



## Ophthalmics for Allergic Conjunctivitis Therapeutic Class Review (TCR)

---

**April 4, 2018**

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, digital scanning, or via any information storage or retrieval system without the express written consent of Magellan Rx Management.

All requests for permission should be mailed to:

Magellan Rx Management  
Attention: Legal Department  
6950 Columbia Gateway Drive  
Columbia, Maryland 21046

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to [PSTCREditor@magellanhealth.com](mailto:PSTCREditor@magellanhealth.com).

---

**April 2018**

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.  
© 2004-2018 Magellan Rx Management. All Rights Reserved.

**MagellanRx**  
MANAGEMENT<sup>SM</sup>

## FDA-APPROVED INDICATIONS

Drug	Manufacturer	Approved Age Range	Indication(s)
<b>Ophthalmic Antihistamines</b>			
alcaftadine (Lastacaft®) <sup>1</sup>	Allergan	≥ 2 years	Prevention of itching of the eye due to allergic conjunctivitis
azelastine <sup>2</sup>	generic	≥ 3 years	Treatment of itching of the eye associated with allergic conjunctivitis
bepotastine (Bepreve®) <sup>3</sup>	Bausch & Lomb	≥ 2 years	Treatment of ocular itching associated with allergic conjunctivitis
emedastine (Emadine®) <sup>4</sup>	Alcon/Novartis	≥ 3 years	Temporary relief of the signs and symptoms of allergic conjunctivitis
epinastine (Elestat®) <sup>5</sup>	generic, Allergan	≥ 3 years	Prevention of itching of the eye due to allergic conjunctivitis
ketotifen (Alaway® OTC, Zaditor® OTC) <sup>6</sup>	generic, Bausch & Lomb, Alcon/Novartis	≥ 3 years	Temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair, and dander
olopatadine (Patanol®) <sup>7</sup>	generic, Alcon/Novartis	≥ 3 years	Treatment of the signs and symptoms of allergic conjunctivitis
olopatadine (Pataday®) <sup>8</sup>	generic, Alcon/Novartis	≥ 3 years	Treatment of ocular itching associated with allergic conjunctivitis
olopatadine (Pazeo™) <sup>9</sup>	Alcon/Novartis	≥ 2 years	Treatment of ocular itching associated with allergic conjunctivitis
<b>Ophthalmic Mast Cell Stabilizers</b>			
cromolyn <sup>10</sup>	generic	≥ 4 years	Treatment of vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis
lodoxamide (Alomide®) <sup>11</sup>	Alcon/Novartis	≥ 2 years	Treatment of vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis
nedocromil (Alocril®) <sup>12</sup>	Allergan	≥ 3 years	Treatment of itching associated with allergic conjunctivitis
<b>Ophthalmic Anti-Inflammatory Agents</b>			
loteprednol (Alrex®) <sup>13</sup>	Bausch & Lomb	≥ 12 years	Temporary relief of the signs and symptoms of seasonal allergic conjunctivitis

Ketorolac ophthalmic solution 0.5% (Acular®) is indicated for the temporary relief of ocular itching due to seasonal allergic conjunctivitis and for the treatment of post-operative inflammation in patients who have undergone cataract extraction.<sup>14</sup> Its safety and efficacy have not been established in patients < 2 years of age.

## OVERVIEW

Conjunctivitis, or inflammation of the conjunctiva, may occur secondary to infectious or non-infectious stimuli.<sup>15</sup> Seasonal, vernal, atopic, and Giant papillary conjunctivitis (GPC) are non-infectious types of conjunctivitis; infectious types include viral and bacterial. Estimated prevalence of seasonal allergic conjunctivitis is 15%, the condition occurs in both adults and children, and is one of the most common reasons for patient self-referral.<sup>16,17</sup> Signs and symptoms of the disorder may cause extreme discomfort. Seasonal allergic conjunctivitis usually presents bilaterally and occurs during seasonal exposure to allergens, such as ragweed. Perennial allergic conjunctivitis has a similar initial presentation; however, symptoms do not have seasonal variation. The range of symptoms varies from itching and redness to swelling, excessive lacrimation, and mucous discharge. As with allergic rhinitis, avoidance of identified allergens is a part of comprehensive therapy for allergic conjunctivitis.

The American Academy of Ophthalmology (AAO) **2017** treatment guidelines recommend an over-the-counter (OTC) antihistamine/vasoconstrictor agent or use of the more effective second-generation topical histamine H<sub>1</sub>-receptor antagonists (e.g. alcaftadine, azelastine, bepotastine, emedastine, epinastine, olopatadine) for treatment of mild allergic conjunctivitis.<sup>18,19</sup> The guidelines do not recommend any particular ophthalmic antihistamine over another. For persistent or frequent symptoms, an agent with mast cell stabilizer activity may be used. Combination antihistamine/mast-cell stabilizing agents can be utilized for either acute or chronic disease.<sup>20</sup> Short courses (1 to 2 weeks) of ophthalmic corticosteroids, at the lowest potency and frequency based on response and tolerance, may be used to treat disease flares or severe symptoms. The nonsteroidal anti-inflammatory, ketorolac (Acular), is also indicated for the treatment of allergic conjunctivitis. Use of artificial tears, cool compresses, oral antihistamines, and allergen avoidance can also be employed to control symptoms.

Vernal keratoconjunctivitis (VKC) is an unusually severe chronic condition with exacerbations during spring and summer months. It is more common in children and young adults and is more prevalent in hot, dry climates.<sup>21</sup> Patients present with severe eye itching, constant tearing, eye redness, discharge, and photophobia. Eyelid thickening, conjunctival scarring, ptosis, corneal thinning, ulcerations, infection, and giant papillae can occur. If left untreated, VKC can lead to permanent vision loss. Common therapies include topical antihistamines and topical mast-cell stabilizers. Topical corticosteroids are usually needed to treat acute exacerbations. Topical cyclosporine can be added to reduce the required dose of corticosteroid, particularly in severe cases. Although not FDA-approved, the AAO recommends that for patients 2 years and older with eyelid involvement, topical pimecrolimus 1% cream or tacrolimus 0.03% ointment may be used.

## PHARMACOLOGY<sup>22,23,24,25,26,27,28,29,30,31,32,33,34,35</sup>

Therapeutic efficacy is independent of pharmacological activity.<sup>36</sup>

Drug	Antihistamine	Anti-Inflammatory	Mast Cell Stabilizer
<b>Ophthalmic Antihistamines</b>			
alcaftadine (Lastacaft)	X		X
azelastine	X		X
bepotastine (Bepreve)	X		X
emedastine (Emadine)	X		
epinastine (Elestat)	X		X
ketotifen	X		X
olopatadine (Patanol)	X		X
olopatadine (Pataday)	X		X
olopatadine (Pazeo)	X		X
<b>Ophthalmic Mast Cell Stabilizers</b>			
cromolyn			X
lodoxamide (Alomide)			X
nedocromil (Alocril)			X
<b>Ophthalmic Anti-Inflammatory Agents</b>			
loteprednol (Alrex)		X	

## PHARMACOKINETICS<sup>37,38,39,40,41,42,43,44,45,46,47,48,49,50</sup>

Drug	Systemic absorption	Preservative
<b>Ophthalmic Antihistamines</b>		
alcaftadine (Lastacaft)	Below level of detection	benzalkonium chloride
azelastine	Systemic absorption does occur with reported plasma concentrations of 0.02 to 0.25 ng/mL after 56 days of treatment	benzalkonium chloride
bepotastine (Bepreve)	Plasma concentrations peak at 1 to 2 hours post-instillation, with a maximum concentration of 7.3 ng/mL	benzalkonium chloride
emedastine (Emadine)	Below level of detection	benzalkonium chloride
epinastine (Elestat)	Average maximum plasma concentrations of 0.04 ± 0.014 ng/ml were reached after about 2 hours	benzalkonium chloride
ketotifen	Below level of detection	benzalkonium chloride
olopatadine (Patanol)	Measurable levels within 2 hours of dosing ranged from 0.5 to 1.3 ng/mL in a small percentage of patients	benzalkonium chloride
olopatadine (Pataday)	No data	benzalkonium chloride
olopatadine (Pazeo)	Below level of detection	benzalkonium chloride
<b>Ophthalmic Mast Cell Stabilizers</b>		
cromolyn	Systemic absorption has been reported, but at low levels	benzalkonium chloride
lodoxamide (Alomide)	Below level of detection	benzalkonium chloride
nedocromil (Alocril)	< 4% of the total dose is systemically absorbed	benzalkonium chloride
<b>Ophthalmic Anti-Inflammatory Agents</b>		
loteprednol (Alrex)	Below level of detection	benzalkonium chloride

## CONTRAINDICATIONS/WARNINGS<sup>51,52,53,54,55,56,57,58,59,60,61,62</sup>

Loteprednol (Alrex) is contraindicated in patients with most viral diseases of the cornea and conjunctiva, including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in patients with mycobacterial or fungal infections of ocular structures.

In addition, hypersensitivity to a product or its excipients is a contraindication for any product in this class.

The agents in this review should not be used to treat contact lens-related irritation. All agents contain the preservative benzalkonium chloride which may be absorbed by soft contact lenses and, therefore, should not be instilled while wearing contact lenses. Lenses may be reinserted after 10 minutes following administration.

In March 2016, the FDA warned that eye drop bottles that have loose plastic safety seals or tamper-evident rings below the bottle cap may fall onto the eye when the product is used.<sup>63</sup> The FDA is in the process of identifying all relevant products and will require a change in the packaging design. No further information is available at this time.

## DRUG INTERACTIONS

Due to the topical route of administration of the products, clinically significant systemic drug interactions are not well identified.

## ADVERSE EFFECTS<sup>64,65,66,67,68,69,70,71,72,73,74,75,76,77</sup>

Drug	Stinging/ Burning	Headache	Eyelid Edema	Naso- pharyngitis	Conjunctival Infection	Blurred Vision	Altered Taste
<b>Ophthalmic Antihistamines</b>							
alcaftadine (Lastacaft)	< 4	< 3	reported	< 3	nr	reported	nr
azelastine	30	15	nr	1–10	nr	1–10	10
bepotastine (Bepreve)	2–5	2–5	nr	2–5	nr	nr	25
emedastine (Emadine)	< 5	11	nr	nr	nr	< 5	< 5
epinastine (Elestat)	1–10	1–3	nr	1–3	nr	nr	nr
ketotifen	< 5	10–25	< 5	10–25	10–25	nr	< 5
olopatadine (Patanol)	< 5	7	< 5	< 5	nr	< 5	< 5
olopatadine (Pataday)	< 5	< 5	< 5	< 5	nr	< 5	< 5
olopatadine (Pazeo)	nr (< 5 abnormal eye sensation)	nr	nr	nr	nr	< 5	< 5
<b>Ophthalmic Mast Cell Stabilizers</b>							
cromolyn	reported	nr	reported	nr	reported	reported	nr
lodoxamide (Alomide)	15	1.5	< 1	nr	nr	1–5	nr
nedocromil (Alocril)	10–30	40	nr	1–10	nr	nr	10–30
<b>Ophthalmic Anti-Inflammatory Agents</b>							
loteprednol (Alrex)	5–15	< 15	nr	< 15	5–15	5–15	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

Bepotastine (Bepreve) has been noted to cause a mild taste following instillation in approximately 25% of subjects.

## SPECIAL POPULATIONS<sup>78,79,80,81,82,83,84,85,86,87,88,89</sup>

### Pediatrics

Most of the agents in this class are safe and effective in children as young as 3 years of age. Cromolyn sodium for patients 4 years or older, and loteprednol (Alrex) for those 12 years and older, are exceptions. Alcaftadine (Lastacraft), lodoxamide (Alomide), bepotastine (Bepreve), and olopatadine (Pazeo) are approved for use in children as young as 2 years of age.

### Pregnancy

Alcaftadine (Lastacraft), cromolyn, and nedocromil (Alocril) are Pregnancy Category B; there are no available human data for the use of bepotastine (Bepreve), lodoxamide (Alomide), or emedastine (Emadine) in pregnant women; all of the other ophthalmic products in this review are classified as Pregnancy Category C.

## DOSAGES<sup>90,91,92,93,94,95,96,97,98,99,100,101,102</sup>

Drug	Dosage (in affected eye[s])	Availability
<b>Ophthalmic Antihistamines</b>		
alcaftadine (Lastacraft)	1 drop once daily	0.25% solution (3mL)
azelastine	1 drop twice daily	0.05% solution (6 mL)
bepotastine (Bepreve)	1 drop twice daily	1.5% solution (5 mL, 10 mL)
emedastine (Emadine)	1 drop up to 4 times daily	0.05% solution (5 mL)
epinastine (Elestat)	1 drop twice daily	0.05% solution (5 mL)
ketotifen (Alaway OTC, Zaditor OTC)	1 drop twice daily every 8 to 12 hours, no more than twice daily	0.025% solution (Zaditor OTC: 5 mL; Alaway OTC: 10 mL)
olopatadine (Patanol)	1 drop twice daily at an interval of 6 to 8 hours	0.1% solution (5 mL)
olopatadine (Pataday)	1 drop once daily	0.2% solution (2.5 mL)
olopatadine (Pazeo)	1 drop once daily	0.7% solution (2.5 mL)
<b>Ophthalmic Mast Cell Stabilizers</b>		
cromolyn	1 to 2 drops 4 to 6 times daily	4% solution (10 mL)
lodoxamide (Alomide)	1 to 2 drops 4 times daily for up to 3 months	0.1% solution (10 mL)
nedocromil (Alocril)	1 to 2 drops twice a day	2% solution (5 mL)
<b>Ophthalmic Anti-Inflammatory Agents</b>		
loteprednol (Alrex)	1 drop 4 times daily (shake well)	0.2% suspension (5 mL, 10 mL)

## CLINICAL TRIALS

### Search Strategy

Articles were identified through searches performed on PubMed and review of information submitted by manufacturers. Search strategy included the FDA-approved use of all drugs in this class and allergic conjunctivitis. Randomized, controlled, comparative trials with multiple doses for ophthalmic FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance; use data analysis techniques consistent with the study question; and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and clinical importance.

Many of the studies of the ophthalmic agents for the treatment of allergic conjunctivitis are performed as single-dose studies. The studies give very little information regarding efficacy and safety regarding chronic use of these agents. Additionally, many of the studies are done using the conjunctival allergen challenge (CAC) model in an effort to induce an allergic response and evaluate drug efficacy in a short-term model. The number of patients enrolled in the studies was generally less than 100. Several comparisons to levocabastine appear in the literature; levocabastine is no longer available in the United States.

### Allergic Conjunctivitis

#### *alcaftadine (Lastacaft) versus placebo*

Fifty-eight subjects with a history of allergic conjunctivitis were enrolled in a double-masked, multicenter, vehicle-controlled study.<sup>103</sup> Outcome measures were ocular itching and conjunctival redness. The signs and symptoms of allergic conjunctivitis were induced in the subjects by a CAC. The subjects were randomized to be given either 1 drop of alcaftadine 0.25% ophthalmic solution bilaterally or vehicle bilaterally. Alcaftadine significantly lessened conjunctival redness after both 15 minutes and 16 hours of the drug administration. With an onset of action within 3 minutes and the duration of action lasting up to 16 hours, alcaftadine was more effective than its vehicle in preventing ocular itching.

#### *azelastine versus epinastine (Elestat) versus and ketotifen (Zaditor)*

A study compared the short-term (5-minute) ocular comfort and drying effects of epinastine, azelastine, and ketotifen in 40 patients with allergic conjunctivitis. This was a single-center, randomized, double-blind, crossover study.<sup>104</sup> At the first visit, patients were randomized to receive 1 drop of epinastine in 1 eye and either azelastine or ketotifen in the other eye. Ocular comfort was assessed by patients on an 11-point scale immediately and at 0.5, 1, 2, and 5 minutes after instillation. Patients were also asked to describe how their eyes felt at 3 minutes using a standardized list of positive, neutral, and negative descriptor words. The mean comfort score indicated more comfort with



epinastine compared with azelastine at 0.5, 1, 2, and 5 minutes ( $p < 0.001$ ,  $p < 0.001$ ,  $p = 0.001$ , and  $p = 0.019$ , respectively) and compared with ketotifen immediately after instillation ( $p = 0.014$ ). The mean ocular comfort score was significantly lower with ketotifen compared with azelastine at 0.5, 1, and 2 minutes ( $p = 0.001$ ,  $p = 0.023$ , and  $p = 0.028$ , respectively). A majority (85%) of patients chose positive comfort descriptors to describe epinastine versus 34% with azelastine.

### ***bepotastine (Bepreve) versus placebo***

A randomized, double-masked, placebo-controlled, multicenter CAC study compared 130 patients with allergic conjunctivitis treated with bepotastine 1% or 1.5% or placebo.<sup>105</sup> Both strengths of bepotastine significantly reduced CAC ocular itching at onset of action and at least for 8 hours after dosing ( $p \leq 0.0001$ ). Conjunctival hyperemia reductions for bepotastine were seen only at onset of action of CAC test ( $p \leq 0.0125$ ). Only the 1.5% bepotastine strength is FDA-approved.

### ***bepotastine (Bepreve) versus olopatadine hydrochloride 0.2% (Pataday)***

In a randomized, observer-masked, single-center, crossover study 30 patients with ocular itching associated with allergic conjunctivitis accompanied by nasal symptoms were treated with bepotastine besilate 1.5% twice daily (7:00 a.m. and 4:00 p.m.) or olopatadine hydrochloride 0.2% once daily (7:00 a.m.) for 14 days.<sup>106</sup> Following a 7-day washout period during which only preservative-free artificial tears were used twice daily, patients were crossed over to the alternative treatment for 14 days. According to the patient mean daily diary responses, bepotastine besilate offered significantly better relief of evening ocular itch, relief of morning and evening itchy/runny nose, and relief of morning and evening ocular allergy symptoms. At study end, 63.3% and 66.7% of patients preferred bepotastine besilate 1.5% for all-day relief of ocular itching and all-day relief of itchy/runny nose, respectively. At study end, there was no significant difference in the number of patients preferring 1 treatment over the other for comfort. Overall, 66.7% of patients stated that they would prefer to treat their allergic conjunctivitis with bepotastine besilate 1.5% over olopatadine hydrochloride 0.2%.

### ***emedastine (Emadine) versus ketorolac (Acular)***

Thirty-six subjects were randomized into 2 groups in a double-blind, single-center crossover study comparing emedastine 0.05% and ketorolac 0.5%.<sup>107</sup> The first group received emedastine 0.05% in 1 eye and placebo in the other eye. The second group received ketorolac 0.5% in 1 eye and placebo in the other eye. Ten minutes after instillation, patients underwent allergen challenge. After the challenge, patients graded ocular itching and were assessed for hyperemia. Approximately 14 days later, subjects entered the crossover treatment phase. Emedastine 0.05% significantly inhibited ocular itching and redness ( $p < 0.05$ ). Ketorolac 0.5% failed to significantly inhibit ocular itching or redness. Patients also stated emedastine was more comfortable than ketorolac upon administration ( $p < 0.05$ ).

### ***emedastine (Emadine) versus ketotifen (Zaditor)***

Forty-five subjects were enrolled in a single-center, double-masked study to compare efficacy of 2 agents and placebo for temporary relief of ocular itching related to allergic conjunctivitis.<sup>108</sup> Patients were randomized to treatment in 1 of 3 groups: emedastine 0.05% in 1 eye and placebo in the other; ketotifen 0.025% in 1 eye and placebo in the other; or emedastine 0.05% in 1 eye and ketotifen 0.025% in the other. Patients eliciting a positive allergic response were identified. In 25 subjects, bilateral CAC was performed 5 minutes after study medication instillation. In a second group of 20 subjects, CAC was performed 15 minutes after medication instillation. Both emedastine and ketotifen significantly

inhibited itching ( $p < 0.05$ ) compared with placebo at all time points after the 5- and 15-minute CAC. Itching scores were similar in the 2 active treatment groups. No adverse events were reported.

#### ***epinastine (Elestat) versus olopatadine 0.1% (Patanol)***

Olopatadine 0.1% and epinastine 0.05% were compared for safety and itching and conjunctival redness prevention using the CAC model in a prospective, randomized, double-blind study.<sup>109</sup> Screening for response to allergen challenge ( $n=96$ ) occurred prior to randomization. A total of 66 evaluable patients with allergic conjunctivitis were randomized to olopatadine in 1 eye with epinastine in the other eye, olopatadine in 1 eye with placebo in the other, or epinastine in 1 eye with placebo in the other eye. Allergen was applied to both eyes 5 minutes after treatment administration. Olopatadine was associated with significantly less itching and conjunctival redness than contralateral epinastine-treated eyes ( $p=0.003$ ,  $p < 0.001$ , respectively). Olopatadine-treated eyes also had less chemosis ( $p < 0.001$ ), ciliary redness ( $p < 0.001$ ), and episcleral redness ( $p < 0.001$ ) than epinastine-treated eyes in the single-dose CAC model trial.

#### ***epinastine (Elestat) versus olopatadine 0.2% (Pataday)***

In a 7-week, double-masked, placebo-controlled patients with ocular allergic responses were randomized into 1 of 4 treatment groups to receive 1 drop of study medication in each eye: (1) olopatadine 0.2%/placebo, (2) epinastine 0.05%/placebo, (3) olopatadine 0.2%/epinastine 0.05%, (4) placebo/placebo.<sup>110</sup> At separate visits, patients were allergen CAC challenged at 12 hours after drop instillation to evaluate duration of action and at 5 minutes after drop instillation to evaluate onset of action. Eyes treated with olopatadine 0.2% showed significantly lower mean ocular itching scores compared to those treated with epinastine 0.05% at 5 ( $p=0.024$ ) and 7 min ( $p=0.003$ ) after CAC challenge. Eyes treated with olopatadine 0.2%-treated eyes also showed significantly lower mean redness scores versus epinastine 0.05%-treated eyes at all time points post-challenge (ciliary,  $p \leq 0.013$ ; conjunctival,  $p \leq 0.015$ ; episcleral,  $p \leq 0.006$ ). Olopatadine 0.2% was reported to be significantly more comfortable than epinastine 0.05% at 1 minute after instillation ( $p=0.003$ ).

#### ***ketotifen (Zaditor) versus nedocromil (Alocril)***

In a double-blind, single-center study of 85 patients, the CAC model was used to test 3 treatments: ketotifen 0.025%, nedocromil 2%, and placebo.<sup>111</sup> Patients ( $n=85$ ) underwent CAC screening on 2 occasions prior to randomization. During 2 different visits 14 days apart, subjects ( $n=59$ ) were randomized to 1 of the 3 treatment groups. Allergen challenges were conducted at 5 minutes post-treatment at the first visit and at 12 hours post-treatment at the second visit. Ketotifen-treated eyes exhibited significantly less ocular itching than both nedocromil-treated and placebo-treated eyes at both the 5-minute and 12-hour post-treatment challenges ( $p < 0.05$  for all). Ketotifen was tolerated as well as placebo. Ketotifen instillation was significantly more comfortable than nedocromil up to 10 minutes after instillation ( $p < 0.05$ ). Based on comfort and subjective efficacy, 60% of patients preferred ketotifen, 21% preferred nedocromil, and 19% preferred placebo.

#### ***ketotifen (Zaditor) versus olopatadine (Patanol)***

A randomized, double-masked, single-center, CAC study comparing ketotifen 0.025% and olopatadine 0.1% was conducted in 53 patients.<sup>112</sup> Primary efficacy endpoints were ocular itching and patient satisfaction. Itching was graded on a 5-point scale at 3, 5, and 10 minutes post-challenge. After screening, the remaining 32 patients were randomized to 2 groups. The first group instilled

olopatadine 1 drop in the right eye and ketotifen 1 drop in the left eye. The second group instilled ketotifen 1 drop in the right eye and olopatadine 1 drop in the left eye. Twelve hours after instillation, subjects underwent allergen challenge. Efficacy scores for olopatadine were significantly higher than ketotifen at 3 and 5 minutes post-challenge ( $p < 0.05$ ). Olopatadine-treated eyes were rated significantly more comfortable than those treated with ketotifen both immediately after drug instillation and 12 hours later ( $p < 0.05$ ).

In a double-masked study, 66 patients with seasonal allergic conjunctivitis were randomized to treatment with ketotifen 0.025% or olopatadine 0.1% instilled twice daily.<sup>113</sup> Patients were assessed on days 5 and 21. Responder rate was higher on day 5 for ketotifen versus olopatadine (72% and 54% for patient assessment; 88% and 55% for investigator assessment, respectively). Responder rates on day 21 for ketotifen versus olopatadine were 91% versus 55% for patient assessment and 94% versus 42% for investigator assessment, respectively. Severity scores for hyperemia and itching were significantly lower for the ketotifen group. In both groups, the most common adverse effects were burning/stinging and headache. Patients rated both drugs similarly for comfort.

In a randomized, double-blind trial, ketotifen 0.025% and olopatadine 0.1% ophthalmic solutions were compared in patients with seasonal allergic conjunctivitis.<sup>114</sup> Forty-nine patients were randomized to ketotifen, olopatadine, or artificial tears administered 2 drops twice daily to both eyes for 30 days. Thirty-nine patients completed the trial. At baseline, day 15, and the end of the trial, clinical sign and symptom scores for itching, tearing, physician's assessment of eyelid swelling, redness and chemosis, conjunctival cytology specimens, and occurrence of adverse events were reported. For clinical sign and symptom scores, both active treatment groups reported significant improvement in tearing and itching at day 15 and 30 compared to baseline. The artificial tears group experienced a significant reduction in tearing at both days 15 and 30. Inflammatory markers were significantly lower in active treatment groups at both day 15 and 30 compared to artificial tears. Adverse events were not reported during the 1-month trial.

#### ***ketotifen (Zaditor) versus placebo in children***

Efficacy and safety of ketotifen 0.025% were evaluated in a double-blind, multicenter, placebo-controlled trial.<sup>115</sup> The study was of conjunctival allergen challenge (CAC) design using both single and multiple doses. Patients ( $n=133$ ) were between 8 to 16 years old and exhibited a positive response to allergen challenge. Patients were given 1 drop of ketotifen in 1 eye and placebo in the other eye. CAC was administered 15 minutes and 8 hours after the dose. Patients with a positive allergen reaction in both eyes were randomized to multiple dose treatment ( $n=60$ ). Patients administered ketotifen in 1 eye and placebo in the other eye twice daily for 4 weeks. CAC was performed 8 hours after the last dose. Of the 55 evaluable patients, ketotifen significantly reduced ocular itching compared to placebo after CAC ( $p < 0.001$ ). Hyperemia, chemosis, and lid swelling were also significantly reduced with ketotifen ( $p=0.031$ ). Adverse effects were similar to placebo.

#### ***loteprednol etabonate (Alrex) versus olopatadine (Patanol)***

In a single-center, double-masked CAC study, 50 subjects were randomized to receive olopatadine 0.1%, loteprednol 0.2%, or placebo.<sup>116</sup> One drop was instilled in each eye. Because loteprednol requires a higher dose loading period for efficacy, patients in the loteprednol group received loteprednol bilaterally 4 times daily for 14 days. Fifteen minutes after drug instillation, patients underwent allergen challenge. Subjects evaluated itching at 3, 5, and 10 minutes after challenge using

a standardized 5-point scale. The investigator evaluated redness at 10, 15, and 20 minutes after challenge. Difference in inhibition of itching and redness was clinically significant ( $\geq 1$  unit difference) and statistically significant ( $p < 0.05$ ) in favor of olopatadine compared with loteprednol at all 3 time points.

### ***olopatadine (Patanol) versus azelastine***

In a prospective, multicenter, double-masked, allergen challenge study, 180 patients were randomized to 1 of 3 treatment groups: olopatadine 0.1% solution in 1 eye and azelastine 0.05% solution in the other eye; olopatadine in 1 eye and placebo in the other eye; or azelastine in 1 eye and placebo in the other eye.<sup>117</sup> The placebo was artificial tears. Two screening phases were performed to identify appropriate allergen challenge. Five minutes after the drops were instilled, subjects ( $n=111$ ) were bilaterally challenged with an allergen concentration previously determined to elicit a positive conjunctival allergic response. Subjects rated itching every 30 seconds for a total of 20 minutes. Both treatments were significantly more effective than placebo at reducing itching post-challenge. Olopatadine was significantly more effective than azelastine in reducing itching at 3.5 minutes through 20 minutes post-challenge (average mean unit difference of  $-0.31$ ;  $p < 0.05$ ) in the CAC model. Single-dose administration did not result in any serious adverse events.

### ***olopatadine (Patanol) versus ketorolac (Acular)***

Olopatadine 0.1% solution and ketorolac 0.5% solution were compared in a randomized, double-blind, cross-over study.<sup>118</sup> Patients received active treatment in 1 eye (either olopatadine or ketorolac) and placebo in the other eye. Allergen challenge was administered 27 minutes after drug instillation. Two weeks later, active drug was applied to the other eye. Olopatadine was significantly more effective than ketorolac ( $p < 0.001$ ) and placebo ( $p < 0.0001$ ) in reducing hyperemia and ocular itching at all time points (3, 10, and 20 minutes). Ketorolac was not associated with a reduction in itching. Olopatadine was also significantly more comfortable than ketorolac, as reported by subjects immediately following drug instillation ( $p < 0.05$ ).

### ***olopatadine (Pataday) versus olopatadine (Patanol)***

In a double-blind, 24-hour study, efficacy of 2 doses of olopatadine 0.1% (Patanol) was compared to 1 dose of olopatadine 0.2% (Pataday) in prevention of ocular itching associated with allergic conjunctivitis.<sup>119</sup> Using conjunctival allergen challenge (CAC), no significant difference in the mean itching scores between 2 drops of olopatadine 0.1% and 1 drop of olopatadine 0.2% was observed. Both products showed significant activity at the 24-hour time point and were statistically superior to placebo. No adverse events occurred were reported.

### ***olopatadine 0.7% (Pazeo) versus olopatadine 0.2% (Pataday) versus placebo***

The efficacy of olopatadine 0.7% was established in 2 randomized, double-blind, placebo-controlled, conjunctival allergen challenge (CAC) clinical studies in patients with a history of allergic conjunctivitis. In the first study, patients were randomized to receive olopatadine 0.7% solution, olopatadine 0.2% solution, or a vehicle ophthalmic solution and, in the second study, patients could also be randomized to an olopatadine 0.1% solution (Patanol) arm in addition to the other 3 arms. Patients were evaluated with an ocular itching severity score ranging from 0 (no itch) to 4 (incapacitating itch) at several time points after CAC administration. Olopatadine 0.7% demonstrated statistically significantly improved relief of ocular itching compared to vehicle at 30 to 34 minutes, 16 hours, and 24 hours after study

treatment. Olopatadine 0.7% demonstrated statistically significantly improved relief of ocular itching compared to olopatadine 0.2% at 24 hours after study treatment, but not at 30 to 34 minutes after study treatment.

### ***olopatadine 0.2% (Pataday) versus placebo in children***

Olopatadine 0.2% was evaluated for safety in 126 children and adolescents (ages 3 to 17 years) with asymptomatic eyes in a 6-week, randomized, double-blind trial.<sup>120</sup> Patients were randomized to once daily olopatadine 0.2% or vehicle. Safety was assessed at 3 visits and 3 interviews. No clinically relevant treatment-related changes in visual acuity, intraocular pressure, slit-lamp assessments, fundus examinations, or cardiovascular parameters were observed. Adverse events were mild or moderate.

## **Vernal Keratoconjunctivitis**

### ***Iodoxamide (Alomide) versus cromolyn sodium***

A small randomized study compared the efficacy of Iodoxamide 0.1% and cromolyn sodium 4% in 31 patients between the ages of 6 and 19 years diagnosed with VKC.<sup>121</sup> Dosage of each agent was 2 drops 4 times daily. Eye symptom severity scores and clinical signs were evaluated pre- and post-treatment. Conjunctival impression cytologic specimens were also obtained pre- and post-treatment to detect percentages of CD4+, CD8+, CD45RA+, and CD23+ cells. While patient symptom scores and clinical signs were significantly improved after treatment in both groups, significantly lower symptom scores and clinical signs were reported with Iodoxamide compared to cromolyn sodium. The percentages of CD4+ and CD23+ cells in tear samples of patients in both groups A and B were significantly higher in the pretreatment stage than post-treatment stage. In the post-treatment stage, Iodoxamide was associated with significantly lower CD4+ and CD23+ cell values compared to cromolyn sodium.

## **SUMMARY**

Numerous comparative trials using allergic conjunctivitis agents have been conducted. The trials used 1-time administration of a single dose in the eye and evaluated effects based on a conjunctival allergen challenge (CAC) model. From the results of the trials, it is difficult to declare 1 drug superior to another. Another factor used to evaluate the drugs is ocular comfort. This evaluation was also made from 1-time single dose trials. Again, the results of the trials do not support superiority of any product in the class.

Azelastine, bepotastine (Bepreve), epinastine (Elestat), ketotifen (Zaditor), nedocromil (Alocril), and olopatadine 0.1% (Patanol) require administration 2 or 3 times daily versus other products which require 4 times per day dosing. Alcaftadine (Lastacaft), olopatadine 0.2% (Pataday), and olopatadine 0.7% (Pazeo) are administered once daily.

The majority of the agents in this class are indicated for acute treatment or temporary relief of allergic ocular symptoms. The published literature gives very little information regarding efficacy and safety in chronic use of these agents. Alcaftadine (Lastacaft) and epinastine (Elestat) carry an indication for prevention of itching of the eye due to allergic conjunctivitis. Additionally, ketorolac (Acular), which is not included in this review, is indicated for reducing inflammation and pain after cataract extraction. Mast-cell stabilizers, cromolyn and Iodoxamide (Alomide), are indicated for the treatment of vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis.

## REFERENCES

- 1 Lastacaft [package insert]. Irvine, CA; Allergan; September 2015.
- 2 Optivar [package insert]. Somerset, NJ; Meda; April 2009.
- 3 Bepreve [package insert]. Bridgewater, NJ; Bausch and Lomb; February 2018.
- 4 Emadine [package insert]. Fort Worth, TX; Alcon; March 2018.
- 5 Elestat [package insert]. Irvine, CA; Allergan; December 2011.
- 6 Zaditor [package insert]. Fort Worth, TX; Alcon; July 2015.
- 7 Patanol [package insert]. Fort Worth, TX; Alcon; January 2007.
- 8 Pataday [package insert]. Fort Worth, TX; Alcon; December 2010.
- 9 Pazeo [package insert]. Fort Worth, TX; Alcon; April 2016.
- 10 Opticrom [package insert]. Irvine, CA; Allergan; February 1998.
- 11 Alomide [package insert]. Fort Worth, TX; Alcon; March 2018.
- 12 Alocril [package insert]. Irvine, CA; Allergan; December 2012.
- 13 Alrex [package insert]. Tampa, FL; Bausch and Lomb; May 2016.
- 14 Acular [package insert]. Irvine, CA; Allergan; June 2012.
- 15 American Academy of Ophthalmology. Preferred Practice Pattern Guidelines: Conjunctivitis September 2013. Available at: <https://www.aao.org/guidelines-browse>. Accessed April 9, 2018
- 16 Abelson MB and Schaefer K. Conjunctivitis of allergic origin: Immunologic mechanisms and current approaches to therapy. *Surv Ophthalmol.* 1993; 38(suppl):115-132.
- 17 American Academy of Ophthalmology. Preferred Practice Pattern Guidelines: Conjunctivitis September 2013. Available at: <https://www.aao.org/guidelines-browse>. Accessed April 9, 2018.
- 18 American Academy of Ophthalmology. Summary benchmarks for preferred practice pattern guidelines. 2017. Available at <https://www.aao.org/guidelines-browse>. Accessed April 9, 2018.
- 19 Simons FER, Simons KJ. Histamine and H1-antihistamines: Celebrating a century of progress. *J. Allerg. And Clin. Immun.* 2011;128(6):1139-1150. DOI: 10.1016/j.jaci.2011.09.005.
- 20 American Academy of Ophthalmology. Preferred practice pattern guidelines: conjunctivitis September 2013. Available at: <https://www.aao.org/guidelines-browse>. Accessed April 9, 2018.
- 21 American Academy of Ophthalmology. Clinical Education: Vernal keratoconjunctivitis April 2016. Available at <https://www.aao.org/pediatric-center-detail/vernal-keratoconjunctivitis-5>. Accessed April 9, 2018.
- 22 Lastacaft [package insert]. Irvine, CA; Allergan; September 2015.
- 23 Optivar [package insert]. Somerset, NJ; Meda; April 2009.
- 24 Bepreve [package insert]. Bridgewater, NJ; Bausch and Lomb; February 2018.
- 25 Emadine [package insert]. Fort Worth, TX; Alcon; March 2018.
- 26 Elestat [package insert]. Irvine, CA; Allergan; December 2011.
- 27 Zaditor [package insert]. Fort Worth, TX; Alcon; July 2015.
- 28 Patanol [package insert]. Fort Worth, TX; Alcon; January 2007.
- 29 Pataday [package insert]. Fort Worth, TX; Alcon; December 2010.
- 30 Pazeo [package insert]. Fort Worth, TX; Alcon; April 2016.
- 31 Opticrom [package insert]. Irvine, CA; Allergan; February 1998.
- 32 Alomide [package insert]. Fort Worth, TX; Alcon; March 2018.
- 33 Alocril [package insert]. Irvine, CA; Allergan; December 2012.
- 34 Alrex [package insert]. Tampa, FL; Bausch and Lomb; May 2016.
- 35 Available at: <http://www.clinicalpharmacology.com>. Accessed April 9, 2018.
- 36 Bielory L, Lien KW, Bigelsen S. Efficacy and tolerability of newer antihistamines in the treatment of allergic conjunctivitis. *Drugs.* 2005; 65(2):215-28.
- 37 Lastacaft [package insert]. Irvine, CA; Allergan; September 2015.
- 38 Optivar [package insert]. Somerset, NJ; Meda; April 2009.
- 39 Bepreve [package insert]. Bridgewater, NJ; Bausch and Lomb; February 2018.
- 40 Emadine [package insert]. Fort Worth, TX; Alcon; March 2018.
- 41 Elestat [package insert]. Irvine, CA; Allergan; December 2011.
- 42 Zaditor [package insert]. Fort Worth, TX; Alcon; July 2015.
- 43 Patanol [package insert]. Fort Worth, TX; Alcon; January 2007.
- 44 Pataday [package insert]. Fort Worth, TX; Alcon; December 2010.
- 45 Pazeo [package insert]. Fort Worth, TX; Alcon; April 2016.
- 46 Opticrom [package insert]. Irvine, CA; Allergan; February 1998.
- 47 Alomide [package insert]. Fort Worth, TX; Alcon; March 2018.
- 48 Alocril [package insert]. Irvine, CA; Allergan; December 2012.
- 49 Alrex [package insert]. Tampa, FL; Bausch and Lomb; May 2016.
- 50 Available at: <http://www.clinicalpharmacology.com>. Accessed April 9, 2018.
- 51 Lastacaft [package insert]. Irvine, CA; Allergan; September 2015.
- 52 Optivar [package insert]. Somerset, NJ; Meda; April 2009.
- 53 Emadine [package insert]. Fort Worth, TX; Alcon; March 2018.
- 54 Elestat [package insert]. Irvine, CA; Allergan; December 2011.
- 55 Zaditor [package insert]. Fort Worth, TX; Alcon; July 2015.
- 56 Patanol [package insert]. Fort Worth, TX; Alcon; January 2007.

- 
- 57 Cromolyn. Available at Micromedex online: <http://www.micromedexsolutions.com/home/dispatch>. Accessed April 10, 2017.
- 58 Alomide [package insert]. Fort Worth, TX; Alcon; March 2018.
- 59 Alrex [package insert]. Tampa, FL; Bausch and Lomb; May 2016.
- 60 Alocril [package insert]. Irvine, CA; Allergan; December 2012.
- 61 Bepreve [package insert]. Bridgewater, NJ; Bausch and Lomb; February 2018.
- 62 Pazeo [package insert]. Fort Worth, TX; Alcon; April 2016.
- 63 Available at: <https://www.fda.gov/drugs/drugsafety/ucm490693.htm>. Accessed April 11, 2018.
- 64 Lastacaft [package insert]. Irvine, CA; Allergan; September 2015.
- 65 Optivar [package insert]. Somerset, NJ; Meda; April 2009.
- 66 Bepreve [package insert]. Bridgewater, NJ; Bausch and Lomb; February 2018.
- 67 Emadine [package insert]. Fort Worth, TX; Alcon; March 2018.
- 68 Elestat [package insert]. Irvine, CA; Allergan; December 2011.
- 69 Patanol [package insert]. Fort Worth, TX; Alcon; January 2007.
- 70 Pataday [package insert]. Fort Worth, TX; Alcon; December 2010.
- 71 Pazeo [package insert]. Fort Worth, TX; Alcon; April 2016.
- 72 Opticrom [package insert]. Irvine, CA; Allergan; February 1998.
- 73 Alomide [package insert]. Fort Worth, TX; Alcon; March 2018.
- 74 Alocril [package insert]. Irvine, CA; Allergan; December 2012.
- 75 Alrex [package insert]. Tampa, FL; Bausch and Lomb; May 2016.
- 76 Available at: <http://www.clinicalpharmacology.com>. Accessed April 9, 2018.
- 77 Available at: <http://www.micromedexsolutions.com>. Accessed April 9, 2018.
- 78 Lastacaft [package insert]. Irvine, CA; Allergan; September 2015.
- 79 Optivar [package insert]. Somerset, NJ; Meda; April 2009.
- 80 Emadine [package insert]. Fort Worth, TX; Alcon; March 2018.
- 81 Elestat [package insert]. Irvine, CA; Allergan; December 2011.
- 82 Zaditor [package insert]. Fort Worth, TX; Alcon; July 2015.
- 83 Patanol [package insert]. Fort Worth, TX; Alcon; January 2007.
- 84 Cromolyn. Available at Micromedex online: <http://www.micromedexsolutions.com/home/dispatch>. Accessed April 10, 2018.
- 85 Alomide [package insert]. Fort Worth, TX; Alcon; March 2018.
- 86 Alrex [package insert]. Tampa, FL; Bausch and Lomb; May 2016.
- 87 Alocril [package insert]. Irvine, CA; Allergan; December 2012.
- 88 Bepreve [package insert]. Bridgewater, NJ; Bausch and Lomb; February 2018.
- 89 Pazeo [package insert]. Fort Worth, TX; Alcon; April 2016.
- 90 Lastacaft [package insert]. Irvine, CA; Allergan; September 2015.
- 91 Optivar [package insert]. Somerset, NJ; Meda; April 2009.
- 92 Bepreve [package insert]. Bridgewater, NJ; Bausch and Lomb; February 2018.
- 93 Emadine [package insert]. Fort Worth, TX; Alcon; March 2018.
- 94 Elestat [package insert]. Irvine, CA; Allergan; December 2011.
- 95 Zaditor [package insert]. Fort Worth, TX; Alcon; July 2015.
- 96 Patanol [package insert]. Fort Worth, TX; Alcon; January 2007.
- 97 Pataday [package insert]. Fort Worth, TX; Alcon; December 2010.
- 98 Pazeo [package insert]. Fort Worth, TX; Alcon; April 2016.
- 99 Opticrom [package insert]. Irvine, CA; Allergan; February 1998.
- 100 Alomide [package insert]. Fort Worth, TX; Alcon; March 2018.
- 101 Alocril [package insert]. Irvine, CA; Allergan; December 2012.
- 102 Alrex [package insert]. Tampa, FL; Bausch and Lomb; May 2016.
- 103 Torkildsen, S.A., The safety and efficacy of alcaftadine 0.25% ophthalmic solution for the prevention of itching associated with allergic conjunctivitis. *Curr Med Res Opin.* 2011;27(3):623-31.
- 104 Torkildsen GL, Ousler GW 3rd, Gomes P. Ocular comfort and drying effects of three topical antihistamine/mast cell stabilizers in adults with allergic conjunctivitis: a randomized, double-masked crossover study. *Clin Ther.* 2008; 30(7):1264-71.
- 105 Macejko TT, Bergmann MT, Williams JI, et al. Bepotastine Besilate Ophthalmic Solutions Study Group. Multicenter clinical evaluation of bepotastine ophthalmic solutions 1.0% and 1.5% to treat allergic conjunctivitis. *Am J Ophthalmol.* 2010; 150(1):122-127.e5.
- 106 McCabe CF, McCabe SE. Comparative efficacy of bepotastine besilate 1.5% ophthalmic solution versus olopatadine hydrochloride 0.2% ophthalmic solution evaluated by patient preference. *Clin Ophthalmol.* 2012;6:1731-8.
- 107 Discepolo M, Deschenes J, Abelson M. Comparison of the topical ocular antiallergic efficacy of emedastine 0.05% ophthalmic solution to ketorolac 0.5% ophthalmic solution in a clinical model of allergic conjunctivitis. *Acta Ophthalmol Scand Suppl.* 1999; 228:43-46.
- 108 D'Arienzo PA, Leonardi A, Bensch G. Randomized, double-masked, placebo-controlled comparison of the efficacy of emedastine difumarate 0.05% ophthalmic solution and ketotifen fumarate 0.025% ophthalmic solution in the human conjunctival allergen challenge model. *Clin Ther.* 2002; 24:409-416.
- 109 Lanier BQ, Finegold I, D'Arienzo P, et al. Clinical efficacy of olopatadine vs. epinastine ophthalmic solution in the conjunctival allergen challenge model. *Curr Med Res Opin.* 2004; 20(8):1227-33.
- 110 Mah FS, Rosenwasser LJ, Townsend WD, et al. Efficacy and comfort of olopatadine 0.2% versus epinastine 0.05% ophthalmic solution for treating itching and redness induced by conjunctival allergen challenge. *Curr Med Res Opin.* 2007;23(6):1445-52. DOI: 10.1185/030079907X188206.
- 111 Greiner JV, Minno G. A placebo-controlled comparison of ketotifen fumarate and nedocromil sodium ophthalmic solutions for the prevention of ocular itching with the conjunctival allergen challenge model. *Clin Ther.* 2003; 25(7):1988-2005.
- 112 Berdy GJ, Spangler DL, Bensch G, et al. A comparison of the relative efficacy and clinical performance of olopatadine hydrochloride 0.1% ophthalmic solution and ketotifen fumarate 0.025% ophthalmic solution in the conjunctival antigen challenge model. *Clin Ther.* 2000; 22:826-833.
-

- 
- 113 Ganz M, Koll E, Gausche J, et al. Ketotifen fumarate and olopatadine hydrochloride in the treatment of allergic conjunctivitis: a real-world comparison of efficacy and ocular comfort. *Adv Ther.* 2003; 20(2):79-91.
- 114 Avunduk AM, Tekelioglu Y, Turk A, et al. Comparison of the Effects of ketotifen fumarate 0.025% and olopatadine HCl 0.1% ophthalmic solutions in seasonal allergic conjunctivitis: A 30-day randomized, double-masked, artificial tear substitute controlled trial. *Clin Ther.* 2005; 27(9):1392-1402.
- 115 Abelson MB, Ferzola NJ, McWhirter CL, et al. Efficacy and safety of single- and multiple-dose ketotifen fumarate 0.025% ophthalmic solution in a pediatric population. *Pediatr Allergy Immunol.* 2004; 15(6):551-7.
- 116 Berdy GJ, Stoppel JO, Epstein AB. Comparison of the clinical efficacy and tolerability of olopatadine hydrochloride 0.1% ophthalmic solution and loteprednol etabonate 0.2% ophthalmic suspension in the conjunctival allergen challenge model. *Clin Ther.* 2002; 24:918-929.
- 117 Spangler DL, Bensch G, Berdy GJ. Evaluation of the efficacy of olopatadine hydrochloride 0.1% ophthalmic solution and azelastine hydrochloride 0.05% ophthalmic solution in the conjunctival allergen challenge model. *Clin Ther.* 2001; 23(8):1272-1280.
- 118 Deschenes J, Discepolo M, Abelson M. Comparative evaluation of olopatadine ophthalmic solution (0.1%) versus ketorolac ophthalmic solution (0.5%) using the provocative antigen challenge model. *Acta Ophthalmol Scand Suppl.* 1999; 228:47-52.
- 119 Abelson MB, Spangler DL, Epstein AB, et al. Efficacy of once-daily olopatadine 0.2% ophthalmic solution compared to twice-daily olopatadine 0.1% ophthalmic solution for the treatment of ocular itching induced by conjunctival allergen challenge. *Curr Eye Res.* 2007; 32(12):1017-22.
- 120 Lichtenstein SJ, Pasquine TA, Edwards MR, et al. Safety and tolerability of olopatadine 0.2% in children and adolescents. *J Ocul Pharmacol Ther.* 2007; 23(4):366-71.
- 121 Avunduk AM, Avunduk MC, Kapicioqlu Z, et al. Mechanisms and comparison of anti-allergic efficacy of topical lodoxamide and cromolyn sodium treatment in vernal keratoconjunctivitis. *Ophthalmology.* 2000; 107(7):1333-1337. DOI: 10.1016/S0161-6420(00)00089-0.