours, in the affected eye.

10. Summary of comparative effectiveness in a variety of clinical settings:

"Local and systemic tolerance"

Important considerations for ocular allergy treatment include comfort upon instillation, good local tolerance, restricted systemic exposure, and minimum drug-induced adverse events (AEs).

One pivotal clinical study was specifically focused on the tolerability and safety of ketotifen 0.025% ophthalmic solution.\textsuperscript{3} In this study, the drug safety was established using a higher-than-recommended daily dosage (i.e. 4x instead of 2x/day regimen as recommended in clinical practice). Treatments were applied for 6 weeks.

Study design and safety assessment

This trial was a multicentre, randomised, double-masked, placebo-controlled, parallel-group clinical study conducted in volunteers, including children (aged over 3 years), with normal ocular health. A total of 465 healthy subjects were randomised into 2 parallel groups:

- 330 (including 42 children) received ketotifen eye drops
- 165 (including 19 children) received a placebo (vehicle solution)

Safety evaluation included ocular signs and symptoms, pupillary size and reactivity, distant corrected visual acuity (VA), slit lamp and dilated ophthalmoscopy findings, and intraocular
pressure (IOP). All ocular examinations were performed before treatment initiation (Day 0, baseline), during the treatment period (Day 7, Day 14, and Day 42), and 24 to 48 hrs after stopping it. On Day 7, the ophthalmic examination and the assessment of ocular signs and symptoms were performed before and 30 minutes following instillation. All systemic adverse events occurring during the course of the study were also recorded.

**Adverse events**

During the course of the trial, one or more emergent AEs were reported by 196/330 (59.4%) subjects treated with ketotifen and by 90/165 (54.5%) subjects given placebo (p=0.335).

The most frequently reported emergent adverse events in the ketotifen group were headache, ocular injection, itching, and dry eyes, but there was no significant difference versus placebo (Table 1).

### Table 1. Most frequently reported emergent adverse events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Number of patients (%)</th>
<th>Ketotifen (n=330)</th>
<th>Placebo (n=165)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non ocular</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>64 (19.4)</td>
<td>41 (24.5)</td>
<td>0.164</td>
<td></td>
</tr>
<tr>
<td><strong>Ocular</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection</td>
<td>36 (10.9)</td>
<td>17 (10.3)</td>
<td>0.879</td>
<td></td>
</tr>
<tr>
<td>Dry eyes</td>
<td>15 (4.5)</td>
<td>7 (4.2)</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Itching</td>
<td>12 (3.6)</td>
<td>5 (3.0)</td>
<td>0.800</td>
<td></td>
</tr>
</tbody>
</table>

(adapted from Abelson[30]).

Three patients in each group reported at least one serious AE. In the ketotifen group, all of the serious AEs were considered by the investigators as unrelated to the study medication.
Ocular signs and symptoms

No significant changes in mean scores from baseline occurred for any sign or symptom with ketotifen throughout the 6-week study. No ocular rebound vasodilatation or itching was observed within 48 hours after treatment.

Other ocular assessments

No significant differences between ketotifen- and placebo-treated eyes for all other assessed ocular parameters were detected. All parameters were within normal limits in both eyes for all participants at all evaluations.

Tolerance in pediatric subgroup

The study included 61 children aged between 3 and 11 years (42 in the ketotifen group and 19 in the placebo group) treated for 6 weeks four times daily.

The safety profile in the paediatric subgroup was similar to that in the adult population, with no significant between- or within-group differences in all ocular assessments.

Adverse events related or possibly related to study medication were reported in 2/42 (4.8%) ketotifen-treated children (one abnormal vision and one burning/stinging sensation upon drug instillation) and 1/19 (5.3%) children given placebo (conjunctivitis). None of these AEs was serious and led to treatment withdrawal.

In summary, ketotifen fumarate 0.025% ophthalmic solution is safe and well tolerated in adult and paediatric populations.4

"Ocular comfort upon instillation

Ocular comfort during instillations is particularly essential in patient compliance with topical medications.

Ocular comfort upon instillation of ketotifen 0.025% eye drops was investigated in several randomised controlled studies in comparison with placebo or other anti-allergic products.

In 59 atopic patients (without ocular symptoms), ketotifen has been estimated to be as comfortable upon instillation as artificial tears, using an 8-point scale (from 0=very
comfortable to 8=very uncomfortable).\textsuperscript{5} When the subjects were asked to choose among a series of terms to describe the tolerability of the drug, a great majority (72\%) rated ketotifen 0.025\% eye drops as “comfortable” (Figure 1). The proportion of unfavourable descriptive terms (burning/stinging or irritating) was 6\% for ketotifen and 12\% for placebo, at 5 minutes post-instillation.

**Figure 1. Descriptive comfort of ketotifen 0.025\% eye drops**

Subjects (N=59) chose one term among a series to describe ketotifen 0.025\% eye drops and placebo (artificial tears) tolerability 5 minutes after instillation (adapted from Greiner).

![Diagram showing descriptive comfort of ketotifen and placebo](image)

In comparison with other ophthalmic solutions,\textsuperscript{5-7} ketotifen 0.025\% was:

- more comfortable than necrodomicil 2\%
- more comfortable than cromolyn sodium 4\%
- as comfortable as olopatadine 0.1\%\textsuperscript{4}

"Efficacy"

The efficacy of ketotifen 0.025\% eye drops for the symptomatic treatment of SAC have been demonstrated in randomised, double-blind clinical trials, in comparison with placebo and other anti-allergic drugs.
The efficacy of ketotifen versus placebo or other anti-allergic agents was mainly established in provocation test studies outside the pollen season in asymptomatic patients with documented ocular allergy. The design of these studies is in agreement with the recommendation of the European Medicines Agency (EMA) on the clinical development of medicinal products for the treatment of allergic conjunctivitis. The Conjunctival Allergen Challenge (CAC) test is a valid model to provide evidence of superiority over placebo or reference products. Clinical signs (e.g. redness) and symptoms (e.g. itching) can be quantified and are reproducible. The provoked reaction can be used to evaluate and compare any allergic topical ocular products, following a standard methodology with the patient acting as his/her own control.

**Ketotifen versus placebo**

Few studies investigated the efficacy of ketotifen 0.025% ophthalmic solution in the symptomatic relief of allergic conjunctivitis compared to placebo. Placebo used was either ketotifen vehicle ophthalmic solution or artificial tear substitute depending on the study.

- In a recent prospective, randomised, double-masked, contralateral eye, placebo-controlled study in 20 patients with seasonal allergic conjunctivitis, ketotifen was significantly (p<0.001) more effective than placebo in alleviating itching, redness, tearing, chemosis and eyelid swelling (Figure 2).

**Figure 2. Effect of ketotifen on ocular signs and symptoms in patients with SAC versus placebo**

![Graph showing the effect of ketotifen on ocular signs and symptoms in patients with SAC versus placebo over weeks 1 and 2.](image-url)
In conjunctivitis allergen challenge studies, ketotifen had significantly superior effect on ocular itching and hyperaemia than placebo after one single eye drop instillation.\textsuperscript{10-11}

- In the Greiner study,\textsuperscript{11} baseline itching score ranged between 2.55 and 2.83 without difference between eyes. After a single ketotifen drop instillation, ocular itching decreased to extremely mild scores ranging between 0.51 and 0.81, whereas it remained moderate in vehicle-treated eyes (1.52-2.32). Benefits were seen at the 15 min posttreatment allergen challenge and the duration of action lasted for at least 8 hours (Figure 3) and 12 hours in another Greiner's study.\textsuperscript{5} The activity of ketotifen occurred rapidly within 3 minutes following the allergen challenge.

\textbf{Figure 3. Effect of ketotifen on ocular itching (one single administration)}

\textit{versus} placebo

The allergen challenge was performed in N=89 patients 15 min (visit 3), 6 hours (visit 4) or 8 hours (visit 5) following single instillation of ketotifen in one eye and placebo in the fellow eye (adapted from Abelson).
• Ketotifen was also significantly superior to placebo in reducing ocular injection in all vessel beds and at all time points after instillation (p<0.001), with a maximum reduction at 7 minutes postchallenge (Table 2).

Table 2. Effect of ketotifen on vascular injection after one single drop versus placebo

<table>
<thead>
<tr>
<th>Vascular injection mean score – 7 minutes post-allergen challenge N=89 patients</th>
<th>Time after treatment (hrs)</th>
<th>Ketotifen</th>
<th>Placebo</th>
<th>Treatment difference</th>
<th>% reduction*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctival vascular injection</td>
<td>0.25</td>
<td>1.34</td>
<td>1.81</td>
<td>-0.47</td>
<td>26%</td>
</tr>
<tr>
<td></td>
<td>6.00</td>
<td>1.53</td>
<td>1.96</td>
<td>-0.43</td>
<td>22%</td>
</tr>
<tr>
<td></td>
<td>8.00</td>
<td>1.48</td>
<td>1.79</td>
<td>-0.31</td>
<td>17%</td>
</tr>
<tr>
<td>Ciliary vascular injection</td>
<td>0.25</td>
<td>1.16</td>
<td>1.68</td>
<td>-0.52</td>
<td>31%</td>
</tr>
<tr>
<td></td>
<td>6.00</td>
<td>1.35</td>
<td>1.79</td>
<td>-0.44</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>8.00</td>
<td>1.36</td>
<td>1.73</td>
<td>-0.36</td>
<td>21%</td>
</tr>
<tr>
<td>Episcleral vascular injection</td>
<td>0.25</td>
<td>1.37</td>
<td>1.79</td>
<td>-0.47</td>
<td>26%</td>
</tr>
<tr>
<td></td>
<td>6.00</td>
<td>1.61</td>
<td>2.03</td>
<td>-0.43</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>8.00</td>
<td>1.54</td>
<td>1.82</td>
<td>-0.29</td>
<td>16%</td>
</tr>
</tbody>
</table>

* from placebo value (adapted from Greiner).

• After repeated instillations for 4 weeks, ketotifen (last dose instilled 8 hours before allergen challenge) was superior to placebo in reducing itching (p<0.001) and hyperaemia (p<0.003). The protective effect of ketotifen against ocular itching and injection was rapid with an onset of 3 minutes after allergen challenge. Significant (p<0.001) reductions in chemosis, tearing, and lid swelling were observed at each postchallenge time (Table 3).
Table 3. Effect of ketotifen on other ocular symptoms after repeated eye drops instillation versus placebo

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Ketotifen</th>
<th>Placebo</th>
<th>Treatment difference**</th>
<th>P value***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itching</td>
<td>1.19</td>
<td>2.47</td>
<td>-1.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Composite injection*</td>
<td>5.30</td>
<td>6.01</td>
<td>0.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chemosis</td>
<td>0.52</td>
<td>0.66</td>
<td>-0.14</td>
<td>0.001</td>
</tr>
<tr>
<td>Tearing</td>
<td>0.31</td>
<td>0.44</td>
<td>-0.13</td>
<td>0.023</td>
</tr>
<tr>
<td>Lid swelling</td>
<td>0.22</td>
<td>0.48</td>
<td>-0.26</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Sum of ciliary, conjunctival and episcleral scores; ** treatment difference: ketotifen – placebo; *** Student’s t-test (adapted from Greiner\(^{35}\)).

- In the Torkildsen’s conjunctival allergen challenge study,\(^{12}\) at the 8-hour posttreatment allergen challenge, the mean ocular itching scores for ketotifen-treated eyes were 1.16, 1.27, and 1.30 units lower at 3, 5, and 7 minutes, respectively than for placebo-treated eyes. At 15-minute posttreatment allergen challenge, the mean ocular itching scores for reference formulation-treated eyes at 3, 5, and 7 minutes were 1.48, 1.62, and 1.57 units lower, respectively, than for eyes that were administered placebo.

**Effect of ketotifen on rhinitis symptoms versus placebo**

- In a randomised, placebo-controlled, parallel, single centre study,\(^{13}\) one single drop of ketotifen 0.025% ophthalmic solution was also shown to offer protection against nasal
signs and symptoms associated with acute allergic rhinoconjunctivitis reaction, as induced by the CAC model (Figure 4).

Figure 4. Effect of Ketotifen on nasal symptoms after single drop instillation versus placebo

Nasal symptoms (sneezing, rhinorrhea and postnasal drip, nasal pruritus, palatal pruritus, nasal congestion) 10, 20 and 30 min after the allergen challenge. N=19 patients treated with ketotifen and N=13 patients treated with placebo (adapted from Crampton).

Taken together, these results support the efficacy of ketotifen 0.025% eye drops versus placebo:

- itching, redness tearing eye swelling and chemosis are all significantly reduced after 1 week of treatment in symptomatic patients with SAC

- the duration of action of ketotifen is sustained between 8-12 hours

- the onset of action of ketotifen is observed within 3 minutes after allergen contact

- ketotifen eye drops reduce nasal symptoms in patients with rhinoconjunctivitis

"Ketotifen versus other antiallergic products

H1-receptor antagonists
The relative clinical efficacy of ketotifen 0.025% ophthalmic solution and other common antihistamines (levocabastine, emedastine) was evaluated in randomised, double-masked clinical studies.

**Ketotifen versus levocabastine**

Levocabastine is a potent histamine H1-receptor antagonist indicated for the treatment of allergic conjunctivitis.

- In a double-masked parallel group controlled study, patients with symptoms of SAC (N=519) were randomly assigned to ketotifen fumarate 0.025%, eye drops, placebo (as vehicle), or levocabastine hydrochloride 0.05% eye drops, twice daily in each eye for 4 weeks. Ocular sign and symptoms (5-point rating scale) and global patient satisfaction were assessed after one and four weeks.\(^\text{14}\)

  All of the acute symptoms of SAC resolved rapidly regardless of the treatment group. Ketotifen produced a more rapid and significantly greater symptom relief (itching, redness, watery eyes, and overall symptoms) compared with placebo and levocabastine (Figure 5).
Global efficacy was rated as “excellent” or “good” by 49.5% of the ketotifen-treated patients versus 33% in placebo-treated patients (p=0.02), and tended to be higher than in levocabastine-treated patients (41.1%, p=0.20).

Moreover, patients in the ketotifen group reported a significantly higher number of symptom-free days compared with patients given placebo (11.2 vs 8.7 days, p=0.02) versus 10.3 days in levocabastine-treated patients. According to Kidd et al., this indicates that in addition to alleviating the signs and symptoms of acute episodes of SAC, ketotifen can prevent recurrent episodes of the disease.
Ketotifen versus emedastine

Emedastine is a potent and highly selective histamine H1-receptor antagonist.

- In a double-masked, randomised, contralateral eyes, placebo-controlled, parallel group conjunctival allergen challenge study, ketotifen and emedastine 0.05% eye drops were shown to have similar efficacy in inhibiting ocular itching in the conjunctival allergen challenge 5 min (Table 4) or 15 min following drug administration.\textsuperscript{15}

<table>
<thead>
<tr>
<th>Table 4. Efficacy of ketotifen versus emedastine in relieving itching symptoms in ocular allergy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean score (SD) difference</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>N=14</strong></td>
</tr>
<tr>
<td>Allergen challenge performed 5 min after treatment instillation (n=25)</td>
</tr>
<tr>
<td>Time after challenge</td>
</tr>
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<td></td>
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<td></td>
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</tbody>
</table>

Symptoms were score using a 5-point rating scale: 0 = no itching to 4 = severe itching.

* p<0.05 (adapted from D’Arienzo).

- In the cross-over study performed by Horak et al.,\textsuperscript{16} patients with an allergy to grass pollen (N=37) were exposed to the allergen in a pollen chamber for 4 hours, followed by a 3-hour break and then a second exposure for 3 hours. Compared to emedastine, ketotifen provided a significantly greater relief of composite ocular symptoms (p = 0.026) and total symptom score (p=0.014) in the first 2 hours following drug administration. The drugs were similarly effective in reducing the ocular and nasal symptoms 5 to 8 hours after instillation. The median time to onset of action was significantly (p=0.048) shorter for ketotifen (15 min) than for emedastine (30 min) (Figure 6).
Ketotifen consistently showed good efficacy compared to other H1-receptor antagonists:

- Ketotifen proves to be superior to levocabastine in reducing all the symptoms of SAC
- Ketotifen is at least as efficient as emedastine, with however a more rapid onset of action

Mast cell stabilizers

Cromolyn sodium

Cromolyn sodium is the first mast cell stabilizer indicated for the symptomatic treatment of ocular allergic diseases.

- In a single-masked, randomised, contralateral eyes, placebo-controlled, parallel group conjunctival allergen challenge study,\(^6\) at the 15 minutes and 4-hour challenge, ketotifen
was superior to cromolyn 4% (p<0.001) in the prevention of itching at all assessments and redness (ciliary, conjunctival, and episcleral) at most assessments (p<0.001) (Figure 7).

Figure 7. Ketotifen versus cromolyn in relieving conjunctival hyperaemia

Allergen challenge was performed in 56 patients 15 minutes or 4 hours after instillation of one drop of ketotifen 0.025% eye drops in one eye and one drop of cromolyn 4% in the fellow eye. Symptoms (redness and itching) were assessed 7 minutes post-challenge using a 5-points scale (0, none to 4, extremely severe). *P<0.05 between treatments. C: clinically significant (adapted from Greiner)

Nedocromil sodium

Nedocromil sodium is a mast cell stabilizer with additional anti-inflammatory actions on cells involved in the allergic response.17

- In a double-masked, randomised contralateral, placebo-controlled conjunctival allergen challenge study,5 ketotifen 0.025% eye drops were significantly more efficacious (p<0.05) and comfortable (p<0.05) than nedocromil 2.0 % eye drops both at 5 minutes and 12 hours after drug administration (Figure 8).
Ocular itching was assessed in 59 patients 5 minutes (A) and 12 hours (B) after drug instillation. Ocular itching scores were recorded every 30 seconds for 20 minutes after allergen challenge using 5-point grading scale. *p<0.05 vs placebo, †p<0.05 vs nedocromil (adapted from Greiner).

On the basis of subjective efficacy and comfort, 60% of the subjects preferred ketotifen, while 21% and 19% privileged necrodomil and placebo, respectively (Figure 9).
Figure 9. Preference of patients (N=59) for ketotifen compared to nedocromil eye drops

(adapted from Greiner).

In summary, in clinical studies, ketotifen consistently showed good efficacy in reducing itching and redness compared to standard mast cell stabilizers:

- Ketotifen was significantly superior to cromolyn sodium 4% eye drops
- Ketotifen was significantly superior to nedocromil 2%
- Ketotifen provides superior ocular comfort compared to nedocromil 2% as judged by the patient’s preference

Multiple-acting agents

Olopatadine is a widely used topical agent effective in long-term control of symptoms associated with allergic conjunctivitis. As ketotifen, olopatadine is a therapeutic molecule with dual mode of action, acting both as antihistamine and as mast cell stabiliser.

- In a double-masked, randomised, parallel-group study, patients with SAC were assigned either ketotifen 0.025% (N=32) or olopatadine 0.1% (N=34) twice daily in both eyes for 3 weeks. The responder rate was significantly (p<0.0001) higher with ketotifen than with olopatadine on Day 5 (72% versus 54% according to patients, and 88% versus 55%
according to the investigators) and Day 21 (91% versus 55%, and 94% versus 42%, respectively) (Figure 10).

Figure 10. Efficacy of ketotifen versus olopatadine eye drops

Global efficacy was evaluated by patients and investigators at Day 5-8 (A) and Day 21-24 (B) after treatment initiation. A score of 0 (complete relief of ocular allergy symptoms) or 1 (distinct relief) defined a responder. *p<0.0001 (analysis of variance and mixed model) (adapted from Ganz).
Regarding individual ocular signs and symptoms, severity scores for conjunctival hyperemia and itching were significantly lower in the ketotifen group on Day 5 and Day 21. These results indicated that the higher symptom relief in favour of ketotifen is maintained over time.

- In another double-masked, randomised, placebo-controlled, parallel-group study,\(^\text{18}\) patients with SAC were assigned to ketotifen 0.025% (N=16) or olopatadine 0.1% (N=16) or artificial tear substitutes (N=17) twice daily in both eyes for 4 weeks. Both ketotifen and olopatadine significantly reduced ocular itching and tearing on Day 15 and Day 30 of treatment, compared to baseline or artificial tear substitute (Figure 11).

**Figure 11. Efficacy of ketotifen eye drops versus olopatadine on ocular signs and symptoms in SAC**

(adapted from Avunduk)

- In a single-centre, simple-masked, parallel-group study,\(^\text{19}\) patients with vernal keratoconjunctivitis (VKC) were assigned either ketotifen 0.025% (N=19) or olopatadine 0.1% (N=19) twice daily in both eyes for 3 weeks. Both ketotifen and olopatadine were efficient in relieving the main signs and symptoms of VKC. At the same evaluation time points (Day 7, Day 14 and Day 21) during treatment, there was a statistically significant difference in favour of ketotifen-treated patients (p<0.05), with a greater improvement of itching, tearing, conjunctival hyperemia, mucous discharge and photophobia.
Taken together, clinical studies suggest that:

- Ketotifen 0.025% eye drops may produce a more rapid onset of action and a higher response rate than olopatadine 0.1% eye drops over 3 weeks in one clinical study.

- Ketotifen 0.025% eye drops were shown to be a better treatment than olopatadine 0.1% eye drops in reducing symptoms (itching, tearing, hyperaemia, mucous discharge, and photophobia) of vernal conjunctivitis.

- Ketotifen 0.025% and olopatadine 0.1% eye drops are similar in terms of ocular tolerability and comfort.\(^4\)

"Ketotifen use in paediatric population"

Allergies represent one of the most common chronic conditions diagnosed in children. While their prevalence is increasing over time, they are estimated to affect up to 40% of the paediatric population, regardless of the age group.\(^{20}\)

Ketotifen efficacy in paediatric population (N=133) was reported in one double-masked, randomised, fellow-eye placebo-controlled, conjunctival allergen challenge trial after single or repeated dosing.\(^{21}\)

- After single and multiple dose (b.i.d. instillation for 4 weeks), ketotifen fumarate 0.025% significantly inhibits ocular itching (p<0.001) compared to placebo in children (8-16 year-old) with a documented history of SAC or PAC. Symptom relief was shown within 15 min after ketotifen instillation and was sustained for at least 8 hours (Figure 12). The potent relieving effect of ketotifen was observed 3 minutes after allergen challenge. Statistically significant baseline-adjusted reduction of other ocular signs and symptoms was also demonstrated, including hyperaemia, chemosis and lid swelling (p=0.031). No drug-related systemic adverse events were reported, and ocular adverse events were comparable to placebo, making ketotifen fumarate 0.025% ophthalmic solution suitable for children.
In conclusion, ketotifen 0.025% eye drops provided children with:

- a strong efficacy in reducing ocular symptoms within 3 min
- a long-lasting effect sustained for at least 8 hours
- a rapid onset of action of 3 minutes following allergen contact

This study support the use ketotifen with the same dosing regimen in children and adults.
Quality of Life

The visual function is a central component of functional, social and psychological well-being. By affecting visual acuity and/or other parameters such as visual field, color perception, contrasts, and resistance to blinding, ocular pathologies or negative conditions can seriously impair daily activities and, more generally, quality of life (QoL).

The relationship between ocular health and health-related QoL is well documented, leading to the recognition that QoL is an important outcome of eye care.\textsuperscript{22}

With a prevalence estimated at 15 to 20\% in the general population, SAC is the most common form of ocular allergy, affecting adults and children alike. Due to the frequency and duration of the disease, the very distressing signs and symptoms of SAC can cause extreme discomfort and may highly affect the patient QoL. The most frequently occurring ocular signs and symptoms associated with SAC can be particularly distressing and troublesome to children. They can limit their daily activities, increase school absences, impair alertness and learning, cause anxiety, and interfere with the child's ability to interact with peers and family members.

The improvement of QoL by ketotifen 0.025\% eye drop treatment was shown in a large, multicentre, longitudinal, prospective study conducted in patients with untreated SAC.\textsuperscript{23}

- In this study, 1145 subjects (at least 12 year-old) suffering from an untreated episode of SAC at the time of the study were included. Ketotifen 0.025\% eye drop treatment (1 drop every 12 hours) was initiated during a unique ophthalmologist consultation. QoL analysis was performed on the basis of questionnaires collected from 510 patients (with both evaluable consultation and home questionnaires). One week-treatment or more with ketotifen 0.025\% eye drops resulted in a significant reduction in all perceived ocular symptoms. As a consequence, limitations in patients' daily activities and the impact on their mind state were significantly decreased (Figure 13).
Thus, in addition to its strong and safe activity against signs and symptoms of ocular allergy, its sustained duration of action and convenient dosing regimen:

- ketotifen 0.025% eye drops significantly improve the impact of ocular symptoms on daily activities, and mind state observed one week after initiation of treatment

11. **Summary of comparative evidence on safety**:
- Estimate of total patient exposure to date
- Description of adverse effects/reactions
- Identification of variation in safety due to health systems and patient factors
- Summary of comparative safety against comparators

"Local and systemic tolerance"

Important considerations for ocular allergy treatment include comfort upon instillation, good local tolerance, restricted systemic exposure, and minimum drug-induced adverse events (AEs).
One pivotal clinical study was specifically focused on the tolerability and safety of ketotifen 0.025% ophthalmic solution. In this study, the drug safety was established using a higher-than-recommended daily dosage (i.e. 4x instead of 2x/day regimen as recommended in clinical practice). Treatments were applied for 6 weeks.

**Study design and safety assessment**

This trial was a multicentre, randomised, double-masked, placebo-controlled, parallel-group clinical study conducted in volunteers, including children (aged over 3 years), with normal ocular health. A total of 465 healthy subjects were randomised into 2 parallel groups:

- 330 (including 42 children) received ketotifen eye drops
- 165 (including 19 children) received a placebo (vehicle solution)

Safety evaluation included ocular signs and symptoms, pupillary size and reactivity, distant corrected visual acuity (VA), slit lamp and dilated ophthalmoscopy findings, and intraocular pressure (IOP). All ocular examinations were performed before treatment initiation (Day 0, baseline), during the treatment period (Day 7, Day 14, and Day 42), and 24 to 48 hrs after stopping it. On Day 7, the ophthalmic examination and the assessment of ocular signs and symptoms were performed before and 30 minutes following instillation. All systemic adverse events occurring during the course of the study were also recorded.

**Adverse events**

During the course of the trial, one or more emergent AEs were reported by 196/330 (59.4%) subjects treated with ketotifen and by 90/165 (54.5%) subjects given placebo (p=0.335).

The most frequently reported emergent adverse events in the ketotifen group were headache, ocular injection, itching, and dry eyes, but there was no significant difference versus placebo (Table 1).

**Table 1. Most frequently reported emergent adverse events**

<table>
<thead>
<tr>
<th></th>
<th>Number of patients (%)</th>
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<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Event</td>
<td>Ketotifen (n=330)</td>
</tr>
<tr>
<td>----------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Non ocular</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>64 (19.4)</td>
</tr>
<tr>
<td>Ocular</td>
<td></td>
</tr>
<tr>
<td>Injection</td>
<td>36 (10.9)</td>
</tr>
<tr>
<td>Dry eyes</td>
<td>15 (4.5)</td>
</tr>
<tr>
<td>Itching</td>
<td>12 (3.6)</td>
</tr>
</tbody>
</table>

(adapted from Abelson).  

Three patients in each group reported at least one serious AE. In the ketotifen group, all of the serious AEs were considered by the investigators as unrelated to the study medication.

**Ocular signs and symptoms**

No significant changes in mean scores from baseline occurred for any sign or symptom with ketotifen throughout the 6-week study. No ocular rebound vasodilatation or itching was observed within 48 hours after treatment.

**Other ocular assessments**

No significant differences between ketotifen- and placebo-treated eyes for all other assessed ocular parameters were detected. All parameters were within normal limits in both eyes for all participants at all evaluations.

**Tolerance in pediatric subgroup**

The study included 61 children aged between 3 and 11 years (42 in the ketotifen group and 19 in the placebo group) treated for 6 weeks four times daily.

The safety profile in the paediatric subgroup was similar to that in the adult population, with no significant between- or within-group differences in all ocular assessments.
Adverse events related or possibly related to study medication were reported in 2/42 (4.8%) ketotifen-treated children (one abnormal vision and one burning/stinging sensation upon drug instillation) and 1/19 (5.3%) children given placebo (conjunctivitis). None of these AEs was serious and led to treatment withdrawal.

In summary, ketotifen fumarate 0.025% ophthalmic solution is safe and well tolerated in adult and paediatric populations."

"Ocular comfort upon instillation"

Ocular comfort during instillations is particularly essential in patient compliance with topical medications.

Ocular comfort upon instillation of ketotifen 0.025% eye drops was investigated in several randomised controlled studies in comparison with placebo or other anti-allergic products.

In 59 atopic patients (without ocular symptoms), ketotifen has been estimated to be as comfortable upon instillation as artificial tears, using an 8-point scale (from 0=very comfortable to 8=very uncomfortable). When the subjects were asked to choose among a series of terms to describe the tolerability of the drug, a great majority (72%) rated ketotifen 0.025% eye drops as “comfortable” (Figure 1). The proportion of unfavourable descriptive terms (burning/stinging or irritating) was 6% for ketotifen and 12% for placebo, at 5 minutes post-instillation.

Figure 1. Descriptive comfort of ketotifen 0.025% eye drops

Subjects (N=59) chose one term among a series to describe ketotifen 0.025% eye drops and placebo (artificial tears) tolerability 5 minutes after instillation (adapted from Greiner).
In comparison with other ophthalmic solutions,\textsuperscript{5-7} ketotifen 0.025% was:

- more comfortable than necrodomiil 2%
- more comfortable than cromolyn sodium 4% 
- as comfortable as olopatadine 0.1% \textsuperscript{4}

12. Summary of available data on comparative cost\textsuperscript{**} and cost-effectiveness within the pharmacological class or therapeutic group:

There is limited data on the cost effectiveness of ketotifen. "In a cost analysis, lowest treatment cost was established by fluorometholon (US$ 38.94) and followed by ketotifen (US$ 43.41), epinastine (US$ 43.60), olopatadine (US$ 44.05) and emedastine (US$ 44.92), respectively. When the drugs compared for incremental cost-effectiveness, emedastine was dominated by ketotifen and emedastine dominated by olopatadine; ketofien could be compared with fluorometholon and olopatadine."\textsuperscript{24}

However, ketotifen eye drops are generic and can be purchased relatively inexpensively, especially in India. A 5 ml bottle of the drops costs approximately Indian Rs. 55 (approximately 1 US dollar).

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

Generic ketotifen fumarate 0.025% was approved by the US Food and Drug Administration in May 2005.


Ketotifen fumarate met United States and British pharmacopoeial standards. Ketotifen hydrogen fumarate met European pharmacopoeial standards.

15. Proposed (new/adapted) text for the WHO Model Formulary

Per http://dailymed.nlm.nih.gov:

Please note: The text references Zaditor™, the brand name version of ketotifen fumarate 0.025%.

ZADITOR™ Ketotifen Fumarate Ophthalmic Solution, 0.025%

DESCRIPTION
ZADITOR™ is a sterile ophthalmic solution containing ketotifen for topical administration to the eyes. Ketotifen fumarate is a finely crystalline powder with an empirical formula of C23H23NO5S and a molecular weight of 425.50.

Established Name: ketotifen fumarate ophthalmic solution

CHEMICAL NAME

4-(1-Methyl-4-piperidylidene)-4H-benzo[4,5]cyclohepta[1,2-b] thiophen-10(9H)-one hydrogen fumarate

Each mL of ZADITOR™ contains: Active: 0.345 mg ketotifen fumarate equivalent to 0.25 mg ketotifen. Inactives: glycerol, sodium hydroxide/hydrochloric acid (to adjust pH) and purified water. Preservative: benzalkonium chloride 0.01%. It has a pH of 4.4 to 5.8 and an osmolality of 210-300 mOsm/kg.

CLINICAL PHARMACOLOGY

Ketotifen is a relatively selective, non-competitive histamine antagonist (H1-receptor) and mast cell stabilizer. Ketotifen inhibits the release of mediators from cells involved in hypersensitivity reactions. Decreased chemotaxis and activation of eosinophils has also been demonstrated.

Ketotifen has been shown to have little systemic exposure following topical ocular administration. A study conducted with 15 healthy volunteers dosed bilaterally with ketotifen fumarate ophthalmic solution twice daily for 14 days demonstrated plasma concentrations generally below the quantitation limit of assay (< 20 pg/mL).

In human conjunctival allergen challenge studies, ZADITOR™ was significantly more effective than placebo in preventing ocular itching associated with allergic conjunctivitis. The action of ketotifen occurs rapidly with an effect seen within minutes after administration.

INDICATIONS AND USAGE

ZADITOR™ (ketotifen fumarate ophthalmic solution) is indicated for the temporary prevention of itching of the eye due to allergic conjunctivitis.
CONTRAINDICATIONS
ZADITOR™ is contraindicated in persons with a known hypersensitivity to any component of this product.

WARNINGS
For topical ophthalmic use only. Not for injection or oral use.

PRECAUTIONS
Information for patients
To prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep the bottle tightly closed when not in use. Patients should be advised not to wear a contact lens if their eye is red. ZADITOR™ should not be used to treat contact lens related irritation. The preservative in ZADITOR™, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses and whose eyes are not red, should be instructed to wait at least ten minutes after instilling ZADITOR™ before they insert their contact lenses.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Ketotifen fumarate was determined to be non-mutagenic in a battery of in vitro and in vivo mutagenicity assays including: Ames test, in vitro chromosomal aberration test with V79 Chinese hamster cells, in vivo micronucleus assay in mouse, and mouse dominant lethal test.

Treatment of male rats with oral doses of ketotifen ≥ 10 mg/kg/day orally [6,667 times the maximum recommended human ocular dose of 0.0015 mg/kg/day on a mg/kg basis (MRHOD)] for 70 days prior to mating resulted in mortality and a decrease in fertility. Treatment with ketotifen did not impair fertility in female rats receiving up to 50 mg/kg/day of ketotifen orally (33,333 times the MRHOD) for 15 days prior to mating.

Pregnancy
Pregnancy Category C

Oral treatment of pregnant rabbits during organogenesis with 45 mg/kg/day of ketotifen (30,000 times the MRHOD) resulted in an increased incidence of retarded ossification of the sternebrae. However, no effects were observed in rabbits treated with up to 15 mg/kg/day (10,000 times the MRHOD). Similar treatment of rats during organogenesis with 100 mg/kg/day of ketotifen (66,667 times the MRHOD) did not reveal any biologically relevant effects.

Oral treatment of pregnant rats (up to 100 mg/kg/day or 66,667 times the MRHOD) and rabbits (up to 45 mg/kg/day or 30,000 times the MRHOD) during organogenesis did not result in any biologically relevant embryofetal toxicity. In the offspring of the rats that received ketotifen orally from day 15 of pregnancy to day 21 post partum at 50 mg/kg/day (33,333 times the MRHOD), a maternally toxic treatment protocol, the incidence of postnatal mortality was slightly increased, and body weight gain during the first four days post partum was slightly decreased.
Nursing Mothers
Ketotifen fumarate has been identified in breast milk in rats following oral administration. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in breast milk. Nevertheless, caution should be exercised when ketotifen fumarate is administered to a nursing mother.

Pediatric Use
Safety and effectiveness in pediatric patients below the age of 3 years have not been established.

ADVERSE REACTIONS
In controlled clinical studies, conjunctival injection, headaches, and rhinitis were reported at an incidence of 10 to 25%. The occurrence of these side effects was generally mild. Some of these events were similar to the underlying ocular disease being studied.

The following ocular and non-ocular adverse reactions were reported at an incidence of less than 5%:

**Ocular:** Allergic reactions, burning or stinging, conjunctivitis, discharge, dry eyes, eye pain, eyelid disorder, itching, keratitis, lacrimation disorder, mydriasis, photophobia, and rash.

**Non-Ocular:** Flu syndrome, pharyngitis.

OVERDOSAGE
Oral ingestion of the contents of a 5 mL bottle would be equivalent to 1.725 mg of ketotifen fumarate. Clinical results have shown no serious signs or symptoms after the ingestion of up to 20 mg of ketotifen fumarate.

DOSAGE AND ADMINISTRATION
The recommended dose is one drop in the affected eye(s) twice daily, every 8 to 12 hours.

HOW SUPPLIED
NDC 58768-102-05 ZADITOR 5 mL is supplied in a white Polypropylene (PP) 7.5 cc container with a PP dropper tip and closure.

NDC 58768-102-99 ZADITOR 1 mL is supplied in a white Low Density Polyethylene (LDPE) 3.0 cc container with a LDPE dropper tip and PP closure.
References

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