

Efficacy and safety of single- and multiple-dose ketotifen fumarate 0.025% ophthalmic solution in a pediatric population

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Allergic conjunctivitis can seriously disrupt children's daily activities. This study assessed the efficacy (onset and duration of action) and safety of ketotifen fumarate 0.025% ophthalmic solution compared with vehicle placebo in pediatric subjects after single and multiple dosing. This was a double-masked, multicenter, fellow-eye, placebo-controlled, conjunctival allergen challenge trial. Eligible subjects (8–16-yr-olds) who produced a qualifying reaction to allergen were randomized to a single dose (one drop) of ketotifen fumarate in one eye and vehicle placebo in the fellow eye, followed by an allergen challenge at 15 min and 8 h post-dose. Subjects who had a qualifying reaction to allergen in the placebo-treated eye and a qualifying response to ketotifen in the active-treated eye following the single dose were re-randomized to a multiple-dose treatment period. They were instructed to instill one drop of ketotifen fumarate in one eye and placebo in the other eye twice daily for 4 wk. An allergen challenge was conducted 8 h after the last dose. The primary efficacy assessment was ocular itching, judged by the subject at 3, 7, and 10 min post-allergen challenge after single- and multiple-dose treatments. Other ocular signs and symptoms were assessed at 7, 10, and 15 min post-dose. A total of 133 subjects were randomized to single-dose treatment; 105 were evaluable for efficacy. Of these, 60 were re-randomized to multiple-dose treatment, and 55 were evaluable for efficacy. After single and multiple doses, ketotifen fumarate significantly inhibited ocular itching compared with placebo at all post-challenge timepoints ($p < 0.001$) and also significantly reduced hyperemia, chemosis, and lid swelling ($p = 0.031$). No drug-related systemic adverse events were reported, and ocular adverse events were comparable to placebo. No subject discontinued prematurely due to an adverse event. These results indicate that ketotifen fumarate 0.025% ophthalmic solution is an effective and safe treatment option for children with allergic conjunctivitis.

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Allergies are one of the most common chronic conditions diagnosed in children (1). It is estimated that up to 40% of children are affected and that the incidence in children is rising (2). Allergic conjunctivitis is the most common form of ocular allergic disease (3), affecting 5–22% of the population (4). There are several other types of ocular allergy, including vernal and atopic

keratoconjunctivitis; however, these are severe, chronic forms of ocular disease and occur with much less frequency than the seasonal or perennial allergic conjunctivitis pertinent here. The most frequently occurring and distressing ocular signs and symptoms associated with allergic conjunctivitis are itching and redness (1). Swelling, excessive lacrimation, and mucous discharge

are also frequently part of the symptom complex. These symptoms can be particularly troublesome to children. They limit their activities and markedly interfere with their quality of life causing an increased absence from school, learning impairment, inability to integrate with peers, anxiety, and family dysfunction (5–7).

The options for treating allergic conjunctivitis in children are the same as those for adults; however, a balance of efficacy and tolerability is especially important (8). In children and adults, systemic antihistamines are used in the treatment of allergic rhinoconjunctivitis (9). However, their impairment of CNS function, and significant drying effects of the ocular surface, is more common than generally realized (10). While newer generation systemic antihistamines may have less effect on CNS function, they still cause drying of the eye. Several controlled studies have demonstrated significant adverse effects of orally administered antihistamines on cognitive and academic function in children (1, 11). Zaditen®/Zaditor™ (Novartis Pharma AG, Business Unit Ophthalmics, Basel, Switzerland) is an ophthalmic solution of ketotifen fumarate, which possesses three distinct mechanisms of action: H₁-receptor antagonism, mast cell stabilization, and inhibition of eosinophil infiltration, activation and degranulation (12). In adults, ketotifen has shown a rapid onset (as short as 3 min) and a long duration of action of up to 12 h in the allergen challenge model (13), which produces all the signs and symptoms of allergic conjunctivitis (14).

The objective of this study was to assess the efficacy and safety of ketotifen fumarate 0.025% ophthalmic solution compared with vehicle placebo in pediatric subjects at 15 min (onset of action) and 8 h (duration of action) after a single dose and at 8 h after multiple dosing (twice daily) for a 4-wk period (confirmation of lasting effect).

Methods

Subjects

Pediatric subjects (8–16 yr of age) of either gender and any race, with a positive skin test and 12-month allergic (seasonal or perennial) history to cat dander, cat hair, or selected environmental allergens not currently in season (tree, grass, ragweed pollens) in the geographic area of the investigation site, were eligible for this trial. Subjects were required to have a corrected distance visual acuity calculated to 0.30 log minimum angle of resolution (log MAR) or better in both eyes, as measured by an Early

Treatment of Diabetic Retinopathy Study (ETDRS) chart. Also, subjects had to agree to avoid wearing contact lenses for 3 days before the first visit and for the duration of the trial.

Subjects were excluded from the study if they had any of the following: signs or symptoms of allergic conjunctivitis in either eye; any ocular condition or any significant illness that could interfere with the trial parameters; ocular surgery within the prior 2 months or during the trial; a history of retinal detachment, diabetic retinopathy, or other retinal disease; a hypersensitivity to any component of the trial medication; or a history of status asthmaticus or moderate to severe allergic asthma. The following medications were prohibited prior to and during the study: monoamine oxidase inhibitors, H₁-receptor antagonists, aspirin, or aspirin-containing products within 72 h; mast cell stabilizers or corticosteroids within 14 days; and immunotherapeutic agents within 3 months. The trial was conducted in accordance with the Declaration of Helsinki, and approved by the local ethics committee. All participants and their parents or guardians provided written informed consent.

Design

This double-masked, randomized, fellow-eye placebo-controlled, conjunctival allergen challenge trial was conducted between October 2001 and March 2002 at five centers in the United States.

At visit 1 (day 7 ± 2), subjects were screened to assess their eligibility for the study, and a conjunctival provocation test was performed in both eyes of each subject to determine the type and concentration of allergen that would produce a qualifying reaction. Allergens included ragweed, cat hair/dander, and tree/grass pollen, which were instilled into the cul-de-sac of each eye with a micropipette. Allergen selection was based on reactivity to the specific allergens according to prior skin test results. The ocular allergic reaction progresses in a similar manner regardless of which specific allergen is used for each individual. Additionally, each patient attained a similar severity of reaction, as ocular allergen instillation occurred in the following manner: If the subject failed to react within 10 min, increasing concentrations of allergen were instilled every 10 min until a positive, qualifying reaction was elicited, defined as an ocular itching score of at least 2 and above on a 0 (none) to 4 (incapacitating) grading scale and an increase of at least 0.5 units and above (0–4 scale) from baseline in the hyperemia score in one of three vessel beds (conjunctival, ciliary, or episcleral) examined.

At visit 2 (day 0), eligible subjects were randomized to receive a single dose (one drop) of ketotifen fumarate 0.025% in one eye and vehicle placebo in the fellow eye. Allergen challenges were administered 15 min and 8 h post-dose. Randomization codes were unmasked by an independent technician after the 8-h challenge to determine the reproducibility of the qualifying reaction to the allergen in the placebo-treated eye and to determine the response in ketotifen-treated eyes. Subjects whose placebo-treated eye had a qualifying reaction (see visit 1) at the 15-min challenge were classified as allergen responders. Drug responders were defined as subjects whose ketotifen-treated eye had at least a 1 unit and above (clinically significant) lower ocular itching score than the placebo-treated eye, at two of the three timepoints (3, 7, and 10 min) after the 8-h allergen challenge.

At the end of visit 2, eligible subjects (i.e., allergen and drug responders) were re-randomized to the multiple-dose treatment period and instructed to instill one drop of ketotifen fumarate 0.025% in one eye and placebo in the fellow eye twice daily for 4 wk. Subjects returned to the study site 2 wk later (visit 3, day 14 $\pm$ 2) for an interim safety and compliance assessment.

At visit 4 (day 28 $\pm$ 3), an allergen challenge was administered in each eye 8 h after the last dose of study medication. Efficacy, safety, and compliance assessments were conducted at this visit.

At the end of each study visit, subjects were allowed to take Naphcon A® (naphazoline hydrochloride 0.025%/pheniramine maleate 0.3%) if needed to relieve any immediate discomfort caused by the allergen challenge.

Outcomes

Efficacy assessments. The primary efficacy assessment was based on ocular itching scores at 3, 7, and 10 min post-allergen challenge at visit 2 (single dose) and visit 4 (multiple dose). Ocular itching was graded by the subject on a scale of 0 (none) to 4 (incapacitating itch with an irresistible urge to rub).

Composite hyperemia (sum of conjunctival, ciliary, and episcleral hyperemia), chemosis, and mucous discharge were assessed by the investigator, and tearing and lid swelling were assessed by the subject at 7, 10, and 15 min post-challenge at visit 2 (single dose) and visit 4 (multiple dose). Standardized scales were used for each of these assessments, ranging from 0 to 4 (hyperemia, chemosis), 0 to 3 (lid swelling), or present/absent (tearing and mucous discharge). With each scale, higher scores were indicative of greater severity or presence of condition.

Ratings of ± 0.5 units were made if the sign or symptom was judged to fall between two of the scale units. All assessments were made separately for each eye.

Safety assessments. Safety assessments included corrected distance visual acuity, slit-lamp biomicroscopy, and adverse event reporting for both ocular and non-ocular events. Visual acuity was measured at the beginning of each visit using an ETDRS chart. Slit-lamp biomicroscopy was performed at the beginning of each visit and at the end of the last visit, after the final efficacy assessment.

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Statistical methods

Efficacy analyses were performed on the 'evaluable' population for the single-dose assessments at visit 2 (defined as subjects who were allergen responders in the placebo-treated eye) and the 'intent-to-treat' (ITT) population for the multiple-dose assessments at visit 4 (i.e., subjects who were allergen responders in the placebo-treated eye and drug responders in the ketotifen-treated eye). The analysis of safety was based on all randomized subjects who received at least one dose of study medication.

All statistical tests were two-sided, and tests with a corresponding p-value of 0.050 were considered statistically significant. Ocular itching was assessed using paired t-tests on differences in scores between eyes of each subject. Similar analytical methods were used for the secondary efficacy variables, except for mucous discharge and tearing, which were summarized as the number and percentage of subjects who had this symptom. Additionally, McNemar's test was used to test for association between response to ketotifen versus placebo at each timepoint for mucous discharge and tearing.

Results

A total of 198 subjects were screened, with 133 randomized to single-dose treatment at visit 2. Of the 133 subjects, 105 had a qualifying allergen response and were considered evaluable for efficacy. As there were 45 drug non-responders and 28 allergen non-responders, 60 subjects were randomized to the 4-wk multiple-dose treatment. Five subjects discontinued prematurely. Demographic and background characteristics for all subjects randomized and the ITT population at visit 4 are presented in Table 1.

Onset of action

Onset of action was determined by allergen challenge at 15 min after administration of a single dose of trial medication. At all post-challenge timepoints, mean scores for ocular

Table 1. Demographic and background characteristics

	All randomized subjects (N = 133), n (%)	ITT population at visit 4 (N = 55), n (%)
Gender		
Male	75 (56)	29 (53)
Female	58 (44)	26 (47)
Race		
Caucasian	96 (72)	38 (69)
Black	1 (1)	0 (0)
Asian	27 (20)	12 (22)
Hispanic	6 (5)	4 (7)
Other*	3 (2)	1 (2)
Age in years		
8–11	43 (32)	20 (36)
12–16	90 (68)	35 (64)
Mean	13.0	12.8
Range	8.0–16.8	8.2–16.5
Allergen sensitivity		
Cat dander/cat hair	27 (20)	7 (13)
Bermuda grass	1 (1)	0 (0)
Kentucky bluegrass	11 (8)	5 (9)
Maple	3 (2)	0 (0)
Meadow fescue	22 (17)	10 (18)
Oak	5 (4)	3 (5)
Ragweed	18 (14)	9 (16)
Rye grass	22 (17)	10 (18)
White birch	24 (18)	11 (20)

*Black/Caucasian, Black/Asian, and Multiracial.

ITT, intent-to-treat.

itching, composite hyperemia, chemosis, and lid swelling were statistically significant in favor of ketotifen ($n = 105$, $p = 0.002$, Fig. 1, Table 2).

Analysis of subjects with tearing in one eye and no tearing in the other also showed a statistically significant superiority of ketotifen as compared to placebo at all post-challenge timepoints ($n = 105$, $p = 0.004$, Table 3).

Duration of action

To determine the duration of drug effect after a single dose, an allergen challenge was conducted 8 h after instillation of one drop of trial medication. At all post-challenge timepoints, ketotifen was significantly superior to placebo in reducing ocular itching ($n = 105$, $p < 0.001$, Fig. 1) and composite hyperemia, chemosis, and lid swelling ($n = 105$, $p = 0.020$, Table 2).

Analysis of subjects with tearing in one eye and no tearing in the other showed a statistically significant difference in favor of ketotifen at all post-challenge timepoints ($n = 105$, $p = 0.033$, Table 3).

Efficacy after 4 wk of treatment

To confirm the lasting efficacy of ketotifen after repeat dosing, an allergen challenge was performed 8 h after the last administration of trial medication following a 4-wk treatment period with twice daily dosing. At all post-challenge timepoints, the mean ocular itching scores for

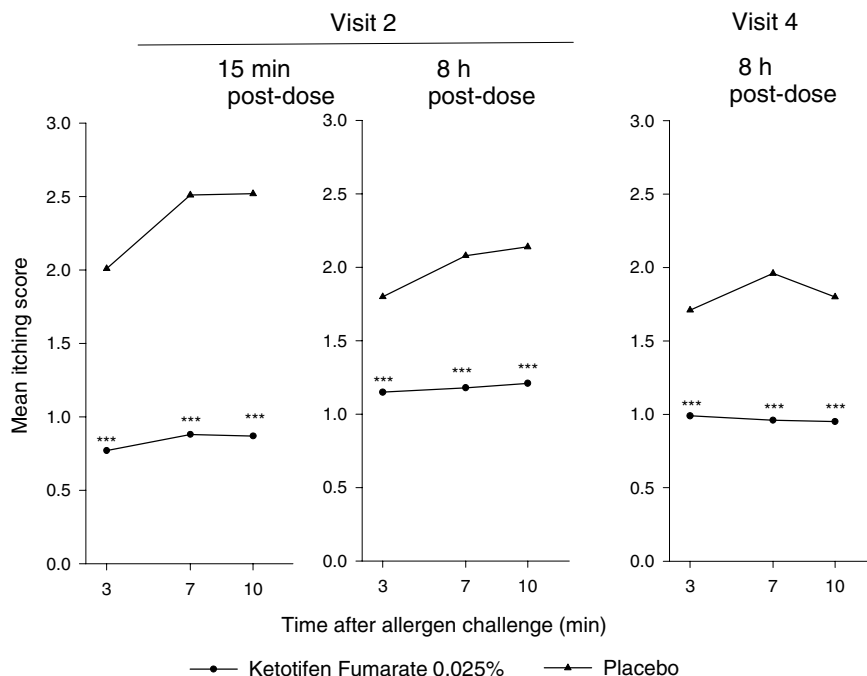


Fig. 1. Ocular itching following single-dose treatment at visit 2 for the evaluable population ($n = 105$) and following multiple-dose treatment (b.i.d. for 4 wk) at visit 4 for the ITT population ($n = 55$). A lower mean itching score indicates less itching. *** indicates statistical significance in favor of ketotifen ($p < 0.001$).

Table 2. Analysis of signs and symptoms at visit 2 (15 min and 8 h after single dose) (n = 105) and at visit 4 (8 h after multiple-dosing) (n = 55)

Assessment time	Mean score		Between-treatment difference (s.d.)	p-value
	KE	PL	KE – PL*	
<i>Composite hyperemia</i> [†]				
15-min post-dose at visit 2				
7 min	2.88	4.45	–1.57 (1.69)	<0.001
10 min	3.24	4.81	–1.61 (1.77)	<0.001
15 min	3.29	4.92	–1.63 (1.89)	<0.001
8-h post-dose at visit 2				
7 min	3.81	4.33	–0.52 (1.46)	<0.001
10 min	4.00	4.69	–0.70 (1.57)	<0.001
15 min	4.05	4.78	–0.73 (1.66)	<0.001
8-h post-dose at visit 4				
7 min	2.48	3.26	–0.78 (1.15)	<0.001
10 min	2.88	3.45	–0.56 (1.17)	<0.001
15 min	3.08	3.59	–0.51 (1.61)	0.023
<i>Chemosis</i>				
15-min post-dose at visit 2				
7 min	0.31	0.49	–0.18 (0.38)	<0.001
10 min	0.40	0.60	–0.20 (0.47)	<0.001
15 min	0.47	0.62	–0.16 (0.51)	0.002
8-h post-dose at visit 2				
7 min	0.50	0.59	–0.09 (0.32)	0.004
10 min	0.60	0.71	–0.11 (0.33)	0.001
15 min	0.65	0.74	–0.09 (0.35)	0.008
8-h post-dose at visit 4				
7 min	0.43	0.56	–0.14 (0.43)	0.021
10 min	0.55	0.68	–0.13 (0.38)	0.015
15 min	0.61	0.70	–0.09 (0.57)	0.242
<i>Lid swelling</i>				
15-min post-dose at visit 2				
7 min	0.23	0.49	–0.26 (0.55)	<0.001
10 min	0.28	0.58	–0.30 (0.65)	<0.001
15 min	0.34	0.66	–0.32 (0.63)	<0.001
8-h post-dose at visit 2				
7 min	0.30	0.41	–0.11 (0.46)	0.020
10 min	0.33	0.47	–0.14 (0.49)	0.005
15 min	0.39	0.56	–0.17 (0.54)	0.002
8-h post-dose at visit 4				
7 min	0.18	0.34	–0.15 (0.35)	0.002
10 min	0.20	0.34	–0.14 (0.42)	0.018
15 min	0.27	0.41	–0.14 (0.46)	0.031

*A negative value indicates that the difference is in favor of ketotifen fumarate 0.025%.

†Sum of conjunctival, ciliary, and episcleral.
KE, ketotifen fumarate 0.025%; PL, placebo.

ketotifen were significantly lower than those for placebo (n = 55, $p < 0.001$, Fig. 1). Mean score differences between ketotifen- and placebo-treated eyes were also significantly in favor of ketotifen for composite hyperemia, chemosis, and lid swelling at all post-challenge timepoints (n = 55, $p = 0.031$), with the exception of the 15-min post-challenge timepoint for chemosis (n = 55, $p = 0.242$, Table 2).

Analysis of subjects with tearing in one eye and no tearing in the other showed a significantly

Table 3. Percentage of subjects with no tearing

Assessment time	% of subjects with tearing in PL eye and no tearing in KE eye	% of subjects with tearing in KE eye and no tearing in PL eye	p-value*
15-min post-dose at visit 2			
7 min	10.5	1.0	0.004
10 min	15.4	1.9	0.001
15 min	8.6	0	0.003
8-h post-dose at visit 2			
7 min	11.5	2.9	0.020
10 min	11.4	1.9	0.008
15 min	10.5	2.9	0.033
8-h post-dose at visit 4			
7 min	7.3	0	0.046
10 min	5.5	0	0.083
15 min	5.5	1.8	0.317

*McNemar's test of association.

KE, ketotifen fumarate 0.025%; PL, placebo.

better outcome for ketotifen at 7 min post-challenge (n = 55, $p = 0.046$, Table 3).

Mucous discharge was only present in approximately 4% of the eyes treated; no significant differences between groups were observed after the single- or multiple-dose treatments.

Subgroup analyses were conducted for age (children 8–11 yr vs. adolescents 12–16 yr) and gender on the ITT population after the 4-wk dosing regimen. At 8-h post-dose, both age subgroups showed a similar, statistically significant ($p = 0.015$) reduction of ocular itching by ketotifen as compared to placebo. The same was observed for the gender subgroups ($p = 0.005$).

Safety

Fifteen subjects (11.3%) reported at least one systemic adverse event. They were all mild or moderate in intensity, and none were judged to be related to study medication. The most frequent systemic adverse events were headache (3%), increased cough (2.3%), rhinitis (2.3%), pain (1.5%), and pharyngitis (1.5%). Other events (fever, flu syndrome, diarrhea, dyspepsia, and skin disorder) were reported by no more than one subject (0.8%).

Only two subjects (1.5%) reported an ocular adverse event. One subject experienced bilateral burning/stinging upon drug instillation, while the other subject had bilateral blurred vision following allergen challenge. Only burning/stinging upon drug instillation was judged by the investigator to be related to the study medication.

No serious adverse events were reported, and no subjects discontinued due to adverse events. No significant changes in corrected visual acuity

or in slit-lamp biomicroscopy were found during the study.

Discussion

The pharmacological treatment of children requires special considerations. Pediatric safety and efficacy cannot always be adequately assessed from studies in adult populations due to differences in body mass and metabolism between adults and children. A number of tragedies related to adverse drug effects to systemic medications in children have led to the development of regulations for drug assessments in pediatric populations (15).

In this study, ketotifen fumarate was evaluated in a pediatric population, 8–16 yr of age, in the allergen challenge model of allergic conjunctivitis. The conjunctival allergen-challenge model is a reproducible and accurate method for evaluating the efficacy of an agent in preventing the signs and symptoms of ocular allergy (14, 16). A number of previous studies have documented its utility in adult populations; however, this study represents one of its first uses of this model in a pediatric population, involving both children (< 12 yr) and adolescents (≥ 12 yr). The choice of subjects older than 8 yr was necessary, since this group can accurately understand the question, formulate consistent responses, and communicate assessments to the investigator.

The results of this study showed that ketotifen fumarate 0.025% ophthalmic solution was effective, safe, and well tolerated in a pediatric population. A single dose of ketotifen was statistically significantly superior to vehicle placebo in inhibiting ocular itching, composite hyperemia, chemosis, lid swelling, and tearing after the 15-min post-dose allergen challenge. Efficacy was maintained for 8 h after a single dose of ketotifen. After a 4-wk multiple-dose regimen, ketotifen continued to significantly reduce the intensity of ocular itching compared with placebo for at least 8 h after instillation, suggesting no development of drug tachyphylaxis. The incidence of adverse events reported with ketotifen in this study was very low and comparable to placebo, corroborating the good safety profile of ketotifen already established in adults (13). The excellent efficacy and tolerability of ketotifen in pediatric subjects justifies the use of the same dose regimen that is recommended for adults.

The symptoms of allergic conjunctivitis, particularly itching, can be very distressing and troublesome for children. Therefore, pharmacotherapy is often needed to minimize the disease effects on children's daily activities, such as attendance at

school. The long duration of action of ketotifen permits twice per day dosing, and is of particular benefit for school-aged children, who can instill the eye drops in the morning without requiring further therapy during the school day.

Conclusions

The results from the present study indicate that over a 4-wk treatment period ketotifen fumarate 0.025% ophthalmic solution is effective and safe for treating children with allergic conjunctivitis. With its rapid onset and long duration of action, together with the convenient twice daily dose regimen, ketotifen fumarate is an important and valuable treatment option for pediatric ocular allergy.

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