Ophthalmics for Allergic Conjunctivitis
Therapeutic Class Review (TCR)

September 1, 2021

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.
### FDA-APPROVED INDICATIONS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Approved Age Range</th>
<th>Indication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ophthalmic Antihistamines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>alcaftadine <em>(Lastacaft®)</em></td>
<td>Allergan</td>
<td>≥ 2 years</td>
<td>Prevention of itching of the eye due to allergic conjunctivitis</td>
</tr>
<tr>
<td>alcaftadine (OTC) <em>(Lastacaft® Once Daily Relief)</em></td>
<td>Allergan</td>
<td>≥ 2 years</td>
<td>Temporarily relief of itchy eyes due to pollen, ragweed, grass, animal hair and dander</td>
</tr>
<tr>
<td>azelastine</td>
<td>generic</td>
<td>≥ 3 years</td>
<td>Treatment of itching of the eye associated with allergic conjunctivitis</td>
</tr>
<tr>
<td>bepotastine <em>(Bepreve®)</em></td>
<td>generic, Bausch/Valeant</td>
<td>≥ 2 years</td>
<td>Treatment of ocular itching associated with allergic conjunctivitis</td>
</tr>
<tr>
<td>cetirizine <em>(Zerviate®)</em></td>
<td>Eyevance</td>
<td>≥ 2 years</td>
<td>Treatment of ocular itching associated with allergic conjunctivitis</td>
</tr>
<tr>
<td>epinastine</td>
<td>generic</td>
<td>≥ 3 years</td>
<td>Prevention of itching of the eye due to allergic conjunctivitis</td>
</tr>
<tr>
<td>ketotifen (OTC) <em>(Alaway®, Systane® Zaditor®)</em></td>
<td>generic, Bausch/Valeant, Alcon Consumer</td>
<td>≥ 3 years</td>
<td>Temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair, and dander</td>
</tr>
<tr>
<td>olopatadine 0.1%</td>
<td>generic</td>
<td>≥ 3 years</td>
<td>Treatment of the signs and symptoms of allergic conjunctivitis</td>
</tr>
<tr>
<td>olopatadine 0.1% (OTC) <em>(Pataday® Twice Daily Relief)</em></td>
<td>generic, Alcon</td>
<td>≥ 2 years</td>
<td>Temporary relief of itchy and red eyes due to pollen, ragweed, grass, animal hair and dander</td>
</tr>
<tr>
<td>olopatadine 0.2%</td>
<td>generic</td>
<td>≥ 2 years</td>
<td>Treatment of ocular itching associated with allergic conjunctivitis</td>
</tr>
<tr>
<td>olopatadine 0.2% (OTC) <em>(Pataday® Once Daily Relief)</em></td>
<td>generic, Alcon</td>
<td>≥ 2 years</td>
<td>Temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair and dander</td>
</tr>
<tr>
<td>olopatadine 0.7% <em>(Pazeo®)</em></td>
<td>generic, Alcon/Novartis</td>
<td>≥ 2 years</td>
<td>Treatment of ocular itching associated with allergic conjunctivitis</td>
</tr>
<tr>
<td>olopatadine 0.7% (OTC) <em>(Pataday® Once Daily Relief - Extra Strength)</em></td>
<td>Alcon</td>
<td>≥ 2 years</td>
<td>Temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair and dander</td>
</tr>
<tr>
<td><strong>Ophthalmic Mast Cell Stabilizers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cromolyn</td>
<td>generic</td>
<td>≥ 4 years</td>
<td>Treatment of vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis</td>
</tr>
<tr>
<td>lodoxamide <em>(Alomide®)</em></td>
<td>Alcon/Novartis</td>
<td>≥ 2 years</td>
<td>Treatment of vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis</td>
</tr>
<tr>
<td>nedocromil <em>(Alocril®)</em></td>
<td>Allergan</td>
<td>≥ 3 years</td>
<td>Treatment of itching associated with allergic conjunctivitis</td>
</tr>
<tr>
<td><strong>Ophthalmic Anti-Inflammatory Agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>loteprednol <em>(Alrex®)</em></td>
<td>Bausch/Valeant</td>
<td>≥ 18 years</td>
<td>Temporary relief of the signs and symptoms of seasonal allergic conjunctivitis</td>
</tr>
</tbody>
</table>
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. Its safety and efficacy have not been established in patients < 2 years of age. This product is not addressed in this therapeutic class review.

OVERVIEW

Conjunctivitis, or inflammation of the conjunctiva, may occur secondary to infectious or non-infectious stimuli. Seasonal, vernal, atopic, and giant papillary conjunctivitis (GPC) are non-infectious types of conjunctivitis; infectious types include viral and bacterial. In non-infectious types, allergens cause cross-linkage of membrane-bound IgE leading to mast cell degranulation followed by a release and cascade of allergic and inflammatory mediators, such as histamine. The estimated prevalence of allergic conjunctivitis is between 15% and 40%. The condition occurs in both adults and children and is one of the most common reasons for patient self-referral. 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) 2018 treatment guidelines recommend an over-the-counter (OTC) antihistamine/vasoconstrictor agent or use of the more effective second-generation topical histamine H1-receptor antagonists (e.g. alcaftadine, azelastine, bepotastine, epinastine, olopatadine) for treatment of mild allergic conjunctivitis. 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. 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 characterized by severe eye itching, discharge, foreign body sensation, photophobia, blepharospasm, mucous discharge, and blurred vision that is exacerbated by environmental allergens. It is most common in children and young adults. VKC typically occurs in hot, dry climates. Eyelid thickening, ptosis, corneal ulcerations, and infection can occur, and if left untreated and severe, VKC can lead to permanent vision loss. Evidence suggests eosinophils, fibroblasts, epithelial cells, mast cells, and T helper 2 (TH2) lymphocytes in the conjunctiva are involved in the inflammatory response. Common therapies include topical antihistamines for mild cases with the addition of topical mast-cell stabilizers for moderate cases. High pulse dosing with quick tapering of a topical corticosteroid is usually needed to reduce inflammation. Topical cyclosporine 0.05% to 2% or tacrolimus 0.1% can be added to reduce the required dose of corticosteroid, particularly in severe cases.
**PHARMACOLOGY**^{29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47}  
Therapeutic efficacy is independent of pharmacological activity.^{48}

<table>
<thead>
<tr>
<th>Drug</th>
<th>Antihistamine</th>
<th>Anti-Inflammatory</th>
<th>Mast Cell Stabilizer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ophthalmic Antihistamines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>alcaftadine (Lastacaft, Lastacaft OTC)</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>azelastine</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>bepotastine (Bepreve)</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>cetirizine (Zerviate)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>epinastine</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>ketotifen</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>olopatadine (Pataday OTC, Pazeo)</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>Ophthalmic Mast Cell Stabilizers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cromolyn</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>lodoxamide (Alomide)</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>nedocromil (Alocril)</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>Ophthalmic Anti-Inflammatory Agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>loteprednol (Alrex)</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

**PHARMACOKINETICS**^{49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67}  

<table>
<thead>
<tr>
<th>Drug</th>
<th>Systemic absorption</th>
<th>Preservative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ophthalmic Antihistamines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>alcaftadine (Lastacaft, Lastacaft OTC)</td>
<td>Below level of detection</td>
<td>benzalkonium chloride</td>
</tr>
<tr>
<td>azelastine</td>
<td>Systemic absorption does occur with reported plasma concentrations of 0.02 to 0.25 ng/mL after 56 days of treatment</td>
<td>benzalkonium chloride</td>
</tr>
<tr>
<td>bepotastine (Bepreve)</td>
<td>Plasma concentrations peak at 1 to 2 hours post-instillation, with a maximum concentration of 7.3 ng/mL</td>
<td>benzalkonium chloride</td>
</tr>
<tr>
<td>cetirizine (Zerviate)</td>
<td>Mean maximum plasma concentrations of 1.7 ng/mL following a single dose and 3.1 ng/mL after twice-daily dosing for one week; mean terminal half-life of 8.6 hours following a single dose and 8.2 hours after twice-daily dosing for one week</td>
<td>benzalkonium chloride</td>
</tr>
<tr>
<td>epinastine</td>
<td>Average maximum plasma concentrations of 0.04 ± 0.014 ng/ml were reached after about 2 hours</td>
<td>benzalkonium chloride</td>
</tr>
<tr>
<td>ketotifen</td>
<td>Below level of detection</td>
<td>benzalkonium chloride</td>
</tr>
<tr>
<td>olopatadine</td>
<td>Measurable levels within 2 hours of dosing ranged from 0.5 to 1.3 ng/mL in a small percentage of patients</td>
<td>benzalkonium chloride</td>
</tr>
<tr>
<td>olopatadine (Pataday OTC)</td>
<td>No data</td>
<td>benzalkonium chloride</td>
</tr>
<tr>
<td>olopatadine (Pazeo)</td>
<td>Below level of detection</td>
<td>benzalkonium chloride</td>
</tr>
</tbody>
</table>
**Pharmacokinetics (continued)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Systemic absorption</th>
<th>Preservative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ophthalmic Mast Cell Stabilizers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cromolyn</td>
<td>Systemic absorption has been reported, but at low levels</td>
<td>benzalkonium chloride</td>
</tr>
<tr>
<td>lodoxamide (Alomide)</td>
<td>Below level of detection</td>
<td>benzalkonium chloride</td>
</tr>
<tr>
<td>nedocromil (Alocril)</td>
<td>&lt; 4% of the total dose is systemically absorbed</td>
<td>benzalkonium chloride</td>
</tr>
<tr>
<td><strong>Ophthalmic Anti-Inflammatory Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>loteprednol (Alrex)</td>
<td>Below level of detection</td>
<td>benzalkonium chloride</td>
</tr>
</tbody>
</table>

**CONTRAINDICATIONS/WARNINGS**

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, 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. 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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Stinging/Burning</th>
<th>Headache</th>
<th>Eyelid Edema</th>
<th>Nasopharyngitis</th>
<th>Conjunctival Infection</th>
<th>Blurred Vision</th>
<th>Altered Taste</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ophthalmic Antihistamines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>alcaftadine (Lastacaft, Lastacaft OTC)</td>
<td>&lt; 4</td>
<td>&lt; 3</td>
<td>reported</td>
<td>&lt; 3</td>
<td>nr</td>
<td>reported</td>
<td>nr</td>
</tr>
<tr>
<td>azelastine</td>
<td>30</td>
<td>15</td>
<td>nr</td>
<td>1–10</td>
<td>nr</td>
<td>1–10</td>
<td>10</td>
</tr>
<tr>
<td>bepotastine (Bepreve)</td>
<td>2–5</td>
<td>2–5</td>
<td>nr</td>
<td>2–5</td>
<td>nr</td>
<td>nr</td>
<td>25</td>
</tr>
<tr>
<td>cetirizine (Zerviate)</td>
<td>1–7</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>1–7</td>
</tr>
<tr>
<td>epinastine</td>
<td>1–10</td>
<td>1–3</td>
<td>nr</td>
<td>1–3</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
</tr>
<tr>
<td>ketotifen</td>
<td>&lt; 5</td>
<td>10–25</td>
<td>&lt; 5</td>
<td>10–25</td>
<td>10–25</td>
<td>nr</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>olopatadine</td>
<td>&lt; 5</td>
<td>7</td>
<td>&lt; 5</td>
<td>&lt; 5</td>
<td>nr</td>
<td>&lt; 5</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>olopatadine (Pataday OTC)</td>
<td>&lt; 5</td>
<td>&lt; 5</td>
<td>&lt; 5</td>
<td>&lt; 5</td>
<td>nr</td>
<td>&lt; 5</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>olopatadine (Pazeo, Pataday Extra Strength [OTC])</td>
<td>nr (&lt; 5 abnormal eye sensation)</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>&lt; 5</td>
<td>&lt; 5</td>
</tr>
</tbody>
</table>

**Ophthalmic Mast Cell Stabilizers**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Stinging/Burning</th>
<th>Headache</th>
<th>Eyelid Edema</th>
<th>Nasopharyngitis</th>
<th>Conjunctival Infection</th>
<th>Blurred Vision</th>
<th>Altered Taste</th>
</tr>
</thead>
<tbody>
<tr>
<td>cromolyn</td>
<td>reported</td>
<td>nr</td>
<td>reported</td>
<td>nr</td>
<td>reported</td>
<td>reported</td>
<td>nr</td>
</tr>
<tr>
<td>lodoxamide (Alomide)</td>
<td>15</td>
<td>1.5</td>
<td>&lt; 1</td>
<td>nr</td>
<td>nr</td>
<td>1–5</td>
<td>nr</td>
</tr>
<tr>
<td>nedocromil (Alocril)</td>
<td>10–30</td>
<td>40</td>
<td>nr</td>
<td>1–10</td>
<td>nr</td>
<td>nr</td>
<td>10–30</td>
</tr>
</tbody>
</table>

**Ophthalmic Anti-Inflammatory Agents**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Stinging/Burning</th>
<th>Headache</th>
<th>Eyelid Edema</th>
<th>Nasopharyngitis</th>
<th>Conjunctival Infection</th>
<th>Blurred Vision</th>
<th>Altered Taste</th>
</tr>
</thead>
<tbody>
<tr>
<td>loteprednol (Alrex)</td>
<td>5–15</td>
<td>&lt; 15</td>
<td>nr</td>
<td>&lt; 15</td>
<td>5–15</td>
<td>5–15</td>
<td>nr</td>
</tr>
</tbody>
</table>

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.

A mild taste following instillation has been reported with bepotastine (Bepreve) in approximately 25% of subjects.

### SPECIAL POPULATIONS

**Pediatrics**

Most of the agents in this class are safe and effective in children as young as 3 years of age, including olopatadine 0.1%. Cromolyn sodium is approved in patients 4 years of age and older. Alcaftadine (Lastacaft, Lastacaft Once Daily Relief), lodoxamide (Alomide), bepotastine (Bepreve), cetirizine (Zerviate), and olopatadine (Pataday Once Daily Relief, Pataday Once Daily Relief-Extra Strength, Pataday Twice Daily Relief, Pazeo) are approved for use in children as young as 2 years of age. Loteprednol (Alrex) is not approved in those less than 18 years old.
Pregnancy

Cromolyn is Pregnancy Category B. There are no adequate well-controlled studies in women for the use of alcaftadine (Lastacaft, Lastacaft Once Daily Relief), bepotastine (Bepreve), cetirizine (Zerviate), lodoxamide (Alomide), loteprednol (Alrex), nedocromil (Alocril), or olopatadine 0.1% (Pataday Twice Daily), olopatadine 0.7% (Pataday Once Daily-Extra Strength, Pazeo) in pregnancy. Olopatadine 0.2% (Pataday Once Daily) and the remaining products in this review are classified as Pregnancy Category C.

DOSAGES

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (in affected eye[s])</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ophthalmic Antihistamines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>alcaftadine (Lastacaft, Lastacaft Once Daily Relief)</td>
<td>1 drop once daily</td>
<td>0.25% solution (3 mL, 5 mL [OTC only])</td>
</tr>
<tr>
<td>azelastine</td>
<td>1 drop twice daily</td>
<td>0.05% solution (6 mL)</td>
</tr>
<tr>
<td>bepotastine (Bepreve)</td>
<td>1 drop twice daily</td>
<td>1.5% solution (5 mL, 10 mL)</td>
</tr>
<tr>
<td>cetirizine (Zerviate)</td>
<td>1 drop twice daily, approximately 8 hours apart</td>
<td>0.24% solution (0.2 mL single-use container packaged as 30 per carton)</td>
</tr>
<tr>
<td>epinastine</td>
<td>1 drop twice daily</td>
<td>0.05% solution (5 mL)</td>
</tr>
<tr>
<td>ketotifen (Alaway OTC, Zaditor OTC)</td>
<td>1 drop twice daily every 8 to 12 hours, no more than twice daily</td>
<td>0.025% solution (Zaditor OTC: 5 mL; Alaway OTC: 5 mL, 10 mL)</td>
</tr>
<tr>
<td>olopatadine (Pataday Once Daily Relief)</td>
<td>1 drop once daily</td>
<td>0.2% solution (2.5 mL, 5 mL [brand only])</td>
</tr>
<tr>
<td>olopatadine (Pataday Twice Daily Relief)</td>
<td>1 drop twice daily at an interval of 6 to 8 hours</td>
<td>0.1% solution (5 mL)</td>
</tr>
<tr>
<td>olopatadine (Pataday Once Daily Relief-Extra Strength, Pazeo)</td>
<td>1 drop once daily</td>
<td>0.7% solution (2.5 mL, 5 mL [OTC only])</td>
</tr>
<tr>
<td><strong>Ophthalmic Mast Cell Stabilizers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cromolyn</td>
<td>1 to 2 drops 4 to 6 times daily</td>
<td>4% solution (10 mL)</td>
</tr>
<tr>
<td>lodoxamide (Alomide)</td>
<td>1 to 2 drops 4 times daily for up to 3 months</td>
<td>0.1% solution (10 mL)</td>
</tr>
<tr>
<td>nedocromil (Alocril)</td>
<td>1 to 2 drops twice a day</td>
<td>2% solution (5 mL)</td>
</tr>
<tr>
<td><strong>Ophthalmic Anti-Inflammatory Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>loteprednol (Alrex)</td>
<td>1 drop 4 times daily (shake well)</td>
<td>0.2% suspension (5 mL, 10 mL)</td>
</tr>
</tbody>
</table>

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 US.

**Allergic Conjunctivitis**

*alcaftadine (Lastacaft, Lastacaft Once Daily Relief) versus placebo*

Fifty-eight subjects with a history of allergic conjunctivitis were enrolled in a double-masked, multicenter, vehicle-controlled study. 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 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. 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. Both strengths of bepotastine significantly reduced CAC ocular itching at onset of action and at least for 8 hours after dosing (p≤0.0001).
Conjunctival hyperemia reductions for bepotastine were seen only at onset of action of CAC test (p≤0.0125). Only the 1.5% bepotastine strength is FDA-approved.

**Bepotastine (Bepreve) versus olopatadine 0.2% (Pataday Once Daily Relief)**

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 0.2% once daily (7:00 a.m.) for 14 days. 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%.

**Cetirizine (Zerviate) versus Placebo**

Two randomized, double-masked, vehicle-controlled, CAC studies evaluated approximately 100 patients in each study with a history of allergic conjunctivitis. Patients were treated with cetirizine ophthalmic solution 0.24% or vehicle ophthalmic solution and ocular itching severity score (0 no itching to 4 incapacitating itch) was assessed. A 1-unit difference was considered to be a clinically meaningful difference in ocular itching severity. In the intention-to-treat population in both trials, 0.24% cetirizine ophthalmic solution resulted in statistically and clinically significant reductions in ocular itching compared to vehicle at 15 minutes and at 8 hours after dosing (p<0.05).

**Epinastine versus Olopatadine 0.1% (Pataday Twice Daily Relief)**

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. 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 versus Olopatadine 0.2% (Pataday Once Daily Relief)**

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. 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 minutes (p=0.024) and 7 minutes (p=0.003) after the 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≤0.013; conjunctival, p≤0.015; episcleral, p≤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. 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 0.1% (Pataday Twice Daily Relief)**

A randomized, double-masked, single-center, CAC study comparing ketotifen 0.025% and olopatadine 0.1% was conducted in 53 patients. 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. 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. 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.\(^{150}\) The CAC-designed study used 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 performed 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 0.1%**

In a single-center, double-masked CAC study, 50 subjects were randomized to receive olopatadine 0.1%,
loteprednol 0.2%, or placebo.\(^{151}\) 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 (> 1 unit difference) and statistically significant (p<0.05) in
favor of olopatadine compared with loteprednol at all 3 time points.

**Olopatadine 0.1% (Pataday Twice Daily Relief) 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.\(^{152}\) 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, -0.31; p<0.05) in the CAC model. Single-dose administration
did not result in any serious adverse events.

**Olopatadine 0.1% (Pataday Twice Daily Relief) versus ketorolac (Acular)**

Olopatadine 0.1% solution and ketorolac 0.5% solution were compared in a randomized, double-blind,
cross-over study.\(^{153}\) 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). Keterolac 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 0.2% (Pataday Once Daily Relief) versus olopatadine 0.1% (Pataday Twice Daily Relief)**

In a double-blind, 24-hour study, efficacy of 2 doses of olopatadine 0.1% was compared to 1 dose of olopatadine 0.2% in prevention of ocular itching associated with allergic conjunctivitis.\(^{154}\) Based on 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, Pataday Once Daily Relief-Extra Strength) versus olopatadine 0.2% (Pataday Once Daily Relief) 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 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 Once Daily Relief) 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.\(^{155}\) 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**

**Iloxdamide (Alomide) versus cromolyn sodium**

A small, randomized study compared the efficacy of iloxdamide 0.1% and cromolyn sodium 4% in 31 patients between the ages of 6 and 19 years diagnosed with VKC.\(^{156}\) 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 cytoxic 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 iloxdamide 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, iloxdamide 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), cetirizine (Zerviate), epinastine, ketotifen (Zaditor), nedocromil (Alocril), and olopatadine 0.1% (Pataday Twice Daily Relief) require administration 2 or 3 times daily versus other products which require 4 times per day dosing. Alcaftadine (Lastacaft, Lastacaft Once Daily Relief), olopatadine 0.2% (Pataday Once Daily Relief), and olopatadine 0.7% (Pataday Once Daily Relief-Extra Strength, Pazeo) are administered once daily. In February 2020, the FDA approved a prescription to over-the-counter (OTC) switch for olopatadine 0.1% (Patanol®) and olopatadine 0.2% (Pataday®). As a result, the OTC versions, Pataday Twice Daily Relief and Pataday Once Daily Relief, respectively, will be replacing the prescription products. Similarly, in December 2021, the FDA approved a prescription to OTC switch for alcaftadine 0.25% (Lastacaft®).

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 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 in addition to the temporary relief of ocular itching due to seasonal allergic conjunctivitis. Mast-cell stabilizers, cromolyn and lodoxamide (Alomide), are indicated for the treatment of vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis.

REFERENCES

3 Azelastine [package insert]. Lake Forest, IL; Akorn; November 2016.
5 Zerviate [package insert]. Fort Worth, TX; Eyevance; February 2020.
6 Epinastine [package insert]. Berlin, CT; Breckenridge; February 2021.
8 Systane Zaditor [package insert]. Fort Worth, TX; Alcon; October 2020.
9 Olopatadine 0.1% [package insert]. Hollywood, FL; Somerset; November 2019.
10 Pataday Twice Daily Relief [package insert]. Fort Worth, TX; Alcon; December 2020.
11 Olopatadine 0.2% [package insert]. Lake Forest, IL; Akorn; December 2017.
12 Pataday Once Daily Relief [package insert]. Fort Worth, TX; Alcon; December 2020.
13 Pazeo [package insert]. Fort Worth, TX; Alcon; April 2017.
14 Pataday Once Daily Relief - Extra Strength [package insert]. Fort Worth, TX; Alcon; December 2020.
15 Cromolyn [package insert]. Lake Forest, IL; Akorn; June 2016.
19 Acular [package insert]. Irvine, CA; Allergan; May 2012.


31 Azelastine [package insert]. Lake Forest, IL; Akorn; November 2016.


33 Zerviate [package insert]. Fort Worth, TX; Eyevance; February 2020.

34 Epinastine [package insert]. Berlin, CT; Breckenridge; February 2021.


36 Systane Zaditor [package insert]. Fort Worth, TX; Alcon; October 2020.

37 Olopatadine 0.1% [package insert]. Hollywood, FL; Somerset; November 2019.

38 Olopatadine 0.2% [package insert]. Lake Forest, IL; Akorn; December 2017.

39 Pataday Twice Daily Relief [package insert]. Fort Worth, TX; Alcon; December 2020.

40 Pataday Once Daily Relief [package insert]. Fort Worth, TX; Alcon; December 2020.

41 Pazeo [package insert]. Fort Worth, TX; Alcon; April 2017.

42 Pataday Once Daily Relief - Extra Strength [package insert]. Fort Worth, TX; Alcon; December 2020.

43 Cromolyn [package insert]. Lake Forest, IL; Akorn; June 2016.

44 Alomide [package insert]. East Hanover, NJ; Novartis; August 2020.


51 Azelastine [package insert]. Lake Forest, IL; Akorn; November 2016.


53 Zerviate [package insert]. Fort Worth, TX; Eyevance; February 2020.

54 Epinastine [package insert]. Berlin, CT; Breckenridge; February 2021.


56 Zaditor [package insert]. Fort Worth, TX; Alcon; July 2015.

57 Olopatadine 0.1% [package insert]. Hollywood, FL; Somerset; November 2019.

58 Olopatadine 0.2% [package insert]. Lake Forest, IL; Akorn; December 2017.

59 Pataday Twice Daily Relief [package insert]. Fort Worth, TX; Alcon; December 2020.

60 Pataday Once Daily Relief [package insert]. Fort Worth, TX; Alcon; December 2020.

61 Pazeo [package insert]. Fort Worth, TX; Alcon; April 2017.

62 Pataday Once Daily Relief - Extra Strength [package insert]. Fort Worth, TX; Alcon; December 2020.

63 Cromolyn [package insert]. Lake Forest, IL; Akorn; June 2016.

64 Alomide [package insert]. East Hanover, NJ; Novartis; August 2020.


70 Azelastine [package insert]. Lake Forest, IL; Akorn; November 2016.

71 Epinastine [package insert]. Berlin, CT; Breckenridge; February 2021.


73 Zerviate [package insert]. Fort Worth, TX; Eyevance; February 2020.

74 Systane Zaditor [package insert]. Fort Worth, TX; Alcon; October 2020.

75 Olopatadine 0.1% [package insert]. Hollywood, FL; Somerset; November 2019.

76 Pataday Twice Daily Relief [package insert]. Fort Worth, TX; Alcon; December 2020.

77 Pataday Once Daily Relief [package insert]. Fort Worth, TX; Alcon; December 2020.

78 Pataday Once Daily Relief - Extra Strength [package insert]. Fort Worth, TX; Alcon; December 2020.

79 Cromolyn [package insert]. Lake Forest, IL; Akorn; June 2016.


84 Pazeo [package insert]. Fort Worth, TX; Alcon; April 2017.
88 Azelastine [package insert]. Lake Forest, IL; Akorn; November 2016.
89 Bepreve [package insert]. Bridgewater, NJ; Bausch and Lomb; September 2019.
90 Zerviate [package insert]. Fort Worth, TX; EyeVance; February 2020.
91 Epinastine [package insert]. Berlin, CT; Breckenridge; February 2021.
93 Olopatadine 0.1% [package insert]. Hollywood, FL; Somerset; November 2019.
94 Olopatadine 0.2% [package insert]. Lake Forest, IL; Akorn; December 2017.
95 Pazeo [package insert]. Fort Worth, TX; Alcon; April 2017.
96 Pataday Once Daily Relief - Extra Strength [package insert]. Fort Worth, TX; Alcon; December 2020.
97 Cromolyn [package insert]. Lake Forest, IL; Akorn; June 2016.
100 Alrex [package insert]. Bridgewater, NJ; Bausch and Lomb; August 2019.
105 Azelastine [package insert]. Lake Forest, IL; Akorn; November 2016.
106 Epinastine [package insert]. Berlin, CT; Breckenridge; February 2021.
108 Systane Zaditor [package insert]. Fort Worth, TX; Alcon; October 2020.
109 Zerviate [package insert]. Fort Worth, TX; EyeVance; February 2020.
110 Olopatadine 0.1% [package insert]. Hollywood, FL; Somerset; November 2019.
111 Pataday Twice Daily Relief [package insert]. Fort Worth, TX; Alcon; December 2020.
112 Pataday Once Daily Relief [package insert]. Fort Worth, TX; Alcon; December 2020.
113 Pataday Once Daily Relief - Extra Strength [package insert]. Fort Worth, TX; Alcon; December 2020.
114 Cromolyn [package insert]. Lake Forest, IL; Akorn; June 2016.
119 Pazeo [package insert]. Fort Worth, TX; Alcon; April 2017.
123 Azelastine [package insert]. Lake Forest, IL; Akorn; November 2016.
125 Zerviate [package insert]. Fort Worth, TX; EyeVance; February 2020.
126 Epinastine [package insert]. Berlin, CT; Breckenridge; February 2021.
128 Systane Zaditor [package insert]. Fort Worth, TX; Alcon; October 2020.
129 Olopatadine 0.1% [package insert]. Hollywood, FL; Somerset; November 2019.
130 Pataday Twice Daily Relief [package insert]. Fort Worth, TX; Alcon; December 2020.
131 Olopatadine 0.2% [package insert]. Lake Forest, IL; Akorn; December 2017.
132 Pataday Once Daily Relief [package insert]. Fort Worth, TX; Alcon; December 2020.
133 Pazeo [package insert]. Fort Worth, TX; Alcon September 2019.
134 Pataday Once Daily Relief - Extra Strength [package insert]. Fort Worth, TX; Alcon; December 2020.
135 Cromolyn [package insert]. Lake Forest, IL; Akorn; June 2016.
143 Zerviate [package insert]. Fort Worth, TX; Eyevance; February 2020.
151 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.
152 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): 1,272-1,280.
153 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.
154 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): 1,017-1,022.