CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

0206276Orig1s005

Trade Name:	PATADAY ONCE DAILY RELIEF (Extra Strength)
Generic or Proper Name:	olopatadine hydrochloride 0.7%
Sponsor:	Alcon Research, LLC
Approval Date:	July 13, 2020
Indication:	Temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair, and dander.

CENTER FOR DRUG EVALUATION AND RESEARCH

0206276Orig1s005

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	**X**
Clinical Review(s)	**X**
Product Quality Review(s)	
Non-Clinical Review(s)	
Statistical Review(s)	
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	**X**
Administrative/Correspondence Document(s)	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

0206276Orig1s005

APPROVAL LETTER

NDA 206276/S-005

SUPPLEMENT APPROVAL

Alcon Research, LLC
Attention: Vincent Nanevie, MS, MBA, RAC
Director, Global Regulatory Affairs - Vision Care
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Mr. Nanevie:

Please refer to your supplemental new drug application (sNDA) dated and received September 13, 2019 and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Pataday Once Daily Relief (olopatadine hydrochloride ophthalmic solution, 0.7%).

This "Prior Approval" supplemental new drug application provides for the full prescription to over-the-counter switch of olopatadine hydrochloride 0.7% ophthalmic solution.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

LABELING

Submit final printed labeling (FPL) as soon as they are available, but no more than 30 days after they are printed. The FPL must be identical to the submitted labeling and must be in the "Drug Facts" format (21 CFR 201.66), where applicable.

Submitted Draft Labeling	Date Submitted
Pataday® Once Daily Relief (Extra Strength) 2.5 mL (0.085 Fl oz) 0.7% carton	July 9, 2020
Pataday® Once Daily Relief (Extra Strength) 2.5 mL (0.085 Fl oz) 0.7% immediate container	June 25, 2020
Pataday® Once Daily Relief (Extra Strength) Two X 2.5 mL (0.085 Fl oz) 0.7% carton - Twin Pack	July 9, 2020
Pataday® Once Daily Relief (Extra Strength) Sample 0.5 mL (0.017 Fl oz) 0.7% carton	July 9, 2020

Pataday® Once Daily Relief (Extra Strength) Sample 0.5 mL (0.017 Fl oz) 0.7% immediate container	June 25, 2020
Pataday® Once Daily Relief (Extra Strength) Sample 0.5 mL (0.017 Fl oz) 0.7% pouch	June 25, 2020

The FPL should be submitted electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.[1] For administrative purposes, designate this submission "**Final Printed Labeling for approved NDA 206276/S-005**." Approval of this submission by FDA is not required before the labeling is used.

DRUG REGISTRATION AND LISTING

All drug establishment registration and drug listing information is to be submitted to FDA electronically, via the FDA automated system for processing structured product labeling (SPL) files (eLIST). At the time that you submit your final printed labeling (FPL), the content of labeling (Drug Facts) should be submitted in SPL format as described at FDA.gov.[2] Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*. In addition, representative container or carton labeling, whichever includes Drug Facts, (where differences exist only in the quantity of contents statement) should be submitted as a JPG file.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[2] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

POSTMARKETING COMMITMENT

As part of an Enhanced Pharmacovigilance Commitment, for a period of 3 years, submit as 15-day alert reports, all initial and follow-up postmarketing adverse event reports of nonprescription overuse and nonprescription misuse from all postmarketing sources, including consumer reports, solicited reports, foreign reports, and clinical study reports. As part of the periodic safety reports, provide a summary analysis of nonprescription overuse and nonprescription misuse adverse events, from postmarketing reports and those published in the medical literature, as well as a cumulative summary of these events.

If you have any questions, call LCDR Jung Lee, Safety Regulatory Project Manager, at (301) 796-3599.

Sincerely,

{See appended electronic signature page}

Karen Murry Mahoney, MD, FACE
Acting Deputy Director
Office of Nonprescription Drugs
Acting Director
Division of Nonprescription Drugs I
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

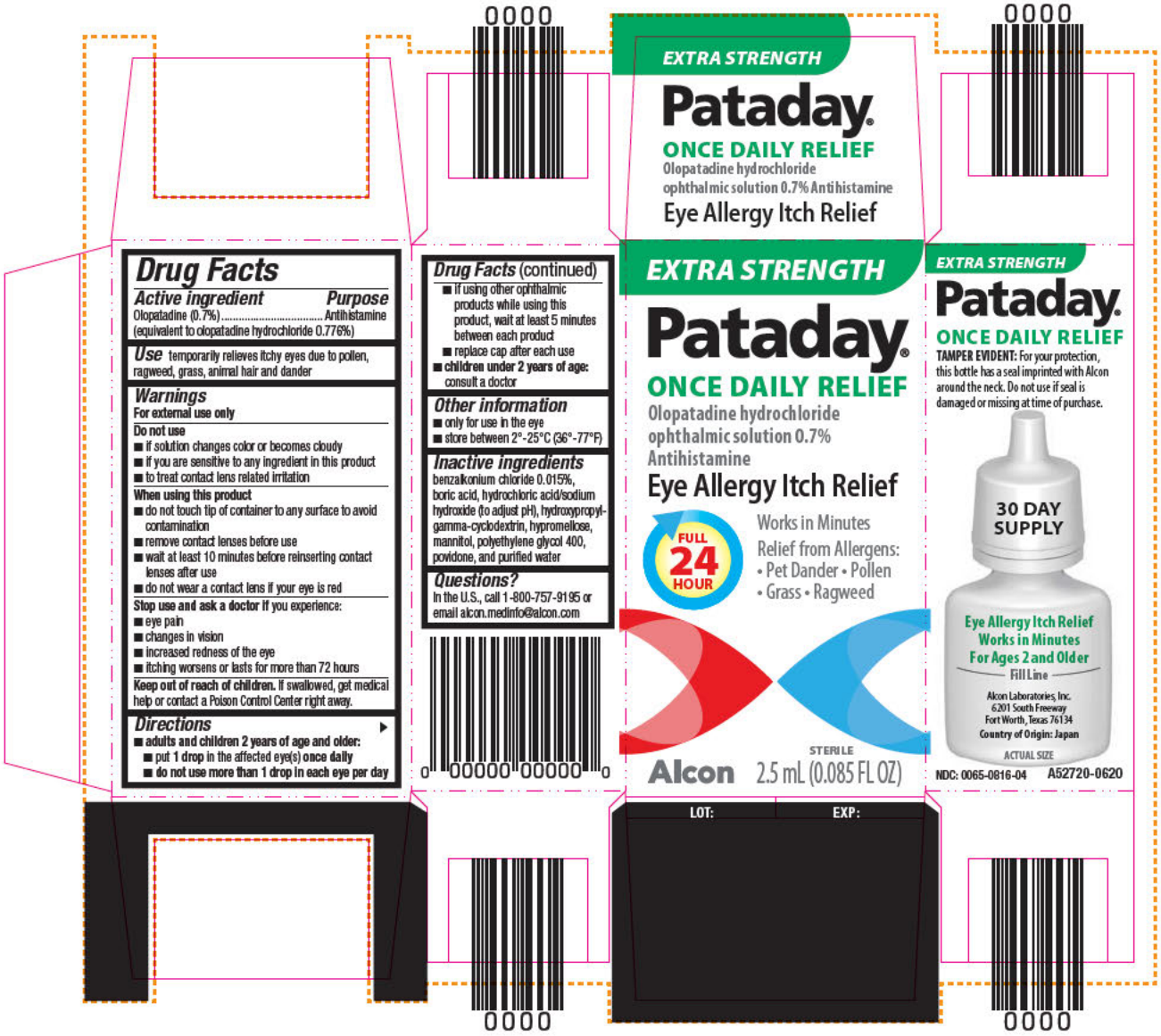
KAREN M MAHONEY
07/13/2020 08:19:30 PM

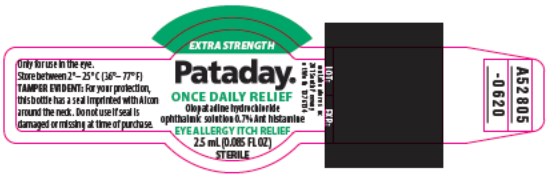
CENTER FOR DRUG EVALUATION AND RESEARCH

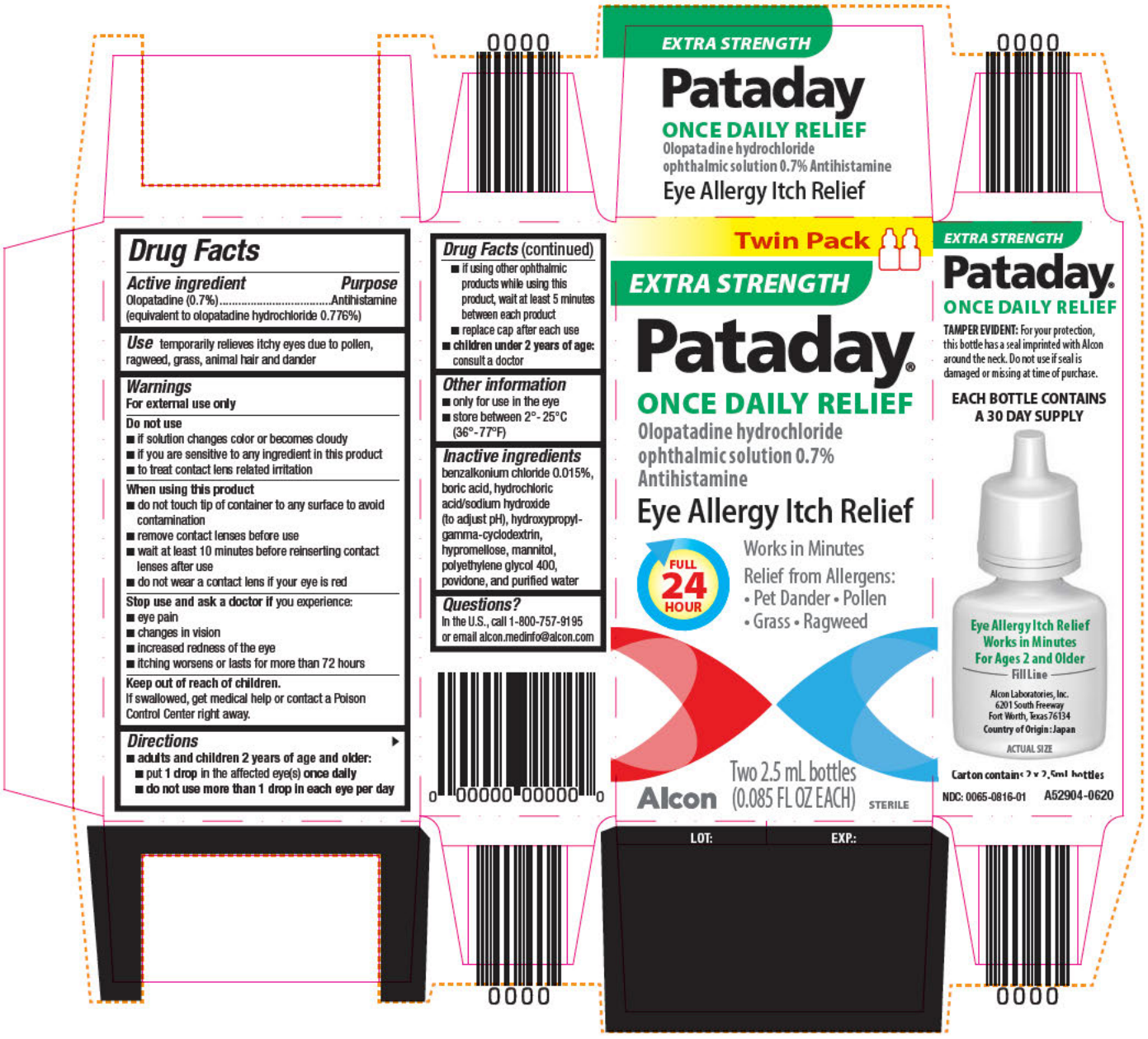
APPLICATION NUMBER:

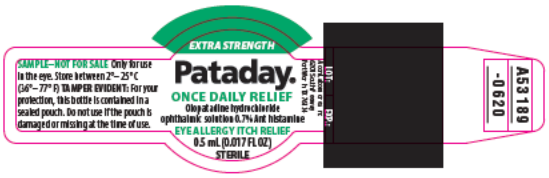
0206276Orig1s005

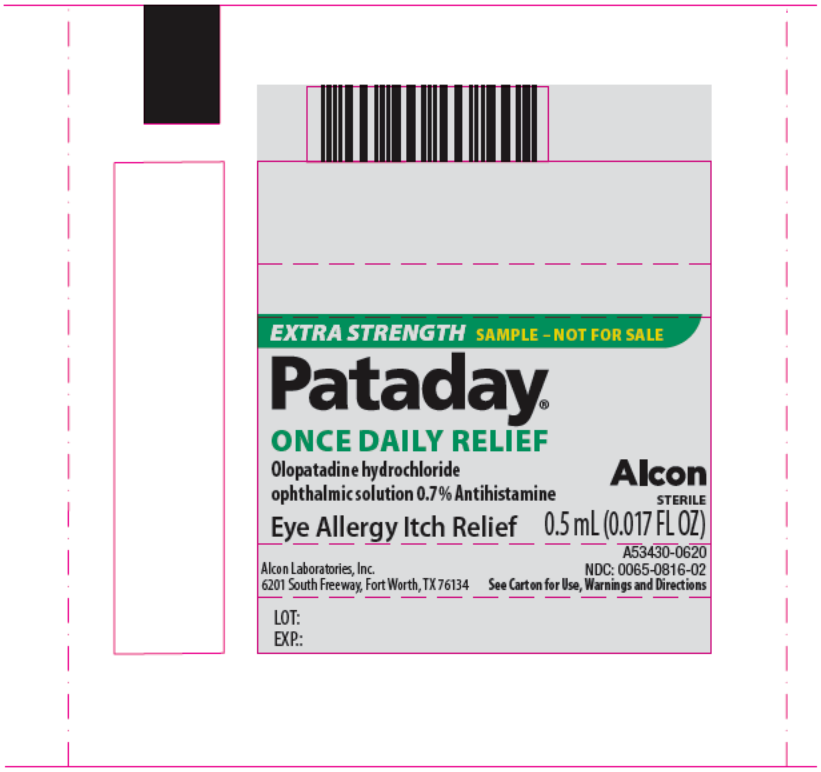
LABELING


EXTRA STRENGTH
Pataday.
ONCE DAILY RELIEF
Olopatadine hydrochloride
ophthalmic solution 0.7% Antihistamine
Eye Allergy Itch Relief
Drug Facts
Active ingredient Purpose
Olopatadine (0.7%) ..... Antihistamine
(equivalent to olopatadine hydrochloride 0.776%)
Use temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair and dander
Warnings
For external use only
Do not use
■ if solution changes color or becomes cloudy
■ if you are sensitive to any ingredient in this product
■ to treat contact lens related irritation
When using this product
■ do not touch tip of container to any surface to avoid contamination
■ remove contact lenses before use
■ wait at least 10 minutes before reinserting contact lenses after use
■ do not wear a contact lens if your eye is red
Stop use and ask a doctor if you experience:
■ eye pain
■ changes in vision
■ increased redness of the eye
■ itching worsens or lasts for more than 72 hours
Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.
Directions
■ adults and children 2 years of age and older:
■ put 1 drop in the affected eye(s) once daily
■ do not use more than 1 drop in each eye per day
Drug Facts (continued)
■ if using other ophthalmic products while using this product, wait at least 5 minutes between each product
■ replace cap after each use
■ children under 2 years of age: consult a doctor
Other information
■ only for use in the eye
■ store between 2°-25°C (36°-77°F)
Inactive ingredients
benzalkonium chloride 0.015%, boric acid, hydrochloric acid/sodium hydroxide (to adjust pH), hydroxypropyl-gamma-cyclodextrin, hypromellose, mannitol, polyethylene glycol 400, povidone, and purified water
Questions?
In the U.S., call 1-800-757-9195 or email alcon.medinfo@alcon.com
0 00000 00000 0
EXTRA STRENGTH
Pataday
ONCE DAILY RELIEF
Olopatadine hydrochloride
ophthalmic solution 0.7%
Antihistamine
Eye Allergy Itch Relief
FULL 24 HOUR
Works in Minutes
Relief from Allergens:
• Pet Dander • Pollen
• Grass • Ragweed
STERILE
Alcon
2.5 mL (0.085 FL OZ)
LOT:
EXP:
EXTRA STRENGTH
Pataday.
ONCE DAILY RELIEF
TAMPER EVIDENT: For your protection, this bottle has a seal imprinted with Alcon around the neck. Do not use if seal is damaged or missing at time of purchase.
30 DAY SUPPLY
Eye Allergy Itch Relief
Works in Minutes
For Ages 2 and Older
Fill Line
Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, Texas 76134
Country of Origin: Japan
ACTUAL SIZE
NDC: 0065-0816-04 A52720-0620




EXTRA STRENGTH
Pataday
ONCE DAILY RELIEF
Olopatadine hydrochloride
ophthalmic solution 0.7% Antihistamine
Eye Allergy Itch Relief
Twin Pack
Drug Facts
Active ingredient Purpose
Olopatadine (0.7%) ..... Antihistamine
(equivalent to olopatadine hydrochloride 0.776%)
Use temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair and dander
Warnings
For external use only
Do not use
■ if solution changes color or becomes cloudy
■ if you are sensitive to any ingredient in this product
■ to treat contact lens related irritation
When using this product
■ do not touch tip of container to any surface to avoid contamination
■ remove contact lenses before use
■ wait at least 10 minutes before reinserting contact lenses after use
■ do not wear a contact lens if your eye is red
Stop use and ask a doctor if you experience:
■ eye pain
■ changes in vision
■ increased redness of the eye
■ itching worsens or lasts for more than 72 hours
Keep out of reach of children.
If swallowed, get medical help or contact a Poison Control Center right away.
Directions
■ adults and children 2 years of age and older:
■ put 1 drop in the affected eye(s) once daily
■ do not use more than 1 drop in each eye per day
Drug Facts (continued)
■ if using other ophthalmic products while using this product, wait at least 5 minutes between each product
■ replace cap after each use
■ children under 2 years of age: consult a doctor
Other information
■ only for use in the eye
■ store between 2°- 25°C (36°-77°F)
Inactive ingredients
benzalkonium chloride 0.015%, boric acid, hydrochloric acid/sodium hydroxide (to adjust pH), hydroxypropyl-gamma-cyclodextrin, hypromellose, mannitol, polyethylene glycol 400, povidone, and purified water
Questions?
In the U.S., call 1-800-757-9195 or email alcon.medinfo@alcon.com
EXTRA STRENGTH
Pataday®
ONCE DAILY RELIEF
Olopatadine hydrochloride
ophthalmic solution 0.7%
Antihistamine
Eye Allergy Itch Relief
FULL 24 HOUR
Works in Minutes
Relief from Allergens:
• Pet Dander • Pollen
• Grass • Ragweed
Alcon
Two 2.5 mL bottles
(0.085 FL OZ EACH)
STERILE
LOT:
EXP:
EXTRA STRENGTH
Pataday.
ONCE DAILY RELIEF
TAMPER EVIDENT: For your protection, this bottle has a seal imprinted with Alcon around the neck. Do not use if seal is damaged or missing at time of purchase.
EACH BOTTLE CONTAINS A 30 DAY SUPPLY
Eye Allergy Itch Relief
Works in Minutes
For Ages 2 and Older
Fill Line
Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, Texas 76134
Country of Origin: Japan
ACTUAL SIZE
Carton contains 2 x 2.5ml bottles
NDC: 0065-0816-01
A52904-0620
0000


EXTRA STRENGTH
Pataday.
ONCE DAILY RELIEF
Olopatadine hydrochloride ophthalmic solution 0.7% Ant histamine
EYE ALLERGY ITCH RELIEF
0.5 mL (0.017 FL OZ)
STERILE
SAMPLE—NOT FOR SALE Only for use in the eye. Store between 2°– 25°C (36°– 77° F) TAMPER EVIDENT: For your protection, this bottle is contained in a sealed pouch. Do not use if the pouch is damaged or missing at the time of use.
A53189
-0620



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

0206276Orig1s005

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 9, 2020
From	Francis E. Becker, M.D., F.A.C.P.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 206276, S-005
Applicant	Alcon Research, LLC.
Date of Submission	September 13, 2019
PDUFA Goal Date	July 13, 2020
Proprietary Name	Olopatadine hydrochloride ophthalmic solution 0.7%
Established or Proper Name	Pataday Once Daily Relief, "Extra Strength"
Dosage Form(s)	Solution (ophthalmic use)
Applicant Proposed Indication(s)/Population(s)	Temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair and dander/adults and children 2 years of age and older
Applicant Proposed Dosing Regimen(s)	One drop in the affected eye(s) once daily, (b) (4) (b) (4)
Recommendation on Regulatory Action	**Approval**: conditional upon strong labeling to help minimize overuse or misuse, coupled with postmarket commitment for Enhanced Pharmacovigilance
Recommended Indication(s)/Population(s) (if applicable)	Temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair and dander/adults and children 2 years of age and older (same as proposed by Applicant)
Recommended Dosing Regimen(s) (if applicable)	One drop in the affected eye(s) once daily, (b) (4) (b) (4) (same as proposed by Applicant)

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

I recommend approval of the prescription (Rx)-to-nonprescription (over-the-counter or OTC) switch of olopatadine hydrochloride ophthalmic solution 0.7%, for the temporary relief of itchy eyes; due to pollen, ragweed, grass, animal hair and dander in adults and children 2 years of age and older. To address concerns about potential overuse/misuse of this product by conusumers in the OTC environment, my recommendation for approval is conditional upon agreement with the Applicant for postmarketing follow-up which will include, in the Applicant's annual and periodic reports, a summary of all experience with overuse and misuse cases (and their consequences). In addition, the Drug Facts label (DFL) should be strengthened to discourage misuse (e.g., "Put **one drop** in the affected eye(s) **once daily. Do not exceed one drop per eye per day.")**

Approval of this product for OTC use will provide an additional safe and effective therapeutic option for consumers to treat symptoms of allergic conjunctivitis. The less frequent (once daily) dosing compared to other OTC topical agents for the same indication, the dual mechanism of action (antihistamine and mast cell stabilizer), and the demonstrated efficacy and safety when dosed regularly (up to 6 weeks in clinical trials) will be of additional benefit to consumers in treating their ocular symptoms.

Recent estimates suggest that 15-20% of the U.S. population (between 50 and 85 million Americans) suffer from allergic conjunctivitis. Symptoms include eye itching, redness, burning, and tearing; with itchy eyes being a primary symptom. Ocular symptoms of allergic disorders can have a profound impact on quality of life. Seasonal allergy sufferers may be unable to sleep at night, go outdoors, wear contact lenses, drive, or go to work. Tearing and ocular itching may be unbearable, and if untreated, ptosis, watery and mucous discharge, and photophobia could occur and lead to visual disturbances. Additionally, ocular infection is a possible consequence of frequent rubbing of irritated tissues.

Treatment of allergic conjunctivitis must include identification and removal of the offending allergen, but this is often not possible. There are numerous OTC ophthalmic drops available for treatment of ocular allergy symptoms. However, effectiveness may be limited by the frequency of use required (up to 2 drops 4 times daily) and potential side effects. Vasoconstrictor eye drops, for example, are associated with rebound vasodilatation and have warnings to "ask a doctor before use" for consumers with heart disease, high blood pressure, trouble urinating due to an enlarged prostate gland, or narrow angle glaucoma. Some consumers who resort to oral antihistamine therapy may suffer from somnolence, functional impairment, and increased occupational risks for accidents or injuries secondary to sedating effects.

The efficacy of olopatadine 0.7% ophthalmic solution, one drop to affected eye(s) daily, for treatment of ocular itching has been adequately demonstrated in two pivotal trials (C-10-126 and C-12-053), and the safety profile of olopatadine products has been well characterized through clinical trials and postmarketing experience. The most common ocular adverse events (AEs) associated with olopatadine ophthalmic solutions across clinical trials included headache, blurred vision, and dry eye (and other ocular effects commonly associated with dry eye, e.g., abnormal sensation in the eye, pruritus, hyperemia, and ocular discomfort). Hypersensitivity is a known adverse event. Another potentially serious adverse event is corneal damage.

Olopatadine ophthalmic solution has not been studied at doses higher than 0.7% once daily. Therefore, during the review cycle, the question arose as to whether, in the OTC environment where overuse or misuse of drug products by some consumers is anticipated, any adverse events might be seen in a higher frequency or severity if a consumer overuses the drug. Several options were considered to address this concern. The Clinical Reviewer, Dr. Steven

Osborne, recommended approval conditional upon strong labeling to help minimize overuse or misuse, coupled with postmarket safety follow-up. Postmarket safety follow-up would be helpful to ensure that misuse is reported such that FDA can take further action if needed. Revisions to labeling would also be helpful, although it is acknowledged that even if stronger labeling was developed and tested in consumer studies, potential comsumer misuse cannot be completely mitigated. Another option which was considered was to require that the Applicant conduct a safety study at doses higher than 0.7% one drop daily. However, the Division of Ophthalmology (DO; formerly known and Division of Transplant and Ophthalmology; DTOP) recommended approval of this application and contended that, based on the known chemical composition of olopatadine ophthalmic products as well as the results of animal studies, there are no safety concerns regarding overuse. Furthermore, Dr. Charles Ganley, Acting Director of Office of Specialty Medicine, pointed out that there is no known pathophysiologic mechanism to justify any safety concern from overuse.

Based on the known pharmacokinetics of olopatadine ophthalmic products, systemic absorption and resulting systemic adverse events is not a concern. Local, ocular adverse events would presumably would be easily identified by a consumer and result in discontinuing of the medication. The proposed DFL will be helpful in this regard as it includes instructions to "Stop use and ask a doctor if you experience (b) (4): eye pain, changes in vision, increased redness of the eye, itching worsens or lasts more than 72 hours." Ultimately, however, the necessity for labeling changes and subsequent consumer studies, which, as noted above, would not be able to completely mitigate the risk of misuse, should be determined based on the degree of safety concern, which, as emphasized by our ophthalmology colleagues, is minimal. Therefore, approval of this application, with labeling language that, in the absence of required consumer studies, would be reasonably expected to discourage misuse, coupled with assurance of adequate postmarketing safety monitoring, is the best option. It is acceptable in this case that, due to the unique chemical characteristics and safety profile of the product which provide adequate assurance of safety for consumers, safety evaluation of higher than approved OTC doses is not required. However, this approval should not be construed as applicable to other drug products for which safety data at higher doses than OTC doses are still required.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Allergic conjunctivitis symptoms include tearing; redness; itching and burning; vasodilatation; and chemosis. Itchy eyes are a primary symptom. • Recent estimates suggest that 15-25% of the U.S. population, or between 50 and 85 million Americans, suffer from allergic conjunctivitis or some form of ocular allergy (Obrien TP 2013) • Although not life-threatening, profound effect on quality of life (Bielory L 2008). • Can be debilitating; tearing and ocular itching may be unbearable; and if untreated, ptosis, watery and mucous discharge, and photophobia could occur and lead to visual disturbances. • Mild allergic conjunctivitis may present itself as little more than a serious annoyance, but more severe forms of seasonal allergic conjunctivitis may significantly disrupt normal daily activities.	• Relief of eye itchiness due to allergic conjunctivitis is important to consumers for physiologic reasons and for physical comfort. • Relief of symptoms of allergic conjunctivitis improves quality of life for consumers.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Patients may be unable to sleep at night, go outdoors, wear contact lenses, drive, or go to work. • Additionally, ocular infection is a possible consequence of frequent rubbing of irritated tissues. Ocular infections are particularly likely to happen in children. .	
Current Treatment Options	• Should include identification and removal of the offending allergen, if possible. • Various types of topical ocular agents (e.g., antihistamines, mast cell stabilizers, vasoconstrictors, combination products, dual-action agents with mast cell stabilizing and antihistamine properties, nonsteroidal anti-inflammatory drugs and topical steroids) have been prescribed. • Multiple antihistamine and vasoconstrictor eye drop solutions are currently marketed OTC. • Most OTC eye drops require frequent dosing (up to 1-2 drops 4 times daily). • Vasoconstrictors associated with rebound vasodilatation and have warnings to "ask a doctor before use" for consumers with heart disease, high blood pressure, trouble urinating due to an enlarged prostate gland, or narrow angle glaucoma.	Pharmacotherapy has been the mainstay of treatment for conjunctival irritation. Frequency of dosing required and potential adverse events may limit consumer use. Most sufferers self-treat for minor eye irritations, which highlights the importance of OTC treatments for control of some of the symptoms.
Benefit	• Olopatadine is a topical antihistamine with selective H1 receptor antagonist activity and mast cell stabilizing effects. • It has been marketed as an ophthalmic agent to treat symptoms of allergic conjunctivitis in the United States since 2015 (as Pazeo, 0.7%). • Since exposure to an offending allergen may not be avoidable and can occur on a continuous basis, therapy that offers a longer duration of efficacy would offer advantages in symptom control	The effectiveness of the product has been established to treat symptoms related to allergic conjunctivitis. This eye drop product provides an additional choice to consumers who experience such symptoms. This eye drop product has both antihistamine and mast cell stabilizing properties.
Risk and Risk Management	For a risk assessment in this application, the Applicant submitted a ISS for all olopatadine products and postmarket safety data from 2000-2018, supplemented by updates from PSURs, Periodic Adverse Drug Experience Reports (PADERs), and a 120-day safety update. The proposed OTC labeling has the essential warnings translated from the current Pazeo Rx label; additional warnings regarding pregnancy and breastfeeding are not warranted.	Olopatadine hydrochloride has a satisfactory safety profile in the prescription environment based on 23 years of clinical use for all olopatadine products and approximately 4 years for Pazeo in the postmarketing experience in the United States. Adverse events associated with olopatadine hydrochloride and its use as an ophthalmic solution

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Adverse events are predominantly non-serious, however a few, such as hypersensitivity and corneal damage are listed in the Rx full prescribing information . However, an unknown for this application is what will happen if a consumer does not follow the proposed Drug Facts Label and misuses (overuses) the drug. In this instance the potential for adverse events is unstudied since the Applicant has not studied, nor is it aware of any data, in which subjects were exposed to more than one drop in each affected eye per day. The longest duration for use was 6 weeks. This length of time may be adequate for seasonal allergic conjunctivitis, however not for perennial allergic conjunctivitis. Consumers may overuse by daily dose and by length of time of use.	are most commonly identified as headaches and eye symptoms. Safety of olopatadine hydrochloride ophthalmic solution 0.7%, in the prescription environment, is supported by clinical trial data (zero SAEs) and generally by postmarket safety data (26 SAEs over approximately 4 years, none fatal). Warnings provided in the proposed OTC labeling may help mitigate the risk of serious adverse events. Potential misuse of the 0.7% olopatadine eye drops exposes a consumer to a dose of olopatadine that, based on information submitted by the Applicant and in the literature, has not been studied.

2. Background

Alcon Research, LLC (the Applicant), a subsidiary of Novartis until April 9, 2019, submitted this NDA supplement for a full prescription (Rx) to over-the-counter (OTC) switch of olopatadine hydrochloride ophthalmic solution 0.77% (or olopatadine 0.7%) for the indication of temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair and dander in adults and children 2 years of age and older. FDA approved NDA 206276, olopatadine hydrochloride ophthalmic solution 0.77% (or olopatadine 0.7%), with a proprietary name of Pazeo, on January 30, 2015, for use as a prescription drug for the treatment of ocular itching associated with allergic conjunctivitis (AC). The proposed dosing regiment for the OTC switch (One drop in the affected eye(s) once daily, (b) (4) (b) (4)), is the same dosing regimen approved for Rx use.

On February 14, 2020, FDA approved the full switch of olopatadine 0.1% from Rx-to-OTC (sNDA 020688) with the OTC name of Pataday Twice Daily Relief (relief of itching and redness) and olopatadine 0.2% (sNDA 021545) with the OTC name of Pataday Once Daily Relief (no descriptor, relief of itching). In the current submission, the Applicant proposes the OTC name of Pataday Once Daily Relief with the labeling descriptor "Extra Strength" for the olopatadine 0.7% product.

Table 1: Olopatadine Ophthalmic Solutions with Successful or Planned Rx-to-OTC Switches

NDA# / (IND#)	Rx Product	Rx Approval Year / OTC Approval	OTC Names
020688 / (107178)	Patanol (olopatadine 0.1%)	1996 / Feb 14, 2020	Pataday Twice Daily Relief
021545 / (142363)	Pataday (olopatadine 0.2%)	2004 / Feb 14, 2020	Pataday Once Daily Relief
206276 (060991)	Pazeo (olopatadine 0.7%)	2015 / Pending	Pataday Once Daily Relief "Extra Strength" PDUFA July 13, 2020

Electronically copied and reproduced from Dr. Osborne's Clinical Review

As the proposed OTC product is unchanged from the current Rx product, except for the proposed OTC labeling, no new clinical, preclinical, or CMC data were submitted. To support approval for the switch of Pazeo Rx to OTC status, the Applicant intends to rely on FDA's prior finding of safety and efficacy for Pazeo (NDA 206276) and for olopatadine at multiple additional doses and routes of administration via cross reference to the approved NDAs for Pataday Twice Daily Relief (olopatadine 0.1%; NDA 020688, previously

marketed Rx under trade name Patanol), Pataday Once Daily Relief (olopatadine 0.2%; NDA 021545, previously marketed Rx under trade name Pataday), and olopatadine 0.6% nasal spray (currently marked Rx under trde name Patanase).

Olopatadine is a topical antihistamine with selective H1 receptor antagonist activity and mast cell stabilizing effects. It is marketed as an ophthalmic agent for the prevention or treatment of ocular pruritus due to allergic conjunctivitis and as a nasal spray for the relief of the symptoms of seasonal allergic rhinitis (SAR). Olopatadine exhibits two distinct mechanisms of action. It inhibits histamine release from mast cells and is a relatively selective antagonist of H1 receptors. As a result, olopatadine prevents type 1 immediate hypersensitivity reactions. Topical ocular administration relieves the ocular pruritus associated with allergic conjunctivitis. Intranasal administration relieves symptoms associated with SAR.

Disease or Condition

Allergic conjunctivitis (ocular allergy) is a mast-cell mediated hypersensitivity reaction that can be an acute or chronic illness that involves inflammation of the conjunctiva. Symptoms of all forms of ocular allergy include tearing; itching and burning; vasodilatation; and chemosis (Singh et al, 2010). Most recent estimates suggest that 15-25% of the U.S. population, or between 50 and 85 million Americans, suffer from allergic conjunctivitis or some form of ocular allergy.

Ocular allergy includes a spectrum of conditions with overlapping symptomatology and progressive severity. These disorders include seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), atopic keratoconjunctivitis (AKC), and vernal keratoconjunctivitis (VKC). SAC and PAC comprise most of the allergic conjunctivitis cases (about 95% of cases in the United States) and are generally considered to be mild forms of ocular allergy (sparing the cornea). Both SAC and PAC are IgE-mediated events for which mast cell response leads to release of histamine, leukotrienes, prostaglandins, and other mediators (O'Brien TP, 2013). The onset of SAC ("hay fever" conjunctivitis), the most common form of allergic conjunctivitis, coincides with seasonal increases in circulating allergens, such as grass pollens. SAC is not generally considered to be serious or sight-threatening but causes much discomfort and loss of productivity during the spring and fall allergy seasons. Individuals with PAC experience symptoms throughout the year; however, seasonal spikes may occur. In patients with PAC, the allergens are often indoor antigens, such as dust mites, animal dander, and molds. VKC and AKC are considered more serious and may be associated with corneal scarring, neovascularization and ulceration, and other sequelae. Therefore, referral to an ophthalmologist is generally warranted.

Current Treatment Options

According to the American Academy of Ophthalmology (Au et al, 2019)[1], OTC antihistamine/vasoconstrictor agents are recommended as first-line
treatment for allergic conjunctivitis. Many products are available containing antazoline phosphate 0.05%, naphazoline HCl 0.05%, oxymetazoline HCl, tetrahydrozoline HCl 0.05%, or phenylephrine 0.12% as the active ingredient(s). However, chronic use of vasoconstrictive agents can lead to rebound vasodilation. Second-generation topical H-1 receptor antagonists, such as pheniramine maleate 0.3% (Naphcon), emedastine (Emadine), and levocabastine HCl 0.05% (Livostin), are considered more effective than vasoconstrictors, but are more expensive and are recommended as second-line treatment. As third-line agents (for recurrent/persistent symptoms), mast cell stabilizers such as cromolyn sodium 4% (Crolom), nedocromil 2% (Alocril), pemirolast 0.1% (Alamast), and lodoxamide tromethamine 0.1% (Alomide) can be used. The third-line agents are only FDA-approved for VKC and are only to be used if other classes of medications have failed.

Ocular surface lubricants such as isotonic saline, artificial tears, and ointments help to rinse antigens from the eye. However, these agents do not have direct efficacy on allergic mediators. These provide only temporary relief and have little or no effect on moderate-to-severe ocular allergy. They may also contain preservatives and when used excessively, can injure an already irritated ocular surface.

Table 2. Examples of OTC Ophthalmic Drops Treatment Armamentarium for Allergic Conjunctivitis

Product(s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Zatidor NDA 021066	Ocular itching alone	2007 OTC 1999 Rx	Ophthalmic route	Effective relief of itching	Safe and tolerable	ketotifen 0.025% "Temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair and dander"

[1] Au, A. and Grigorian, P. et al; Allergic Conjunctivitis; https://eyewiki.aao.org/Allergic_conjunctivitis; accessed 7/29/2019.

Product(s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Alaway NDA 021996	Ocular itching alone	2007 2007	Ophthalmic route	Effective relief of itching	Safe and tolerable	ketotifen 0.025% Same Use on DFL as Zatidor
Patanol olopatadine HCL 0.1% NDA 020688	Ocular itching alone	1996	Ophthalmic route, twice daily		Safe and tolerable	Approved OTC February 2020 Similar Use to Zatidor
Pataday Olopatadine HCl 0.2% NDA 021545	Ocular itching alone	2008	Ophthalmic route, once daily		Safe and tolerable	Approved OTC February 2020 Similar Use to Zatidor
Other treatments						
Opcon-A NDA 020065	Ocular itching and redness	?	Ophthalmic route			0.02675% naphazoline HCL and 0.315% pheniramine "Temporarily relieves itching and redness caused by pollen, ragweed, grass, animal hair and dander"
Visine A NDA 020485	Ocular itching and redness	?	Ophthalmic route	Effective relief of redness due to minor eye irritations	Safe and tolerable, overuse can lead to rebound redness	0.025% naphazoline HCl and 0.3% pheniramine maleate

Electronically copied and reproduced fro Dr. Osborne's Clinical Review

Regulatory Background

Important aspects of teleconferences and communications with the Applicant that are most relevant to this CDTL Review are summarized below. For additional details, please see Dr. Steven Osborne's Clinical Review (June 17, 2020).

Three teleconferences were held for sNDA 206276. Key aspects of the teleconferences were as follows:

Teleconference on April 3, 2019 Under PIND 142363 (sNDA 021545; Olopatadine 0.2%)

- FDA inquired as to why the Applicant proposed to switch only olopatadine 0.1% and 0.2%, and not 0.7%. The Applicant explained that it had only considered switching the olopatadine 0.1% and 0.2% from Rx-to-OTC status and that for business reasons it had not aimed to switch olopatadine 0.7%.
- FDA noted that the distinctions in the indications between olopatadine 0.1%, 0.2%, and 0.7% are based on the frequency of dosing (twice daily versus once daily) and not on concentration. The twice daily dosing is indicated for itching and redness, while the once daily dosing is only indicated for itching. FDA explained that the data submitted in the NDAs for olopatadine 0.1%, 0.2%, and 0.7% demonstrated effectiveness for both itching and redness if the products were dosed twice daily; however, the Applicant chose to retain the once daily dosing for olopatadine 0.2% and 0.7%. The indication of redness relief was not supported with once daily dosing for any of the concentrations. FDA stated that the Applicant will need to address the differences in indications of its products in its submissions.
- At the time of the teleconference, the Applicant proposed the names Pataday Once Daily Relief (0.2%) and Pataday Twice Daily Relief (0.1%). The Applicant stated that it would like to market both olopatadine 0.1% and 0.2% under the same name, Pataday, if approved for OTC. FDA expressed concern that consumers may not be able to differentiate between the two olopatadine products, especially since both products share similar indications. FDA stated that a Label Discernment Study might be necessary "to establish that consumers can properly differentiate between products in terms of indications and directions for use." FDA encouraged the Applicant to mirror existing labeling for other OTC eye drops of the same indication as closely as possible, in both content and placement, in proposed labeling upon submission of the marketing application, "to reduce the need for consumer behavior testing." However, FDA also stated that, "ultimately, the labeling needs to be supported by the safety and efficacy findings of your product."

CDTL Comment: In his Clinical Review of the current application, Dr. Steven Osborne observes that in section 1.6.3 of its submission of sNDA 206276, the Applicant states that it met with FDA (teleconference) on April 3, 2019 in a Type B-Pre-sNDA meeting regarding the Rx-to-OTC switch of Pazeo. However, in that meeting, although FDA recommended Alcon consider switching Pazeo (0.7%), in addition to Patanol (0.1%) and Pataday (0.2%), Alcon stated that Novartis had not granted the Pazeo switch rights, so

Alcon did not submit the Pazeo sNDA. Therefore, the April 3, 2019 meeting was held as a pre-NDA meeting for the 0.1% and 0.2% olopatadine hydrochloride ophthalmic products, not for a switch of Pazeo. FDA and the Applicant did not hold a pre-NDA meeting for Pazeo before the Applicant submitted a switch application on September 13, 2019.

Teleconference on September 10, 2019 Under PIND 060991 (sNDA 206276, Olopatadine Hydrochloride 0.7%)

- Alcon stated that Novartis had now granted switch rights, so Alcon now plans to submit a sNDA for the Rx to OTC switch of Pazeo on September 16, 2019.
- Alcon stated the data they will submit are identical to those submitted for the Rx to OTC switch of Patanol and Pataday. They stated that the only differences between the supplement for Pazeo and the other olopatadine supplements currently under review will be labeling and a request for the proprietary name, (b) (4) as the OTC version for Rx Pazeo.
- Alcon stated that they may submit a request for a different proprietary name for olopatadine 0.2%, initially approved as Pataday Once Daily Relief, namely, (b) (4) which should help consumers distinguish the olopatadine 0.7% from the 0.2% products. FDA did not comment on the acceptability of the proposed proprietary names.
- FDA agreed that no additional Chemistry Manufacturing and Controls (CMC) or nonclinical safety studies need to be conducted to support the approval of a Rx-to-OTC switch of Pazeo. FDA would rely on the findings of safety of the nonclinical program that were reviewed and approved under the original NDA submission for the Rx Pazeo NDA 206276.

Teleconference November 13, 2019 Under sNDA 206276

- The Applicant's label discernment study was conducted with names of the three products that are not names that FDA is comfortable with; namely, (b) (4), (b) (4), and (b) (4). (b) (4) (olopatadine 0,2%, one drop each eye once daily). This presents an issue with FDA's precedent of not allowing a specific number of hours of relief except possibly 24 hours for a once daily drug. In addition, consumers might dose (b) (4) (b) (4). The Applicant agreed to reconsider the names of the three olopatadine ophthalmic products.

Letter From DTOP to Alcon on May 9, 2019 Asking Whether Pazeo Has Any Safety Issues That Could Preclude It From Being OTC

"We have reviewed the referenced material and request that you identify whether Pazeo has any toxicity or other potentiality for harmful effect, method of use, or collateral measures necessary for its use that would make Pazeo not safe for use without the supervision of a practitioner licensed by law to administer the product."

Letter From Alcon to FDA DTOP Submitted on July 19, 2019

The Applicant submitted a response to the Advice Letter from DTOP on May 9, 2019. Novartis stated that it "considers Pazeo to be safe when used under the supervision of a healthcare professional and has no intention to switch Pazeo to nonprescription status at this time."

sNDA 206276 Submitted on September 13, 2019

The Applicant submitted sNDA 206276 requesting the Rx-to-OTC full switch of Pazeo and the proprietary name of (b) (4) (b) (4)

Information Request Sent to Applicant on October 8, 2019 Requesting the Following Information (Summarized)

- Now that there could be a third over-the-counter (OTC) olopatadine HCl ophthalmic solution (0.7%) drug for ocular itching due to allergic conjunctivitis, the potential for confusion with consumers is heightened.
- Provide any data that you have showing how consumers will effectively distinguish the three products with similar indications, directions for use and potentially similar names.

Amendment to sNDA 206276 Submitted on October 22, 2019 (SDN 467)

The Applicant submitted a Clinical Information Amendment to address the Information Request of October 8, 2019 (summarized):

- The Applicant noted it had conducted a pre-test for a "label discernment study." A summary of the study was submitted and according to the Applicant's analysis, results were generally supportive of the proposed OTC labeling for Twice Daily Relief (Patanol), (b) (4), and (b) (4), and supportive of the ability of consumers to distinguish between the three olopatadine eye drop products for proposed OTC use.

Amendment to sNDA 206276 Submitted on November 4, 2019 (SDN 470)

The Applicant submitted a Clinical Information Amendment to address the Information Request sent on October 29, 2019 (SDN 470) requesting the following (summarized):

- Clarify why the Applicant performed a pre-test for a label discernment study (LDS) rather than a pivotal study. FDA also asked for the complete study details for the pre-test LDS, including the complete data collection instrument (coding of responses, screening questions, cross-tabulations, and electronic dataset).

- The Applicant provided details, which will be discussed by the DNPD 2 social scientist, Ms. Barbara Cohen, in her review. The Applicant noted it is now conducting a pivotal LDS, termed a "Project Judo ACE Discernment Study" in male and female subjects 15 years of age and older, with a final report available on December 20, 2019. The goal is to assess whether subjects can discern the indication and dosing directions for the 0.1%, 0.2%, and 0.7% solutions with names/products (b) (4), (b) (4) and (b) (4)

FDA Filed the sNDA 206276 Application for Review on November 21, 2019

FDA filed the sNDA 206276 application with no filing issues identified. However, FDA sent the following Information Request to facilitate the application review in correspondence to the Applicant:

- "Submit any clinical data you are aware of in which olopatadine HCl ophthalmic solution 0.7% is dosed more than one drop in each affected eye(s) per day. These data, if available, could help address safety for any overuse or misuse by a consumer. Provide this information by December 20, 2019."
- We note your plan to submit the final report of the pivotal Label Discernment Study, called "Project Judo" on December 20, 2019. Clarify the product names you are using in this pivotal consumer behavior study, that is, have any product names been modified in your Label Discernment Study since your submission dated November 4, 2019"?

Withdrawal of Proprietary Name Request (SDN 472)

- On November 22, 2019, the Applicant withdrew their name request of (b) (4)" and planned to formally submit a new request for Pataday Once Daily Relief with the descriptor "Extra Strength."

Amendment to sNDA 206276 Submitted on November 25, 2019 (SDN 473)

Submission of new proprietary name request:

- On November 25, 2019, the Applicant submitted a name request of "Pataday Once Daily Relief" with a descriptor of "Extra Strength."Amendment to sNDA 206276 Submitted on November 25, 2019 (SDN 473)

- On November 14, 2019, Alcon accepted the new names proposed by the Agency. Alcon then formally submitted the proposed proprietary names for review on November 25, 2019. Pataday Twice Daily Relief (itching relief and redness relief) remained the same. Subsequently, the proposed product names for the 0.2%, and 0.7% respectively, were adjusted to Pataday Once Daily Relief and Pataday Once Daily Relief (with labeling descriptor Extra Strength).

Amendment to sNDA Submitted December 4, 2019 (SDN 476)

The Applicant submitted a Clinical Information Amendment to address the Information Request sent on November 22, 2019 requesting the following (summarized):

- Clarify whether the Applicant studied or is aware of data for a dose of Pazeo greater than one drop per eye per day. Specifically: "Submit any clinical data you are aware of in which olopatadine HCl ophthalmic solution 0.7% is dosed more than one drop in each affected eye(s) per day. These data, if available, could help address safety for any overuse or misuse by a consumer. Provide this information by December 20, 2019."
- Clarify the names used in the "Project Judo ACE Discernment Study" versus any updated names the Applicant will use for marketing if the sNDAs for Patanol, Pataday, or Pazeo are approved.
- The Applicant replied that "Alcon has never generated nor are we aware of any clinical data in which olopatadine HCl ophthalmic solution 0.7% was dosed more than one drop in each affected eye(s) per day. That said, we note that the established safety profiles of Patanol, Pataday, and Pazeo are very similar and post-market data continue to support positive benefit/risk for the three products. The majority of adverse events reported for these products are ocular in nature, easily detectable by the patient, and non-serious."
- Alcon then provided further discussions of preclinical and post-market safety data, noting 10 reports of incorrect dose administered or inappropriate schedule of product administration, however, with only one SAE.
- Regarding preclinical safety data, Alcon stated, "Likewise, olopatadine demonstrated no significant ocular effects following chronic topical administration to the eyes of rabbits and monkeys delivered 4 times a day at concentration up to 1.0% and 0.5%, respectively (Patanol NDA 020688), and, there were no observed adverse effect levels for rats and dogs after chronic oral administration of olopatadine were 10 and 5 mg/kg/day, respectively. This is approximately 2000-fold greater than the predicted human exposure. (Patanol NDA 020688)."
- Regarding Post-Market Safety Data, Alcon stated, "The post-market safety data for Pazeo was reviewed for cases associated with the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms of 'Incorrect dose administered' and 'Inappropriate

schedule of product administration,' cumulative to October 31, 2019. A total of 10 cases were found, 6 of which were associated with other AEs. The other AEs reported among these cases were 2 reports each of eye pain and drug ineffective and one report each of back pain, cataract, concomitant disease aggravated, dry eye, erythema, seasonal allergy, tremor, and vision blurred. Only one serious event was reported (cataract). The narrative for this case is presented below. Overall, the low number of cases in the safety database do not suggest a pattern of dosing of Pazeo more than the labeled posology. In addition, all but one of the adverse events reported in these cases are nonserious and demonstrate no link to any safety issue when considering the very low number of associated adverse events reported."

- Alcon then summarized: "In summary, if a patient were to dose Pazeo twice daily (worst case scenario among the 3 products), the systemic exposure due to accumulation would not be expected to be markedly higher than on-label dosing as the mean elimination half-life is 3.4 hours. In addition, pre-clinical toxicology demonstrates an adequate margin of safety at exaggerated dosing. Though local ocular adverse events may be more frequent with twice daily dosing of Pazeo, as mentioned above, these events are easily detectable by the patient and non-serious in nature."

Amendment to sNDA 206276 Submitted on December 20, 2019 (SDN 478)

The Applicant submitted a Clinical Information Amendment to address the Information Request sent on December 16, 2019 requesting the following (summarized):

- Submit the actual data from the pivotal Label Discernment Study, even though it was completed using the withdrawn proposed proprietary names of Pataday Twice Daily Relief (0.1%), (b) (4) (0.2%), and (b) (4) (0.7%).
- The Applicant submitted the labeling discernment pivotal study report and the table below comparing the names it used in this study versus the new Agency-proposed proprietary names.

Table 3: Agency Proposed Proprietary Names of Olopatadine Ophthalmic Solutions Used in Applicant's Label Discernment Study

Label Discernment Pivotal Study Proprietary Names: • The PN review request was withdrawn on 22-Nov-2019, SN # 0048	**Agency Proposed Proprietary Names** • Alcon accepted Agency's proposal for PN on 14-Nov-2019, with subsequent amendment on 25-Nov-2019, SN# 0049
Pataday Twice Daily Relief (0.1%)	**Pataday Twice Daily Relief** (0.1%)
(b) (4) 0.2%)	**Pataday Once Daily Relief** (0.2%)
0.7%)	**Pataday Once Daily Relief** with labeling descriptor **Extra Strength** (0.7%)

Electronically copied and reproduced from Dr. Osborne's Clinical Review; Source: Applicant's submission of December 20, 2019
Abbreviations: PN, proprietary names

3. Product Quality

Chemistry, Manufacturing and Controls (CMC) review was conducted by Ping Jiang-Baucom, PhD, and Ramash Raghavachari, PhD of the Office of Pharmaceutical Quality (OPQ). Dr. Jiang-Baucom and Ragavachari concluded that, "From CMC perspective, this supplement is recommended for Approval."

The Applicant is relying on FDA's previous findings under NDA 206276 (Pazeo 0.7%) regarding CMC. The Applicant states that the over the counter (OTC) product will have the same strength, dose, duration of use, dosage form, population and route of administration as the approved prescription (Rx) NDA product. There is no drug substance or drug product changes from the current NDA. As the proposed OTC product is unchanged from the current Rx product, except for the proposed OTC labeling, no new clinical, preclinical or CMC data were submitted.

The Applicant states that pursuant to 21 CFR 25.31(a), Alcon Inc., hereby claims a categorical exclusion from the requirement of preparing an Environmental Assessment for the sNDA for Pazeo, Rx to OTC switch product. Alcon Inc. meets the requirements of 21 CFR 25.31 (a) because the Application does not increase the use of the active moiety. Pazeo (olopatadine ophthalmic solution) 0.7% Rx product is currently marketed in the US. Consequently, switching the product from Rx to OTC, will not increase the use of the active moiety. Therefore, the CMC team concluded that the Applicant's claim for categorical exclusion from the requirement of preparing an Environmental Assessment for the sNDA for Pazeo, Rx-to-OTC switch is acceptable.

Each mL of Pazeo solution contains an active ingredient [7.76 mg of olopatadine hydrochloride (7 mg olopatadine)] and the following inactive ingredients: povidone; hydroxypropyl-gamma-cyclodextrin; polyethylene glycol 400; (b) (4); boric acid; mannitol; benzalkonium chloride 0.015% (preservative); hydrochloric acid/sodium hydroxide (to adjust pH); and purified water. Pazeo solution has a pH of approximately 7.2 and an osmolality of approximately 300 mOsm/kg.

CDTL Comment: The inactive ingredient, benzalkonium chlroride, used as a preservative, is a known portential eye irritant and can be absorbed by soft contact lenses. In his Clinical Review, Dr. Osborne noted that at the mid-cycle meeting on Febreary 12, 2020, Dr. William Boyd of Division of Transplant and Ophthalmology (DTOP) stated that BZK is used in higher total exposure in other ophthalmic drops and that even if a consumer used extra Pazeo or combined it with other olopatadine eyedrops concurrently or simultaneously, it would be unlikely to lead to a SAE due to the BZK component itself.

4. Nonclinical Pharmacology/Toxicology

To support the nonclinical safety of olopatadine, the Applicant is relying on FDA's previous findings of nonclinical safety from the original NDA applications (**NDA 206288** Patanol and **NDA 21545** Pataday) for prescription use. The Applicant did not conduct nonclinical safety studies for the Rx approval of Pazeo.Therefore, no new nonclinical safety data were submitted.

5. Clinical Pharmacology

The Applicant refers to the data presented in the Rx full prescribing information and notes that:

- The mean elimination half-life of olopatadine in humans is approximately 8–12 hours.
- Olopatadine does not appear to have a significant potential for drug - drug interactions.
- Interactions involving cytochrome P-450 enzymes do not appear likely.
- Toxicokinetic studies demonstrated a satisfactory margin of safety for olopatadine. Plasma levels of olopatadine in oral toxicokinetic studies at the no-observed effect levels were 2- to 3- orders of magnitude higher than plasma levels found following topical ocular administration of 0.15% olopatadine ophthalmic solution in clinical studies
- No adjustment of Pazeo is warranted in elderly subjects, or subjects with renal or hepatic impairment

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The proposed olopatadine product will have the same strength, dose, duration of use, dosage form, indication, and route to administration as the approved prescription (Rx) product. Therefore, the Applicant relies on the previous clinical trials conducted for NDA approval of the Rx product to support the efficacy of olopatadine for OTC use. Briefly, as shown in the table below, a total of five studies were conducted for Rx approval with 1125 subjects, ages 2-65. Of these 1125 subjects, 428 received olopatadine 0.7%, including 330 subjects age 2 and older who received olopatadine 0.7%, one drop in each eye daily for 6 weeks, the maximum dose and duration of use studies in the clinical trials.

Table 4: Safety and Efficacy Studies in Patients with Allergic Conjunctivitis for Rx Approval of Pazeo in 2015

Study Number	Design	Ages	Arms	Number of Subjects	Dosing	Duration
C-10-127 Phase 1 Safety and comfort	Randomized, double-masked, crossover, active- and vehicle-controlled study	≥18 years	Olopatadine HCl, 0.7% Vehicle Zaditor	43	1 drop per eye	Single dose
C-11-036 Phase 1 Safety and PK	Randomized, double-masked, parallel-group, vehicle-controlled study	18 to 65 years	Olopatadine HCl, 0.7% Vehicle	24 12	1 drop per eye once daily	7 days
C-10-126 Phase 3 Efficacy CAC	Randomized, double-masked, parallel-group, active- and vehicle-controlled study	≥18 years	Olopatadine HCl, 0.7% Olopatadine HCl, 0.2% Vehicle	66 68 68	1 drop per eye	3 non-consecutive doses over 3 weeks
C-12-053 Phase 3 Efficacy CAC	Randomized, double-masked, parallel-group, active- and vehicle-controlled study	≥18 years	Olopatadine HCl, 0.7% Olopatadine HCl, 0.2% Olopatadine HCl, 0.1% Vehicle	98 99 99 49	1 drop per eye	2 non-consecutive doses over 2 weeks
C-12-028 Phase 3 Safety	Randomized, double-masked, parallel-group, vehicle-controlled study	≥2 years	Olopatadine HCl, 0.7% Vehicle	330 169	1 drop per eye once daily	6 weeks

Source: Dr. Chambers' 2015 NDA 206276 review for Rx olopatadine 0.7%, p.13
Abbreviations: CAC, Conjunctival Allergen Challenge; PK, pharmacokinetics

The pivotal efficacy studies for the 2015 approval of Pazeo, Studies C-10-126 and C-12-053, were controlled trials that used the validated Conjunctival Allergen Challenge (CAC) model and evaluated the efficacy endpoints of relief of itching and redness. Ocular itching was a patient reported outcome on a scale of 0-4 (none to severe), and redness was a clinically observed outcome.

In the Division of Transplant and Ophthalmology (DTOP) Clinical Review for approval or the Rx product (September 15, 2014), Dr. Wiley Chambers wrote (page 26/41), that, regarding Study C-10-126, "Efficacy over vehicle for itching has been demonstrated 30 minutes after administration and continued for a duration of at least 24 hours after administration. The effectiveness of Olopatadine 0.7% is relatively similar to Olopatadine 0.2% (Pataday) at the onset of action, but slightly more evident at 24 hours." Regarding Study C-12-053, Dr. Chambers wrote (Page 27/41), "Efficacy over vehicle for itching has been demonstrated 30 minutes after administration and continued for a duration of at least 24 hours after administration. The effectiveness of Olopatadine 0.7% is relatively similar to Olopatadine 0.2% (Pataday) and Olopatadine 0.1% (Patanol) at the onset of action, but slightly more evident at 24

hours." Regarding redness, Dr. Chambers noted that, for Study C-10-126 (page 28/41), "Olopatadine 0.7% demonstrated efficacy for redness at the onset of action. The duration of action, while not having been established, is less that 16 hours." Dr. Chambers noted that the results were not consistent with Study 12-053. Regarding Study 12-053, he wrote (page 29/41), "Olopatadine 0.7% did not demonstrate efficacy for redness in this trial."

For the Rx-to-OTC switch of the olopatadine products, A clinical review was conducted by William Boyd, M.D., of the Division of Ophthalmology. Dr. Boyd addressed the efficacy and safety of all three olopatadine ophthalmic products [**sNDA 20688** Patanol (olopatadine hydrochloride ophthalmic solution) 0.1%; **sNDA 21545** Pataday (olopatadine hydrochloride ophthalmic solution 0.2%); and **sNDA 206276** Pazeo (olopatadine hydrochloride ophthalmic solution) 0.7%] in a single review (January 11, 2020). Dr. Boyd wrote that "NDA 20688 contains adequate and well controlled studies that support the safety and efficacy of olopatadine hydrochloride ophthalmic solution, 0.1% for the treatment of redness and itching when administered two times per day." In addition, Dr. Boyd wrote that, both **NDA 21545** (Pataday) and **NDA 206276** (Pazeo) contain adequate and well controlled studies that support the safety and efficacy of the two products "for the treatment of itching when administered once or twice a day and for the treatment of itching and redness when administered twice a day." Dr. Boyd concluded, "The Division of Ophthalmology recommends approval of these three supplemental applications for an OTC switch."

CDTL Comment: In my CDTL Review for NDA 20688 and 21545 (February 13, 2020), I agreed with Dr. Boyd's assessment that the clinical trials were adequate and support the efficacy and safety of the olopatadine 0.1%, 0.2%, and 0.7% products when used once or twice daily. However, my assessment was based on the information available to me at that time as it pertained to the 0.1% and 0.2%, as the suitability of the 0.7% product for Rx-to-OTC switch was not the subject of my CDTL Review. In assessment of the current application (NDA 206276 Pazeo), it is apparent that there is no clincal data assessing the safety or efficacy of olopatadine 0.7% when administered more than one drop to each eye once daily. It is, of course, unlikely that efficacy of olopatadine 0.7% when given more than once daily be negatively impacted. Furthermore, based on statements from DTOP indicating that the three products are very similar regarding efficacy, it is unlikely that higher doses would result in a positive dose response.

At present, the 0.1 % and 0.2% products have already been approved for OTC use and are not the subject of this CDTL Review. Nevertheless, it is important to note that in the clinical trials, the Ophthalmology team has confirmed that efficacy for the redness and itching indications was demonstrated for both products when used twice daily. However, when used once daily, only the itching indication demonstrated persistence of effect for the entire treatment period. Therefore, once daily administration of any of these products is only indicated for relief of itching and not redness. The suggestion from the clinical trials that the 0.7% product may have a longer duration of efficacy for itching compared to to the 0.2% product, even though both are administered once daily, formed the basis for the Applicant's initial proposed proprietary names (b) (4) *versus* (b) (4).

*Regarding safety (see also **Section 8** below), it is noted that the clinical trials evaluated doses up to olopatadine 0.7% (7 mg/ml) once daily. Thus, if the 0.2% product (~2 mg/ml) were administered twice daily, the dose would still not exceed the maximum dose assessed for safety in the clinical trials. However, if the 0.7% product were administered twice daily or used in conjunction with the 0.1% or 0.2% product (for example, if a consumer thought to use the 0.1% product for its redness indication and the 0.7% product for its itching indication), then the maximum dose assessed for safety in the clinical trials would be exceeded. Importantly, and as discussed in **Section 8** below, there is no safety data available for use of olopatadine 0.7% more than one drop to each eye once daily.*

8. Safety

Clinical Review of the safety of olopatadine 0.7% was conducted by Steven Osborne, MD, Division of Nonprescription Drugs II, Office of Nonprescription Drugs (DNPD II, ONPD). Dr. Osborne recommended approval of this NDA: conditional upon strong labeling to help minimize overuse or misuse, coupled with postmarket safety follow-up.

Dr. Osborne noted that over ten thousand patients, accounting for (b) (4) patient-months, have been exposed to olopatadine in clinical trials and postmarketing as of December 31, 2018 (NDA 020688/S-032, Module 5, ISS). Ophthalmic formulations of olopatadine are available in 129 countries, including OTC in five countries for the lower strengths; however, there is no overseas OTC marketing for olopatadine 0.7%.

Summary of Safety from Clinical Trials

No new clinical trials were conducted in support of this application. As noted in **Section 7** above, the Applicant relies on the previous clinical trials conducted for NDA approval of the Rx product to support the efficacy of olopatadine for OTC use. The clinical trials are summarized in the table below:

Table 5: Summary of Completed Clinical Trials with Each Olopatadine Product (includes Intranasal Spray, Patanase 0.6% Olopatadine)

Formulation	Phase I	Phase II	Phase III	Phase IV	Total
Eye drops, solution	12	6	42	10	70
Intranasal Spray	7	8	9	1	25
Oral solution	3	0	0	0	3
Total	**22**	**14**	**51**	**11**	**98**

Electronically copied and reproduced from Dr. Osborne's Clinical Review; Source: Applicant's ISS p.12 of 66 for sNDA 020688 and sNDA 021545 (Patanol and Pataday switches)

CDTL Comment: In his Clinical Review, Dr. Osborne pointed out (page 37/77), "Although over 10,000 subjects have been exposed to olopatadine in clinical trials, only 428 subjects were exposed to olopatadine 0.7%. It is not clear that a total of 428 subjects exposed to olopatadine, of which 330 were exposed to olopatadine 0.7% for 6 weeks, is enough to infer that the drug will be safe for an OTC population of potentially millions of consumers. This is a valid concern.

There were no deaths reported in the clinical trials. No SAEs were reported in clinical trials for the 428 subjects exposed to Pazeo.

Although Dr. Osborne's review focused on postmarketing safety, Dr. Osborne observed that some mention of safety issues in the prescription labeling is warranted. Specifically, Dr. Osborne noted that prescription labeling of Pazeo states the following:

> *In a randomized, double-masked, vehicle-controlled trial, patients at risk for developing allergic conjunctivitis received one drop of either Pazeo (N=330) or vehicle (N=169) in both eyes for 6 weeks. The mean age of the population was 32 years (range 2 to 74 years). Thirty-five percent were male. Fifty-three percent had brown iris color and 23% had blue iris color. The most commonly reported adverse reactions occurred in 2-5% of patients treated with either Pazeo or vehicle. These events were blurred vision, dry eye, superficial punctate keratitis, dysgeusia, and abnormal sensation in eye.*

CDTL Comment: Dr. Osborne noted that some of these adverse events are symptoms found in the underlying disease being studies, allergic conjunctivitis, and I agree.

Postmarketing Exposure

Estimated postmarketing exposure in patient-months, based on sales data across all formulations (0.1%, 0.2%, 0.7%, and 0.6% nasal) from May 1, 2012 through April 30, 2018, is shown in the table below:

Table 6: Estimated Postmarketing Exposure

Olopatadine Formulation	Units Sold	Estimated Exposure*	Units Sold	Estimated Exposure*	Units Sold	Estimated Exposure*
Eye drops	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
IN spray						
Total						

Source: Applicant's ISS p.14 of 66 for sNDA 020688 and sNDA 021545 (Patanol and Pataday switches)
This table includes cumulative and interval exposure data obtained from Novartis Pharma (Jan 2000 to Apr 2018), Sandoz (Oct 2006 to Apr 2018).
* Estimated exposure = number of patient months, with each Unit Sold intended for use over 1 month
Abbreviations: IN, intranasal

Electronically copied and reproduced from Dr. Osborne's Clinical Review.

The estimated sales of all olopatadine ophthalmic products (0.1%, 0.2%, 0.7%) through December 2018 are shown in the table below:

Table 7: Estimated Postmarketing Exposure by Olopatadine Ophthalmic Solution (Eye Drops) Brands Through December 31, 2018

Brand	Cumulative Sales
Patanol (olopatadine 0.1%)	(b) (4)
Pataday (olopatadine 0.2%)	
Pazeo (olopatadine 0.7%)	
Total	

Source: Applicant's ISS for sNDA 020688 and sNDA 021545 (Patanol and Pataday switches)

Electronically copied and reproduced from Dr. Osborne's Clinical Review.

Risks Identified in Applicant's Benefit/Risk Conclusions

The Applicant provided the summarized risks below; this mirrors information submitted previously in the Applicant's Safety Reports. The noted categories correspond to those used in the CCDS.

Important identified risks: Hypersensitivity.

Neither Prescription Labeling nor the proposed Drug Facts Label (DFL) for Pazeo mention a risk of hypersensitivity. However, hypersensitivity and eyelid edema are listed as adverse events in the Rx label for olopatadine 0.1% and 0.2% eye drops. Apparrently, hypersensitivity or eyelid edema were not observed in clinical trials involving 428 subjects exposed to olopatadine 0.7%. Note that exposure to benzalkonium chloride, a preservative in Pazeo solution, has been associated with allergic contact sensitivity (Fisher et al, 1972; Sarkar et al, 2012) and corneal neurotoxicity and inflammation. It is also important to note that reports of hypersensitivity reactions may be confounded by the underlying condition for which the patient was receiving olopatadine eye drops.

Important potential risks: Corneal damage

Corneal disorders, keratitis, and punctate keratitis are listed adverse events as per the current CCDS for olopatadine eye drops, whether 0.1%, 0.2%, or 0.7%. Only a few serious cases of corneal disorders have been reported through Post-Marketing Surveillance. Dr. Osborne noted that, upon review of cases, a causal relationship is difficult to establish due to different confounders such as the allergic disease itself. Corneal events due to use of preservatives (e.g. benzalkonium chloride) rarely result in hospitalization.

However, cytotoxic effects induced by the anti-allergic eye drop products may not be exclusively due to the preservatives, with an increased toxicity having been observed in vitro when BAK was accompanied with ketotifen or olopatadine than with BAK vehicle alone (Guzman-Aranguez et al, 2014).

The corneal disorders of keratitis and punctate keratitis are potential adverse events per the current CCDS for olopatadine 0.1% and 0.2% eye drops, but not for 0.7% eye drops. Since olopatadine 0.7% eye drops solution contains the same preservative in similar concentration as the other ophthalmic formulations of olopatadine, the Applicant states they are monitoring this risk for olopatadine 0.7% eye drops.

Other Less-Serious Warnings or Nonserious Adverse Events

The FDA-approved product labeling for Pazeo includes Warnings and Precautions regarding topical use only, contamination of tip and solution, and contact lens use. In clinical trials, most commonly reported adverse reactions occurred in 2% to 5% of patients treated with either Pazeo or vehicle. These events were blurred vision, dry eye, superficial punctate keratitis, dysgeusia, and abnormal sensation in eye.

Postmarketing Safety Data

The postmarketing safety data submitted by the Applicant encompassed all three products (olopatadine 0.1%, 0.2%, and 0.7%). The Integrated Summary of Safety (ISS) for the three applications was identical and consisted of postmarketing data from the following sources, which was reviewed by Dr. Osborne:

- Alcon's / Novartis' pharmacovigilance database, "Argus"
- FAERS
- WHO International Drug Monitoring Program
- NPDS from American Association of Poison Control Centers (AAPCC)
- Literature Review
- FDA requested the Applicant also provide the following information:
    - List of countries where olopatadine is marketed either as an Rx or OTC product; including certified English translations of foreign nonprescription labels
    - Whether olopatadine has been withdrawn from any foreign markets due to safety or regulatory reasons
    - Worldwide distribution data for both prescription and nonprescription use

Dr. Osborne correctly noted that there are limitations of post-marketing adverse drug event reporting since repost are submitted voluntarily and the magnitude of underreporting is unknown. In addition, the total numbers for AE reports for any one product between databases also vary as do the respective dates included in queries. The raw numbers of reports or cases also vary widely. Detailed comparisons between databases are not appropriate, although general impressions of safety findings are similar. Furthermore, in this application the Applicant refers to the safety data submitted in NDA 020688 (olopatadine 0.1%) and NDA 021545 (olopatadine 0.2%) for all olopatadine ophthalmic solution drug products (0.1%, 0.2%, and 0.7%). In some instances, the data in sNDA 020688 and sNDA 021545 are lumped together with sNDA 206276, when it is not clear which adverse event reported relates to which strength. In other areas, the Applicant has been able to separate AEs for Pazeo only. In particular, the Applicant's ISS and Benefit-Risk assessment are identical for all three sNDAs.

Alcon/Novartis' Pharmacovigilance Database, Argus (January 1, 2019 to October 31, 2019):

The Applicant stratified its submitted postmarket data by marketing status, year of reporting, and duration of use, as shown in the tables below. Note that Pazeo has not been marketed OTC. In his Clinical Review, Dr. Osborne noted that it is unclear if 58 postmarket adverse events (AEs) reported from OTC marketing in six countries for Pataday plus Patanol will be indicative of

anticipated AEs for OTC use of the Pazeo product, and the United States OTC market could be multiples of any of the six countries (Italy, Myanmar, Namibia, South Africa, Hong Kong,and Zimbabwe) and Pazeo is 3.5-7 times stronger than Pataday and Patanol, respectively. Dr. Osborne also observed that most nonserious AEs with Pazeo (742 of 763 total AEs) are reported in the first 1-7 days of use. The Applicant's data do not show when 19 of the 21 SAEs with Pazeo occurred (e.g. first 7 days of use or sometime during marketing from 2015 to 2018).

Table 8: Frequency of Postmarket AEs for Olopatadine-Containing Products, Stratified by Marketing Status Through December 21, 2018 - Data From Applicant's Internal Database (Argus)

	Market Status		
Dosage Strength	**Prescription**	**OTC**	**Total**
Patanol (olopatadine 0.1%)*, n			
Serious adverse events	154	6	160
Non-serious adverse events	3864	48	3,912
Total adverse events (serious + non-serious)	4018	54	4,072
Pataday (olopatadine 0.2%), n			
Serious adverse events	55	0	55
Non-serious adverse events	1991	4	1,995
Total adverse events (serious + non-serious)	2046	4	2,050
Patanase (olopatadine 0.6%), n			
Serious adverse events	30	0	30
Non-serious adverse events	672	0	672
Total adverse events (serious + non-serious)	702	0	702
Pazeo (olopatadine 0.7%), n			
Serious adverse events	21	0	21
Non-serious adverse events	742	0	742
Total adverse events (serious + non-serious)	763	0	763

Source: Applicant's ISS p. 26 of 66 for sNDA 020688 and sNDA 021545 (Patanol and Pataday switch)
* Includes generic olopatadine 0.1%
Patanase (olopatadine 0.6%) is a nasal product and not a subject of this review. It appears in the table to inform about olopatadine in general
MedDRA Version 21.1
Abbreviation: AE, adverse event; n, number of adverse events; OTC, over-the-counter

Electronically copied and reproduced from Dr. Osborne's Clinical Review

Table 9: Frequency of Postmarket AEs for Olopatadine-Containing Products, Stratified by Year of Reporting Through December 21, 2018 - Data From Applicant's Internal Database (Argus)

Dosage Strength	Year of Reporting					
AEs	1996-2000	2001-2005	2006-2010	2011-2015	2016-2018	Total
Patanol, n						
SAEs	2	7	31	65	55	160
Non-SAEs	453	846	961	893	759	3912
Total AEs*	455	853	992	958	814	4072
Pataday, n						
SAEs	0	0	2	18	35	55
Non-SAEs	0	0	389	1164	442	1995
Total AEs*	0	0	391	1182	477	2050
Patanase, n						
SAEs	0	0	11	18	1	30
Non-SAEs	0	0	252	398	22	672
Total AEs*	0	0	263	416	23	702
Pazeo, n						
SAEs	0	0	0	0	21	21
Non-SAEs	0	0	0	110	632	742
Total AEs*	0	0	0	110	653	763

Source: Applicant's ISS p. 30 of 66 for sNDA 020688 and sNDA 021545 (Patanol and Pataday switch)
Patanol (olopatadine 0.1%), includes generic olopatadine 0.1%
Pataday (olopatadine 0.2%)
Patanase (olopatadine 0.6%)
Pazeo (olopatadine 0.7%)
MedDRA Version 21.1
* Total AEs = serious AEs + non-serious AEs
Abbreviations: AE, adverse event; n, number of adverse events, SAE, serious adverse event

Electronically copied and reproduced from Dr. Osborne's Clinical Review

Table 10: Frequency of Postmarket AEs for Olopatadine-Containing Products, Stratified by Duration of Use Through December 21, 2018 - Data From Applicant's Internal Database (Argus)

Dosage Strength	Duration of Use					
Type of AE	1d to 7d	>7d to 30d	>1m to 1y	>1y	Other*	Total
Patanol, n						
SAEs	50	6	15	0	89	160
Non-SAEs	1001	417	118	21	2355	3912
Total AEs†	1051	423	133	21	2444	4072
Pataday, n						
SAEs	3	0	0	0	52	55
Non-SAEs	367	113	54	5	1456	1995
Total AEs†	370	113	54	5	1508	2050
Patanase, n						
SAEs	9	3	0	0	18	30
Non-SAEs	168	45	24	2	433	672
Total AEs†	177	48	24	2	451	702
Pazeo, n						
SAEs	0	2	0	0	19	21
Non-SAEs	102	33	7	0	600	742
Total AEs†	102	35	7	0	619	763

Source: Applicant's ISS p. 28 of 66 for sNDA 020688 and sNDA 021545 (Patanol and Pataday switch)
*Value missing or not determinable
Patanol (olopatadine 0.1%) includes generic olopatadine 0.1%
Pataday (olopatadine 0.2%)
Pazeo (olopatadine 0.7%)
Patanase (olopatadine 0.6%)
MedDRA Version 21.1

Electronically copied and reproduced from Dr. Osborne's Clinical Review.

Deaths in the Postmarket Setting (Summarized in Office of Surveillance and Epidemiology Consult):

There are six deaths reported for olopatadine ophthalmic solution products in the postmarket setting. Dr. Elizabeth Donohoe (DNPD II/ONPD) reviewed five of these in her Clinical Reviews (January 21, 2020) for Rx-to-OTC switch for NDA 20688 (olopatadine 0.1%) and NDA 21545 (olopatadine 0.2%) which were associated with olopatadine ophthalmic drops 0.1% and 0.2%. None could be attributed to olopatadine. The sixth death was reviewed by Dr. Osborne and was reported in FAERS in a patient who used Pazeo amongst other medication. Briefly, the patient was a 77-year-old male whose medical history was unknown and whose concomitant medication was not reported, except that he received Sandostatin LAR Depot (octreotide) for the treatment of an unknown indication

from an unknown start date at an unknown dose (route: unknown). The patient received Pazeo (olopatadine) for the treatment of an unknown indication from an unknown start date at an unknown dose (route: unknown). On (b) (6), the patient died. It was unknown if an autopsy was performed. Dr. Osborne concluded that, "Whether Pazeo contributed to the patient's death cannot be determined due to a lack of information about a temporal association with use of Pazeo, past medical history, concomitant medications (except octreotide), clinical course, and cause of death." I agree with Dr. Osbone's conclusion.

FAERS

The Applicant submitted a summary of FAERS reports from 2015-cutoff in 2018, and later supplemented the safety data from FAERS, WHO, and NPDS in the 120-day safety report and PADERs. The Applicant's data were consistent with the FAERS data analyzed by OSE, so these FAERS data are described best by the OSE-Division of Pharmacovigilance II (DPVII) consult discussed below. For completeness, the Applicant's assessment of FAERS reports listing olopatadine (from any drug containing olopatadine) as the primary suspect is shown in the table below.

Table 11: FAERS AE Report Summary with Olopatadine Reported as the Primary Suspect

Drug	Death n (%)	Serious* n (%)	Non-Serious n (%)	Overall Total N
Olopatadine	0 (0)	18 (20.69)	69 (79.31)	87
Patanol/Patanol S	0 (0)	37 (11.71)	279 (88.29)	316
Opatanol	0 (10)	10 (100)	0 (0)	10
Patanase	2 (3.92)	26 (50.98)	25 (49.02)	51
Pazeo	1 (0.29)	17 (4.89)	331 (95.11)	348
Pataday	2 (0.49)	29 (7.16)	376 (92.84)	405
Allelock	0 (0)	0 (0)	0 (0)	0
Olopat	0 (0)	0 (0)	0 (0)	0

* Includes death
Source: Applicant's ISS page 36 of 66 for sNDA 020688 and sNDA 021545 (Patanol and Pataday switch)
Note: Allelock is an olopatadine tablet 5 mg for oral administration marketed overseas.
Olopat is an olopatadine ophthalmic solution 0.2% marketed OTC and overseas by Ajanta Pharma Ltd.
Abbreviations: AE, adverse event; FAERS, FDA Adverse Event Reporting System

Electronically copied and reproduced from Dr. Osborne's Clinical Review.

World Health Organization (WHO)

Postmarket data from the WHO Database Search by Brand from 1997 to March 2019 are shown in Table 17 below. There are 3427 reports or cases, with potentially multiple MedDRA terms generated by each report.

Table 12: Numbers of Adverse Drug Reactions for Olopatadine by Brand; WHO Database, January 1997-March 2019

	Olopatadine Brands									
MedDRA	Unknown Brand	Pataday	Patanase	Patanol	Pazeo	Opatanol	Olopat	Allelock	Other	All Cases
Total number of cases										3427
Blood and lymphatic system disorders	7	1	0	1	0	0	3	47	527	586
Cardiac disorders	6	3	4	1	1	7	0	31	330	383
Congenital, familial and genetic disorders	17	0	0	1	0	0	0	2	277	297
Ear and labyrinth disorders	1	9	2	3	5	0	0	4	75	99
Endocrine disorders	0	0	0	0	0	0	0	1	11	12
Eye disorders	126	218	9	170	382	92	0	20	1661	2678
Gastrointestinal disorders	45	32	14	13	5	8	13	435	3339	3904
General disorders and administration site conditions	81	307	26	276	75	17	2	205	2393	3382
Hepatobiliary disorders	23	0	0	0	0	0	0	135	1227	1385
Immune system disorders	15	19	3	22	18	5	0	23	370	475
Infections and infestations	18	24	4	12	9	7	0	11	646	731
Injury, poisoning and procedural complications	27	50	10	26	41	5	0	25	642	826
Investigations	12	18	13	4	8	5	2	130	1052	1244
Metabolism and nutrition disorders	3	6	2	1	0	0	0	28	273	313
Musculoskeletal and connective tissue disorders	13	19	6	10	6	0	0	26	769	849
Neoplasms benign, malignant and unspecified	3	1	0	1	0	0	0	4	111	120
Nervous system disorders	57	53	26	56	31	26	9	982	6866	8106
Null	0	0	0	4	0	0	0	0	4	8
Pregnancy, puerperium, and perinatal conditions	0	0	0	3	0	1	0	2	33	39
Product issues	19	9	2	5	33	4	0	0	68	140
Psychiatric disorders	25	10	14	10	4	1	6	83	1040	1193
Renal and urinary disorders	16	2	0	1	1	0	1	36	335	392
Reproductive system and breast disorders	3	0	0	1	0	0	0	7	35	46

Respiratory, thoracic, and mediastinal disorders	42	31	28	14	14	23	3	72	1283	1510
Skin and subcutaneous tissue disorders	57	21	7	32	16	27	2	151	1569	1882
Social circumstances	1	1	3	1	1	0	0	0	4	11
Surgical and medical procedures	1	2	0	1	0	0	0	0	24	28
Vascular disorders	1	2	3	11	1	6	0	20	248	292

Abbreviations: ADRs, adverse drug reactions; MedDRA, Medical Dictionary for Regulatory Activities; SOC, system organ class
Source: Applicant's ISS p. 51 of 66 for sNDA 020688 and sNDA 021545 (Patanol and Pataday switch)

Electronically copied and reproduced from Dr. Osborne's Clinical Review.

CDTL Comment: Dr. Osborne observed that in the WHO database, the category "Other" has the largest number of reports for most of the various AEs. Even so, it is notable when the brand is identified, that there are 382 reports of ***eye disorders*** *for Pazeo versus 218 for Pataday and 170 for Patanol. Also, there are 33 "****product issues****" for Pazeo versus 9 for Pataday and 5 for Patanol. Dr. Osborne noted that Pazeo has been approved (2015) only a fraction of the time that Patanol (1996) and Pataday (2004) have been approved. Dr. Osborne concluded that, at a minimum, from the WHO database, the rate of reporting for eye disorders and product issues for Pazeo is higher. However, it is difficult to make firm conclusions based on the data provided.*

National Poison Data System

Total reports by year:

- 2000-2004: 122
- 2005-2009: 191
- 2010-2014: 159
- 2015-2019 (partial): 77

The five top SOCs were:

- Ocular: 262 (48%)
- Miscellaneous: 91 (17%)
- Neurological: 82 (15%)
- Gastrointestinal: 59 (11%)
- Dermal: 38 (7%)

Note: Data broken down by brand (i.e., concentration) not available.

Dr. Osborne concluded that it is not clear that these reports involve "poisoning" since they have ocular and dermal categories. However, he noted that the ocular category has the most reports (262).

120-Day Safety Update

The Applicant submitted the 120-day safety update report for the three NDAs on November 20, 2019. As a Summary of Clinical Safety for Olopatadine Hydrochloride Ophthalmic Solution 0.1%, 0.2%, and 0.7% covering the period January 1, 2019 to October 31, 2019. Alcon reported no new clinical studies, and included data from its Argus database, FAERS, WHO, and the literature. For Pazeo alone, the following data were reported:

Pazeo

- Argus database: 173 AEs, of which 5 are SAEs (2 eye disorders, 2 nervous system disorders, and 1 immune system disorder).
- FAERS: 73 AEs, of which 5 are SAEs.
- WHO: (April 1-October 31, 2019): 152 AEs, and SAEs were not listed.
- Literature:
  - Jagarlamudi et al. (Jagarlamudi et al. 2019) compared the effects of 0.7% [Pazeo] olopatadine hydrochloride eye drops to a fixed dose combination of 0.1% [Patanol] olopatadine hydrochloride plus 0.4% ketorolac tromethamine solution eye drop for the treatment of allergic conjunctivitis over a 14-day treatment period. The most frequently reported treatment-emergent adverse event (TEAE) in both regimens was headache.

Based on the data in this 120-day safety update, the Applicant states that **"**A review of Alcon's internal database as well as the FAERS and WHO data for the olopatadine eye drop solutions Patanol [olopatadine 0.1%], Pataday [olopatadine 0.2%], and Pazeo [olopatadine 0.7%] for the period of January 1, 2019 to October 31, 2019…continues to support the favorable safety profile of these products as demonstrated in clinical trials, as well as previously reported post-market data."

Dr. Osborne concurred that the data from the 120-day safety database supports the safety of Pazeo in the prescription environment.

Office of Surveillance and Epidemiology (OSE) Pharmacovigilence Review

The OSE Division of Pharmacovigilence (DPV) was consulted by ONPD to evaluate serious adverse events (SAEs) associated with Pazeo. ONPD requested review of the following SAEs of special interest: misuse, death, blindness, corneal abrasion, and hypersensitivity. To conduct this evaluation, the DPV II Team (Regina Lee, Pharm D, Reviewer; Lynda McCulley, PharmD, BCPS, Team Leader; and S. Christopher Jones, PharmD, MPH, MS, Division Director) reviewed adverse events reported to the FDA Adverse Event Tracking System (FAERS) through December 22, 2019, the Applicant's Summary of 120-Day Safety Update Report, and most recent Periodic Adverse Drug Expeience Report (PADER).

DPV II identified 26 FAERS cases associated with Pazeo 0.7% ophthalmic solution use that reported misuse (n=2), death (n=1), ocular SAEs (n=19), and non-ocular SAEs (n=4). The top five reported Preferred Terms (PTs) reported among all PTs were *Eye Irritation*, *Hypersensitivity*, *Ocular Hyperaemia*, *Glaucoma,* and *Vision blurred*.

- In the misuse cases (n=2), the contributory role of Pazeo could not be excluded in one case of corneal abrasion associated with the concomitant use of Pazeo and contact lens. The second case did not provide sufficient information for assessment.
- In the death case (n=1), the contributory role of Pazeo was indeterminant due to the lack of clinical information provided.
- In the ocular SAEs cases (n=19), the contributory role of Pazeo could not be excluded in eight cases; the PT described in these cases include *Blindness* (n=1), *Corneal abrasion* (n=2), *Hypersensitivity* (n=2), *Eye irritation* (n=1), *IOP increased* (n=1), and *Periorbital swelling* (n=1). DPV II noted that exposure to benzalkonium chloride in Pazeo solution has been associated with allergic contact sensitivity (Fisher et al, 1972; Sarkar et al, 2012). and corneal neurotoxicity and inflammation; athough the extent of its contribution to the aforementioned ocular events is unclear. The contributory role of Pazeo was indeterminate in 11 cases due to the lack of clinical information provided.
- In the non-ocular SAE cases (n=4), which include *tachycardia* (n=1), *Metal poisoning* (n=1), *Migraine* (n=1), and *Lung disorder* (n=1), the contributory role of Pazeo was indeterminate given the lack of clinical information, including temoporal association, past medical history, concomitant medications, and clinica outcome.

DPV II reported that their review of the Applicant's data "confirms that the SAEs reported in the PADER aand Summary of Clinical Safety are consistent with those reported in FAERS." In addition, DPV II concluded that, "In DPV's opinion, the limited FAERS cases we identified are not sufficient to predict the misuse potential of Pazeo. Therefore, if a concern for potential misuse remains, DPV recommends that ONPD consider requesting the sponsor provide in their annual periodic reports a summary of worldwide experience of all misuse cases."

Breakdown of DPV-Identified FAERS SAEs

For a detailed description of the FAERS SAE cases, the reader is referred to the DPV Review and to Dr. Osborne's Clinical Review. However, for illustrative purposes, selected cases will be summarized here.

Deaths:

The single FAERS case of death is the same case described above (see **Deaths in Postmarketing Setting** section above) and, as previously stated, causality cannot be determined due to lack of information.

Blindness:

The blindness case (#13333654) involved a 57-year-old male who stated that he is legally blind and developed additional AEs of erythema, eye irritation, eye pruritis, ocular hyperaemia, periorbital pain, vision blurred, and visual acuity reduced on an unknown date after taking Pazeo one drop twice daily for 14 days. Outcome of the events was not reported.

CDTL Comment: It appears that the "AE" of blindness may have preceded the use of Pazeo. In any case, I agree that the information provided is insufficient to indicate a causal association of the reported AEs with pazeo. Note that several of the reported ocular symptoms are commonly associated with allergic conjunctivitis.

Hypersensitivity:

Cases of hypersensitivity were also identified and included: Case # 16018100, a 35 year-old female who developed erythema and swelling of eyelid and eyelid pruritis within 15 minutes of Pazeo instillation; Case # 11246237, a 59-year-old female who developed blepharospasm, hypersensitivity, swelling of the eyelid, urticaria, and visual impairment beginning within one minute of Pazeo instillation; Case #15515654, a 38-year-old female who received Pazeo on an unknown date for an unknown indication and, on an unknown date had allergies (hypersensitivity) and asthma (she was subsequently lost to follow-up); and Case # 16244604, and adult female of unspecified age who took Pazeo for an unknown indication and, on unknown date, reported "being on the medication and recently hospitalize due to bad allergies (hypersensitivity)" and also said she fainted (syncope). For the first two cases (#16018100 and #11246237), DPV II concluded that the contributory role of Pazeo cannot be excluded based on the temporal association to the onset of the symptoms, and DPVII again noted that exposure to benzalkonium chloride in Pazeo solution has been associated with allergic contact sensitivity and corneal neurotoxicity and inflammation. For the latter two cases (#15515654 and #16244604), DPV II concluded that the contributory role of Pazeo could not be determined given the lack of information.

CDTL Comment: Overall, I agree with DPV II assessment. For the first two cases (#16018100 and #11246237), the contributory role of Pazeo seems plausible based on temporal association and the known association of benzalkonium chloride with allergic contact hypersensitivity. See also Important ***Identified Risk: Hypersensitivity****, above.*

Misuse:

The two misuse AEs are briefly described as follows:

- Case #12126628 was a 38 year old male who received Pazeo one drop daily for atopic conjunctivitis. He used Pazeo with his contact lens which caused damage to the contact lens (lenses fragmented) and led to corneal abrasion from the fragmented contact lens, and, within the next two months, he developed "ulcerations" of the sclera. DPV II concluded that the contributory role of Pazeo cannot be excluded. The product label advises against use of soft contact lens (*Warnings and Precautions*, and *Patient Counseling Information*), so this is an example of intentional misuse.
- Case #1559627 was a female of unspecified age with pre-existing eye pain who received Pazeo eye drops twice daily for the treatment of itchy eyes. She instilled Pazeo "three or four times daily" and felt it was not working. She stopped taking the product at some point and complained of blurry vision. The outcome of the events, incorrect dose administered, eye pain, concomitant disease aggravated, drug ineffective, and cataract were not reported, and the outcome of the event vision blurred was reported as unchanged. DPV II concluded that the contributory role of Pazeo cannot be determined given the lack of information on temporal association, past medical history, concomitant medicaitons, and clinical outcome. It should also be noted that Pazeo Prescribing Information lists blurred vision as a commonly reported (2-5%) AE in the clinical trials. However, this case is noteworthy because it provides an example of misuse, using more than prescribed dosage, in the prescription setting.

CDTL Comment: Both of these cases illustrate the plausibility of misuse in the prescripotion setting. It can be anticipated that, in the absence of a learned intermediary (ie, OTC setting), the likelihood of misuse may be higher.

Glaucoma, Increased Ocular Pressure, and Ocular Hypertension

Three cases of glaucoma (#13537488, #154272333, and #15728796) were identified. In all three cases, the contributory role of Pazeo could not be determined for various reasons including compelling potential alternate etiologies, lack of information, and confounding factors. A fourth case (#12439878) was identified of a 64-year-old male who received Pazeo one drop in each eye daily for treatment of itchy eyes. Nine days later, during a follow-up appointment, he discovered his intraocular pressure (IOP) increased from 22 to 28 in his left eye, at which time he was instructed to discontinue Pazeo. DPV II concluded that the contributory role of Pazeo cannot be excluded based on temporal association of onset of increased IOP within 9 days of initial Pazeo exposure. However, DPV II noted that potential alternate etiologies cannot be excluded, as information on past medical history, baseline IOP, and concomitant medications is lacking. A fifth case (#16283267) involved an adult female of unspecified age who received Pazeo for treatment of allergic conjunctivitis and on an unknown date developed "ocular hypertension due to a steroid cream." DPV II concluded that the contributory role of Pazeo could not be determined.

CDTL Comment: I agree with DPV II assessment. There is not enough information available at this time to determine a role of Pazeo in these cases. There is no mention of AEs of glaucoma, increased IOP, or ocular hypertension in Pazeo in Prescription Labeling.

Iridocyclitis

One case (#16475926) of iridocyclitis was identified. A female in her mid-50s received Pazeo one drop once daily for the treatment of ocular itch associated with allergic conjunctivitis and, on an unknown date, developed bilateral anterior uveitis (iridocyclitis). It was reported that she discontinued Pazeo and was started on a steroid for inflammation. The outcome of iridocyclitis was not reported. DPV II concluded that the contributory role of Pazeo could not be determined given the lack of informationon temporal association, past medical history, concomitant medications, clinical course, clinical outcome, and contact lens use or presence of trauma. However, DPV II again noted the association a allergic contact sensitivity and corneal neurotoxicity and inflammation with exposure to benzalkonium chloride.

CDTL Comment: I agree with DPV II assessment.

FDAAA Section 915 Non-New Molecular Entity Postmarket Safeety Summary Analysis

Dr. Osborne also reported that OSE performed a Section 915 Review dated January 9, 2017 which summarized postmarket safety from U.S. approval from January 30, 2015 through the first 18 months post approval to December 31, 2016 (the rule states 18 months or 10,000 patients, whichever is later). Dr. Ronald Wassel from OSE determined that there were 134 reports (5 SAEs, all labeled in the Rx labeling, or inadequate information to make an assessment), although none revealed potential or ongoing safety issues that needed to be addressed. A summary of relevant findings is shown in the table below.

Table 13: Most Frequently Reported MedDRA PTs with N≥5 for Pazeo, Received by FDA from January 30, 2015 through December 31, 2016

MedDRA PT	Number of FAERS Reports	Labeled (Yes/No), Location or Other Category
Vision blurred	38	Yes, AR
Drug ineffective	25	U
Eye irritation	16	Yes, AR (as abnormal sensation); also, IR
Eye pain	10	No; see section 3.4
Eyelid margin crusting	9	IR
Dry eye	8	Yes, AR; also, IR
Eye swelling	8	IR
Ocular hyperemia	8	IR
Abnormal sensation in eye	7	Yes, AR
Eye discharge	6	IR
Eyelid edema	6	IR
Dysgeusia	5	Yes, AR
Medication residue present	5	U

* A report may contain more than one preferred term.
Abbreviations: AR, Adverse Reactions; FAERS, FDA Adverse Event Reporting System; IR, Indication-related; MedDRA, Medical Dictionary for Regulatory Activities; PTs, preferred terms; U, Uninformative
Source: OSE 915 review

Electronically copied and reproduced from Dr. Osborne's Clinical Review.

Summary Assessment of Safety

In summary, as described by Dr. Osborne, the Applicant did not conduct any new clinical studies to support this review. Therefore, this safety review analyzes postmarketing data as discussed above. Overall there have been 26 serious adverse events reported for olopatadine 0.7% since approval in 2015 and no fatalities. The number of adverse events reported (per year) are close between the three olopatadine ophthalmic products in **Table 9** above (Applicant's Argus database), however there may be a trend towards more total AEs (not necessarily SAEs) for olopatadine 0.7% (763 total and 21 SAEs in about 4 years or 190 AEs and 5 SAEs per year) than for olopatadine 0.1% (4072 total and 160 SAEs in about 23 years or 177 AEs and 7 SAEs per year) or 0.2% (2050 total and 55 SAEs in about 15 years or 137 total and 3-4 SAEs per year).

Dr. Osborne summarized the important safety concerns relevant to potential approval of olopatadine 0.7% for OTC use and identified potential pathways to address these issues. Dr. Osborne acknowledged that the relative safety of olopatadine 0.7% is established in the prescription setting for patients age 2 and older including geriatric patients, providing they adhere to the approved indication and a

dose of no more than one drop in each affected eye per day, and do not use olopatadine 0.7% with any other olopatadine ophthalmic solutions. However, the Applicant's Argus database plus supplemental safety reports (PADERS, FAERS PSUR, 120-day safety update) and the OSE-DPVII consult still yielded 26 SAEs, 2 of which involved misuse (Pazeo not excluded in one report), and overall 19 ocular SAEs (Pazeo not excluded in eight case reports). In the one SAE reporting a cataract the consumer reported using Pazeo (olopatadine 0.7%) 3 or 4 times per day, which is itself concerning. Thus, Dr. Osborne concluded that it is likely OTC use will lead to SAEs.

Furthermore, Dr. Osborne pointed out that all use of Pazeo is from the prescription environment in the USA. Thus, there are no data for USA consumers or any consumers for the 0.7% solution. Dr. Osborne was unable to locate any clinical trial data or literature information for any of the three concentrations for use in humans of more olopatadine than one drop of the 0.7% solution in each eye per day. The highest dose of olopatadine ophthalmic solution studied by the Applicant, or found in the literature, is one drop of the 0.7% in each eye per day for 6 weeks. The medical consequences of overuse of the 0.7% solution are therefore unstudied.

The systemic safety of the 0.7% solution was studied in animals, reaching a systemic exposure about 60-80 times, or more, than expected in a human administered an ophthalmic dose of one drop. In the Patanol development program (NDA 20688), two humans were given a 80mg dose of olopatadine with no adverse consequences, and multiple subjects received a 5 mg oral tablet in the Pazeo development program. This is much more systemic exposure than the amount of olopatadine that would be absorbed from an eye drop containing about 0.3 mg of olopatadine, only a small fraction of which would be absorbed into the systemic circulation. Therefore, Dr. Osborne noted that there are no concerns about systemic safety. However, Dr. Osborne ponted out that such a comparison is not relevant given the adverse events in humans are ophthalmic, not systemic. In the Patanol development program, monkeys received four drops daily of a 0.5% solution for months with no apparent serious problems. Thus, Dr. Osborne calculated that the maximum amount of drug instilled daily in the eyes of monkeys without allergic conjunctivitis is just below the amount of drug in 3 drops of Pazeo (4 drops x 0.5% ="2" vs 3 drops x 0.7% = "2.1"). No animal studies were conducted with Pataday or Pazeo, so this study in monkeys is the only potential study comparator for Pazeo in an overuse situation.

Therefore, Dr. Osborne identified as the main concern that consumers might overuse Pataday Once Daily Relief, Extra Strength either by mistake, or intentionally, with unknown and unstudied safety consequences. For example, consumers might confuse the dosing of Pataday Once Daily Relief, Extra Strength with the twice daily dosing of the already approved Pataday Twice Daily Relief (olopatadine 0.1%, one drop in each affected eye twice daily), and then overuse Pataday Once Daily Relief, Extra Strength. Or, consumers may intentionally use Pataday Once Daily Relief, Extra Strength with either of the other two approved OTC olopatadine ophthalmic solutions.

Dr. Osborne created the following table to identify possible options to address overuse/misuse concerns with OTC use.

Table 14: Regulatory Options to Address Overuse/Misuse Concerns with Olopatadine 0.7% Eye Drops for OTC Use

Intervention	Pros	Cons	Comments
(1) Issue a CR for the application and require a Safety Study with a higher dose	Safety related to an overuse condition would be studied prior to OTC approval	CR may be viewed as an overly strong measure given that the drug looks relatively safe in the Rx environment	CR for an OTC drug may not have a precedent when the reason for the CR is a hypothetical safety risk that only occurs if consumers fail to follow the Directions for Use.
(2) Require a safety study (phase 1, of adequate size) with a higher dose prior to PDUFA date.	Avoids a CR, extends clock with a major amendment	Delays approval date	May be reasonable to Applicant, however timing may be rushed
(3) Approve application with strong labeling (e.g., "Do not use more than 1 drop per eye per day" and "Do not use with other Pataday products"	Easiest approach, and justifiable based on submitted safety data (e.g. if we don't go down the path of worrying about the unknown)	May require a quick Label Comprehension Study for new DFL, possibly a targeted Self-selection study Consumers may not follow the Directions (how to Use the drug) Possibly no precedent for Do Not Use on DFL with another specific OTC product	There are always some SAEs with Rx drugs, however no deaths or irreversible SAEs with Rx Pazeo 0.7%. Social science input considered for this option
(4) Approve, strong labeling and a PMC for a safety study with a higher dose (phase 4 study designed like a phase 1)	Meet PDUFA date Still get safety data in a prospective clinical trial setting	Takes a chance that Applicant may not conduct the PMC promptly	If we see SAEs in the OTC environment, it is unclear whether we could require the PMC to be done immediately.
(5) Approve application and ask Applicant to include in their annual and periodic reports, a summary of all experience with misuse cases (and their consequences)	Meet PDUFA date Still get Safety Data	Safety data arrives months or longer after OTC approval and is retrospective	*This is a suggestion for our consideration from the OSE-DPV2 team which conducted the consult regarding FAERS data*

Intervention	Pros	Cons	Comments
(6) Issue a CR; however, then give Applicant the choice to: a) do safety study above OR b) do LCS/SS with strong DFL wording and if LCS/SS not supportive then Applicant needs to do safety study	Responsibility is on Applicant to decide best course	Delay potential approval date	*Suggestion from clinical reviewer (Dr. Donohoe) for other olopatadine switches.* Request for safety data for "potential overuse/misuse" may be difficult to get (via regulatory authority) without "proving" via LCS/SS that it is a legitimate concern. However, Applicant may choose to do safety study because it may be most efficient.
(7) Approve application with proposed labeling or closely like proposed labeling	Meet PDUFA date	Accepts possibility of overuse with unknown ocular effects	*Recommendation from DTOP.* Use vigilant review of subsequent AE reports and update labeling as needed

Abbreviation: CR, complete response; DFL, drug facts label; FAERS, FDA Adverse Event Reporting System; LCS/SS Label Comprehension study/Self-selection study; OSE-DPVII, Office of Surveillance and Epidemiology - Division of Pharmacovigilance II; OTC, over-the-counter; PMC, postmarket commitment; SAE, serious adverse event

Electronically copied and reproduced from Dr. Osborne's Clinical Review

Dr. Osborne concluded that based on the postmarket safety data and the OSE review, it is likely some consumers will misuse the drug with a goal of more relief, so we need to try practical measures to at least explore the safety of Pazeo for consumers who do not follow the directions. In addition, because consumers typically overuse some OTC drugs, Dr. Osborne noted that a safety study using more than one drop per day for the proposed duration of dosing (e.g. 6 weeks) before consulting a doctor would add to the assurance that OTC marketing of Pazeo will be safe for consumers.

As noted in **Section 7** above, DTOP has recommended approval of this NDA for OTC use. In his Clinical Review, Dr. Boyd wrote that, both **NDA 21545** (Pataday) and **NDA 206276** (Pazeo) contain adequate and well controlled studies that support the safety and efficacy of the two products "for the treatment of itching when administered once or twice a day and for the treatment of itching and redness when administered twice a day." Dr. Boyd concluded, "The Division of Ophthalmology recommends approval of these three supplemental applications for an OTC switch." DTOP has continued to favor approval for OTC use without further changes to OTC labeling and, at a review team internal meeting of May 21, 2020, voiced support for Option 7, that is, approval of the application with the proposed labeling, and use vigilant review of subsequent AE reports and update labeling as needed.

On June 2, 2020, the DNPD2 clinical and social science team met with the DTOP clinical team and the respective office directors, Dr. Theresa Michele, Acting Director, ONPD; and Charles Ganley, MD, Acting Director, Office of Speciality Medicine (OSM), to discuss a path forward. Slides and the Option Table above (**Table 13**) were presented by OTC. Dr. Ganley expressed reasonable comfort that based on the mechanism of action for an antihistamine and mast cell stabilizer drug, wide use and likely overuse of already OTC or OTC-eligible eye drops for itching and redness relief, it would be unlikely that consumers would be harmed by overuse of olopatadine 0.7%. Dr. Ganley considered Option 5 (postmarket adverse event reporting) above to be reasonable. Dr. Mahoney opened a discussion of whether a precedent might be set for other drugs if OTC approved a drug with no data about the potential effects (harm) of overuse, since OTC drugs have typically been studied and often used Rx at higher doses than the dose approved for OTC. Dr. Michele commented that it might be possible to frame reasoning for approval of olopatadine 0.7% without additional safety data, and not opening a door for other drugs that might be riskier.

Also at the June 2, 2020 a few examples of stronger labeling were considered, such as bolding the warning **"Do not use more than 1 drop in each eye per day", or "Do not use more than 1 drop in each eye per day: safety has not been studied above 1 drop in each eye per day", and "If you need to use more than 1 drop in each eye per day, contact your doctor; you may need additional medical care".** DTOP expressed concern with any labeling other than what has previously been used with similar OTC eye drops. The team made a comparison with drug facts labeling on the February 2020 approvals of the 0.1% and 0.2% olopatadine eye drops, and with the 2017 approval of Lumify (brimonidine tartrate), indicated for ocular redness relief. In his Clincal Review, Dr. Osborne opined that Option 6 above appears to be the best choice for safety plus practicality (issue a CR and give the Applicant a choice of a safety study or consumer behavior studies with an optimized label, and a safety study required for approval only if the consumer behavior studies fail). Option 1, (issuing a CR and requiring a safety study, regardless of any consumer behavior studies, is the most conservative and safest approach although it limits options for the Applicant. Option 2 (extend the PDUFA clock and conduct a safety study now) is probably too late in the cycle at the date of this review. Option 3 (Approval with strong labeling in Directions and Warnings) is practical, although it is unclear whether strong labeling will be understood by the consumer, unless it has been previously tested in an OTC DFL. Option 4 (Approval with a required postmarket safety study) is a potentially reasonable approach, although it risks a period of unstudied safety if consumers overuse the drug. Option 5 (Approval and require a breakout of misuse-related adverse events in postmarket reports) is reasonable though riskier due to delays in receiving and reporting adverse event reports). Option 7 (approval without conditions, meaning no required studies and no major changes from the proposed labeling by the Applicant) is inconsistent with previous OTC approvals, which have typically required an understanding of safety in humans at a dose higher than the proposed OTC dose, to cover potential overuse/misuse by consumers.

As noted above, Dr. Osborne recommended approval: conditional upon strong labeling to help minimize overuse or misuse, coupled with postmarket safety follow-up.

9. Advisory Committee Meeting

An advisory committee meeting was not held for this application as it is not a new class switch.

10. Pediatrics

The Division of Pediatrics and Maternal Health evaluated olopatadine ophthalmic solution during the reviews of the 0.1% and 0.2% Rx-to-OTC switch applications and determined there was insignificant risk to a fetus from use by a mother and no need to insert a warning on the proposed Drug Facts label for any of the ophthalmic strengths (please see my CDTL Review for NDA 208288 and 21545; 2/13/20, for further details).

The application does not include a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. Therefore, the Pediatric Research Equity Act (PREA) is not triggered. If the proposed product is approved for OTC use, Drug Facts labeling will include directions for use for adults and children 2 years of age and older. For children under 2 years of age, DFL will advise to consult a doctor.

11. Other Relevant Regulatory Issues

Not applicable.

12. Labeling

Interdisciplinary Scientist (IDS) Labeling Review

The IDS Labeling Review was completed by the IDS Team (Arlene Solbeck, MS, Reviewer; and Sergio Coellho, PhD) on June 23, 2020. The Appicant's proposed DFL is shown below:

On June 17, 2020, the Applicant submitted an email to RPM LCDR Jung E. Lee proposing an alternate design and color scheme (green) for labeling in order to further distinguish the three Pataday products from each other, as shown below:

Labeling Information Request:

On June 19, 2020, the IDS team sent a labeling Information Request (IR) to the Applicant. For a detailed review of the requested labeling revisions, please see the IDS Labeling Review. The IR included numerous revisions to content and format to ensure consistency with current regulations (eg, changes in font size, location of information, use of lower case, etc) and will not be discussed in this review. Highlights of the IR are as follows:

Principal Display Panel:

a. Remove the word (b) (4) and the asterisk following it from (b) (4)….." and replace with "Relief from allergens…." in accordance with prior approved OTC Pataday products.

b. Increase the prominence of the "Once Daily Relief" in accordance with other approved OTC Pataday products.
c. Revise the Statement of Identity (SOI) as follows:
    1. Revise the proposed SOI from "Olopatadine hydrochloride ophthalmic solution 0.7% (b) (4) Antihistamine" by removing the word (b) (4) from the pharmacological category.
d. Revise the claim (b) (4) to read "Eye Allergy Itch Relief" to be consistent with products in this category (also for side panel and top panel).

Back Panel:

1. Under Drug Facts box, remove the claim (b) (4) (b) (4).
2. Immediate container level: Delete the word (b) (4) form the SOI (also for pouch).

Response to Information Request:

In response to the Labeling IR, the Applicant submitted revised labeling on June 25, 2020. Overall, the revised labeling was acceptable. However, in an Addendum to Labeling Review (June 26, 2020), the IDS Team noted the following outstanding issues:

- For the 2x2.5 mL twin pack, in the original submission, the banner was (b) (6) and "EXTRA STRENGTH" was in (b) (6), as shown below:

(b) (4)

- The Applicant was advised that they may use the alternate color scheme ("Green") as proposed in their email to Senior Project Manager LCDR Jung Lee on June 17, 2020. The Applicant did so in the revised labeling. However, DMEPA had recommended in their January 7, 2020 review that, for the (b) (4), (b) (4) and (b) (4) Twin Pack banner from the original submission, the sponsor revise the banner because it appeared to them that the product was (b) (4) (b) (4) in the packaging configuration. (b) (4)

From an IDS perspective, this presents an issue in the color scheme that was not a problem before. IDS concluded that the decision on whether oto ask the Applicant to change the color scheme is pending clinical input.

- Stronger labeling in the DFL for safety has been discussed (see **Table 14**, Options 3 and 4 above), pending clinical input.

- The Applicant did not submit the font specifications for the DFL bullets; however, IDS noted this can be done in an email to the RPM in a future Applicant commuinication once the other issues pending clinical input are addressed.

*CDTL Comments: At a labeling meeting on June 30, 2020 with the IDS Team (Arlene Solbeck, MS and Steve Adah, PhD), Social Scientist Barbara Cohen, the Clinical Team (Dr. Osborne and Dr. Becker), the Associate Director for Labeling (Ruth Scroggs), and Dr. Karen Mahoney, Acting Deputy Director, ONPD, the above outstanding issues were discussed. It was agreed that the Applicants color scheme associates "EXTRA STRENGTH" with the two bottles. The Applicant will be requested to change the color scheme. Regarding stronger labeling to address concerns regarding misuse/overuse, although it is acknowledged that there are limitations to the effectiveness of labeling to prevent all potential misuse (see **Social Science Labeling Assessment** below), it was nevertheless determined that stronger labeling would be helpful. Potential labeling options were discussed based on effective labeling from other OTC products and included: "Do not use more than one drop to each eye daily"; "Do not use more than directed"; and "Do not use with any other drug containing olopatadine." At this time, the final proposed language to strenghthen labeling is still being considered.*

Proprietary Name Review

Proprietary name review was conducted by Grace P. Jones, PharmD, BCPS (Safety Evaluator); Chi-Ming (Alice) Tu (Team Leader), PharmD, BCPS; and Danielly Harris, PharmD, BCPS (Deputy Director) of the Division of Medication Error Prevention and Analysis (DMEPA) in the Office of Surveillance and Epidemiology (OSE).

Alcon seeks to market all three strengths of of the olopatadine ophthalmic solution under the root name Patday. On April 15, 2019, Alcon submitted the proposed proprietary name, Pataday Once Daily Relief, for the proposed full Rx-to-OTC switch of Pataday (olopatadine) ophthalmic solution 0.2% under NDA 21545. On July 9, 2019, DMEPA found the name Pataday Once Daily Relief, acceptable. However, on September 24, 2019, Alcon withdrew the name, Pataday Once Daily Relief, and submitted a new proprietary name, [redacted]. On September 13, 2019, Alcon submitted NDA 206276/Supplement-005 for the proposed Rx-to-OTC switch of Pazeo (olopatadine) ophthalmic solution 0.7% and submitted the proposed proprietary name [redacted], for review. On November 13, 2019, a teleconference was held with Alcon to discuss preliminary concerns with the proposed proprietary name [redacted] and the totality of the proposed proprietary names for the three proposed olopatdine products in the Pataday product line. There was preliminary concern that the modifier [redacted]. On November 22, 2019, Alcon withdrew the proposed proprietary names, [redacted] for the 0.2% strength, and [redacted], for the 0.7% strength. On November 25, 2019, Alcon submitted the proposed proprietary name, Pataday Once Daily Relief, for both the 0.2% and 0.7% strengths. Alcon planned to differentiate the two strengths via the labeling descriptor, Extra Strength, for the 0.7% product.

Table 15: Proposed Pataday Product Line for OTC Marketing

Rx Product Name	Proposed Proprietary Name (PN)	Product Strength	Application Number
Pazeo	**Pataday Once Daily Relief**	0.7%	NDA 206276/S-005
Pataday	**Pataday Once Daily Relief**	0.2%	NDA 021545/S-022
Patanol	**Pataday Twice Daily Relief**[c]	0.1%	NDA 020688/S-032

Electronically coipied and reproduced from DMEPA Proporietary Name Review

DMEPA concluded that, for the current submission, the proposed name, Pataday Once Daily Relief, is acceptable. In their review, DMEPA wrote the following:

> *While we did not identify any application OTC products that incorporate the modifier "Once Daily" in the proprietary name, frequency of dosing is commonly used in OTC nomenclature (e.g., Nasacort Allergy 24 Hour, Xyzal Allergy 24HR, Sudafed Sinus Congestion 12 Hour, etc.). The modifier "Relief" is also commonly used in OTC nomenclature (e.g., Flonase Allergy Relief, Advil Allergy and Congestion Relief, etc.). Because*

we typically see the modifier "Relief" in conjunction with the symptoms that the product provides relief for, it is unclear how consumers would interpret "Relief" when used in conjunction with the frequency of administration "Once Daily". However, from a medication error perspective, we do not anticipate the combination of the words "Once Daily Relief" to introduce any risk of confusion because the product is dosed once daily and will provide relief of the symptoms when used once daily.

Additionally, we learned from discussion with the review team that the safety margin for the 0.2% product is wide such that even if consumers were to use it more than recommended, there is minimal risk of clinical harm. The local effect on the eye(s) from chronic administration at doses higher than recommended with the 0.7% product is unknown, thus, the safety profile for the 0.7% product and whether it is suitable for OTC marketing is an ongoing review issue. Should the review team determine that the 0.7% product is suitable for OTC marketing, DMEPA's evaluation finds that the modifier "Once Daily Relief" in the proposed proprietary name will aid in communicating to consumers that the 0.7% product should be used once daily. Likewise, the modifier "Once Daily Relief" will also aid in communicating to consumers that the 0.2% product should be used once daily. Thus, we do not object to the use of the modifiers, Once Daily Relief, and find the proposed proprietary name, Pataday Once Daily Relief, acceptable.

Social Science Labeling Assessment

Social science assessment was performed by Barbara Cohen, M.P.A., Social Scientist, DNPD 2. No consumer behavior studies were submitted with this application except for a label discernment/targeted self-selection study. Ms Cohen was asked to comment on how consumer behavtior studies and /or revisions to labeling might be helpful to mitigate ONPD clinical concern regarding misuse of the proposed product, given that there appears to be no adequate safety data in dosing in excess of 0.7%.

In her discussion paper (6/3/20), Ms Cohen noted that, "it is important to keep in mind that label comprehension and (some) self-selection studies focus on assessment of cognitive understanding when consumers are asked to focus on a label. They cannot address what might happen if a consumer doesn't read the label prior to self-medicating. They also cannot address what might happen, even if the user has read the label correctly, if subsequently the product of concern is inadvertently mistaken for another product in the medicine cabinet due to a similar packaging look and feel. Moreover, comprehension and stated intention, respectively, can at times be markedly different from actual behavior." Ms Cohen continued, "The general assumption – which is reflected by actual use study findings - is that there will always be some consumer misuse of a product once it is out on the marketplace. There is virtually never 100% correct comprehension, self-selection, and/or actual use of a product…The key is to get misuse to the lowest possible minimum

through research-based labeling, packaging, or other means, and then determine whether that level of risk is acceptable given the stated benefits."

Ms. Cohen pointed out that if Pataday 0.7% is approved in this review cycle, there would be three products with a similar packaging look and feel that arrived on the drugstore shelf approximately within six months to a year of each other. Two of the three are once a day; one of the three is extra strength; one of the three has a redness indication. Thus, potential misuse around Pataday Extra Strength could broadly fall into three different categories:

1. Consumers who don't see/understand the labeling of *not more than* once a day, even if they have only the once a day extra strength product on hand and aren't confusing it with another Pataday product.
2. Consumers who correctly discern that the 0.1% alone has the indication for redness but deliberately decide to use that product along with Pataday Extra Strength, because they don't understand that the 0.7% should not be taken with another olopatadine product; there is nothing currently on the labeling that addresses that.
3. Consumers who have two or three of the products in the medicine cabinet (perhaps they previously purchased Pataday 0.1% but now that the 0.7% is available they want to use that), but they or someone else in the family inadvertently confuses them at the time of administration and mistakenly takes the 0.7% twice in a day.

The Applicant conducted a Label Discernment Study focused on the three proposed product names at the time of NDA submission: (b) (4) olopatadine 0.7% (b) (4) antihistamine – once a day dosing; (b) (4) olopatadine 0.2% (b) (4) antihistamine – once a day dosing; and Pataday Twice Daily Relief olopatadine 0.1% (b) (4) antihistamine and redness reliever – twice a day dosing. However, as discussed above, these names were determined to be not acceptable to FDA and were revised to Pataday Once Daily Relief Extra Strength, Pataday Once Daily Relief, and Pataday Twice Daily Relief respectively. As Ms Cohen pointed out, this development inadvertently negated a good deal of the potential usefulness of the study. The primary objective of ascertaining recognized PDP dosing frequency differences among the three products turned out to be no longer applicable.

Specifically, the primary objective of the study was the percentage of participants who had a correct response for dosing discernment among the three products (defined as dosing frequency or hours of relief) based on the descriptors on the Principal Display Panel (PDP). An a priori success threshold was established at 85% (lower bound). The first stated secondary objective was discernment of the indications (eye itch for Pataday 0.2% and 0.7% vs eye itch plus redness relief for Pataday 0.1%). The above primary objective and secondary objectives were assessed in the first part of the study – the label discernment. The second stated secondary objective was comprehension of dosing instructions. This objective was assessed through a follow-on targeted label comprehension component that immediately followed the label discernment component. As comprehension of dosing instructions was a secondary objective, there were no a priori thresholds.

There were 404 participants in the study, ages 15 and older, which included subgroups for limited literacy (n=117), parents/caregivers of children ages 2-14 (n=103), adolescents ages 15-17 (n=67), and current users of OTC allergy drops (n=166). Participants first viewed the packages of the three products on a store shelf. First, there were open-ended label discernment questions about what differences and similarities they identified among the labeling. Next, participants were asked specifically to look at all sides of the packaging, which included the DFL. There were then two targeted label comprehension questions for each product – one asking about number of drops per day, and one asking about the dosing frequency. The Applicant reported the following relevant results, which were described by Ms Cohen in her discussion paper:

Comprehension of dosing frequency of (b) (4) product (label comprehension component):

- There was an excellent understanding of "once a day" for (b) (4) (olopatadine 0.7%) product (397/404, or 98.3%). However, only 94/404, or 23%, of study participants proactively stated that the products *should not be used more than* once a day. this concept was more likely to be voiced by adults (vs adolescents), and by non-parents/caregivers (vs parents/caregivers). Ms Cohen noted that this doesn't mean that this concept wasn't understood by the others; people often express their ideas in shorthand. It is certainly possible that some or many others understood the concept but simply didn't voice it that way. However, we don't know one way or another what the reality of that comprehension was. Furthermore, Ms Cohen pointed out that there is a difference between not needing to use a product any more than once a day for efficacy, and it being risky to use more than once a day.

Indication (label discernment component):

- In the label discernment component of the study, 310/404 or 76.7% mentioned "redness" as a differentiating factor for the 0.1%.

Packaging Look and Feel (label discernment component):

- In the label discernment component of the study, 206/404, 50.7% stated the packages (graphics, colors, etc.) were different in appearance, and 176/404, 43.5% stated they were similar.

Study Implications:

Ms. Cohen identified the following implications of the study findings as applies to potential misuse and commented on potential solutions for the proposed product as follows:

1. Potential Misuse: Consumers who don't see/understand the labeling of *not more than* once a day, even if they just have the once a day extra strength product on hand and aren't confusing it with another Pataday product.

   Addressed by current LDS/LCS?: The targeted LCS did not adequately address this issue.

   Potential Consumer Behavior Study Path Forward: Improve labeling to highlight further "not more than once a day" and conduct another targeted LCS with relevant scenarios. However, even a very strong comprehension result from such a study doesn't negate the possibility that consumers won't read the label.

2. Potential Misuse: Consumers who correctly discern that the 0.1% alone has the indication for redness and deliberately decide to use that product along with Pataday Extra Strength, because they don't understand that it should not be taken with another olopatadine product.

   Addressed by current LDS/LCS?: The LDS showed that most consumers do see that only one of the products has a redness indication – theoretically providing more evidence for this possibility.

   Potential Consumer Behavior Study Path Forward: Improve labeling, through preliminary iterative testing, to address that it should not be taken with another olopatadine product. Note: this will be challenging because a) previous research shows that many consumers do not understand ingredients and b) the concept of "should not be taken with" can mean different things to different people (some may interpret, for instance, as referring to simply not at the exact same time, but it would be ok to take 30 minutes apart). Then, assess in a targeted LCS with relevant scenarios. However, as noted above, even a very strong comprehension result from such a study doesn't negate the possibility that consumers won't read a label.

   To address this, the Applicant could conduct a follow-on targeted self-selection study which could be a bit more realistic. In such a study, allergy sufferers with redness in their eyes could be presented with the three products and asked to pick what they would purchase, without specifically directing them to read the labels. This would provide important insights into how these consumers would decide what if any combinations of products to use, including asking about whether they would think of using Pataday .1% along with Pataday Extra Strength, in the event that the latter product did not sufficiently relieve their

redness. Although such findings would be conceptually useful and perhaps very helpful, FDA can consider whether asking the Applicant to conduct an additional (self-selection) study beyond targeted label comprehension is the best use of the Applicant's time and resources when this example of misuse might not involve more than 0.8-0.9% total olopatadine per day, and when a self-selection study would not address other examples of misuse with a potentially greater inherent risk.

3. Potential Misuse: Consumers who have two or three of the products in the medicine cabinet (perhaps they previously purchased Pataday 0.1% but now that the 0.7% is available they want to use that), and they or someone else in the family inadvertently confuses the products at the time of administration and mistakenly takes the 0.7% twice a day.

   Addressed by current LDS/LCS?: The LDS showed that approximately 50% of consumers thought the products had a similar look and feel – theoretically providing more evidence for this possibility.

   Potential Consumer Behavior Study Path Forward: None. The Applicant would either have to change the look and feel of the 0.7% package to avoid confusion, or conduct a safety study.

   In summary, Ms Cohen wrote that the lack of safety data is problematic because there is no objective information by which to weigh the impact of the above instances of misuse that will undoubtedly occur. Furthermore, although consumer behavior studies could provide research-based insights with which to minimize instances of misuse (such as in creating and assessing optimized labeling), as well as data to inform predictions of the likelihood of such instances under the circumstances of optimized labeling, as seen in potential misuse above, there are no consumer behavior studies easily envisioned that could help to mitigate this occurrence. As stated in Ms Cohen's paper, "While it could be contended that this is always the case with umbrella branding, and yet we approve products that fall under this rubric, this situation appears to be different because theoretically here a one-time consumer mistake could have significant consequences. In the more typical umbrella branding situation, either a one-time mistake would not have significant consequences or alternatively we would have full safety information with which to weigh its impact."

   Ms. Cohen suggested the following options, but also noted the limitations of these options:

- We could ask the Applicant to conduct the consumer behavior studies outlined above, and if the resulting data merely underscores the above issues, at that point they would need to do a safety study. However, that is still problematic because if the resulting data implies less of a concern, we still know that studies can't perfectly predict behavior, and in any case potential misuse #3 cannot be addressed by a study.

- Another option could be to give the Applicant the choice of either changing the packaging design for Pataday 0.7%, and conducting targeted LCS and self-selection, or doing a safety study. If they opt for a safety study (which may be likely given the marketing strength of umbrella branding) and it turns out that there is no harm related to higher dosing, FDA could decide that there would be no need for further consumer studies. If there is some degree of harm, at that point the requisite studies could be conducted accordingly.

- A third option could be to have the Applicant conduct an actual use study (AUS), where study participants take the products home and use as they ordinarily would. While the findings would certainly be helpful, it would be very difficult for an AUS to sufficiently address the potential misuse scenario of a consumer having more than one Pataday product in the medicine cabinet, nor would it address the misuse scenario of purchasing and using Pataday 0.1% to relieve redness, along with use of Pataday 0.7%. A standard AUS focuses on one product only.

Ms Cohen concluded that, "Ultimately, the role of consumer behavior studies is not to replace safety data, but to 'partner' with it so that the medical officers have full context in making a benefit-risk approval decision."

13. Postmarketing Recommendations

At this time, consideration is being made to requiring a Postmarketing Commitment (PMC) which would include an Enhanced Pharmacovigilance (EPV) over a period of three years in which misuse, abuse, and overuse events will be followed more closely. See Option 4 in **Table 14** above. Approval of this papplication is contingent on the Applicant's agreement to the PMC and agreement to labeling revisions (see **Section 14** below).

14. Recommended Comments to the Applicant

Approval letter will be issued to the Applicant, pending agreement with the Applicant regarding PMC and stronger labeling to discourage misuse and overuse. At the time of this writing, an Information Request is planned to be sent to the Applicant requesting:

1. Revision of the Twin Pack color scheme as pre IDS labeling recommendations
2. Revision of Directions to include bolding as follows:

Put **one drop** in the affected eye(s) **once daily. Do not exceed one drop per eye per day.**

If agreement is reached with the Applicant on labeling and a PMC, the Approval letter will include relevant specific language such as:

For a period of 3 years, submit as 15-day alert reports, all initial and follow-up post marketing adverse event reports of misuse, abuse, and overuse from all post-marketing sources, including consumer reports, solicited reports, foreign reports, and clinical study reports. As part of the periodic safety reports, provide a summary analysis of misuse adverse events, from post-marketing reports and those published in the medical literature, as well as a cumulative summary of these events.

References

Au, A. and Grigorian, P. et al; Allergic Conjunctivitis; https://eyewiki.aao.org/Allergic_conjunctivitis; accessed 7/29/2019.

Bielory, L, 2000, Allergic and immunologic disorders of the eye. Part II: ocular allergy, J Allergy Clin Immunol, 106(6):1019-1032.

Fisher AA, Stillman MA. Allergic Contact Sensitivity to Benzalkonium Chloride. Arch. Dermatol. 1972 Aug; 106(2): 169-71

Guzman-Aranguez, A, P Calvo, I Ropero, and J Pintor, 2014, In vitro effects of preserved and unpreserved anti-allergic drugs on human corneal epithelial cells, J Ocul Pharmacol Ther, 30(9):790-798.

Jagarlamudi, A, E Anushree, S Harika, K Kavya Sri, and C Rohit, 2019, A simple randomized comparative study to evaluate the efficacy of 0.7% w/v Olopatadine hydrochloride ophthalmic solution and the Fixed Dose Combination of 0.1% w/v Olopatadine hydrochloride and 0.4% w/v Ketorolac tromethamine ophthalmic solution for the treatment of allergic conjunctivitis, J Drug Deliv Ther, 9(3):279-285.

O'Brien, TP, 2013, Allergic conjunctivitis: an update on diagnosis and management, Curr Opin Allergy Clin Immunol, 13(5):543-549.

Sarkar J, Chaudhary S, Namavari A et al. Corneal Neurotoxicity Due to Topical Benzalkonium Chloride. *Invest Ophthalmol Vis Sci.* 2012 Apr 6;53(4):1792-802

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

FRANCIS E BECKER
07/09/2020 05:38:29 PM

KAREN M MAHONEY
07/13/2020 08:11:56 PM
I concur with Dr. Becker's recommendation for approval. The applicant agreed with strengthened DFL wording regarding not overusing the product, and to a postmarketing commitment for enhanced pharmacovigilance.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

0206276Orig1s005

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505(b)(1)
Application Number(s)	sNDA 206276, S-005
Priority or Standard	Standard
Submit Date(s)	September 13, 2019
Received Date(s)	September 13, 2019
PDUFA Goal Date	July 13, 2020
Division/Office	Division of Nonprescription Drug Products/ODEIV/OND
Reviewer Name(s)	Steven Osborne, MD
Review Completion Date	June 16, 2020
Established/Proper Name	olopatadine hydrochloride ophthalmic solution 0.7%
(Proposed) Trade Name	Pataday Once Daily Relief with labeling descriptor Extra Strength (Pazeo was Rx name)
Applicant	Alcon Research, LLC (“Alcon”)
Dosage Form(s)	Solution (ophthalmic use)
Applicant Proposed Dosing Regimen(s)	One drop in the affected eye(s) once daily, (b) (4) (b) (4)
Applicant Proposed Indication(s)/Population(s)	Temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair and dander/adults and children 2 years of age and older
Recommendation on Regulatory Action	Conditional Approval: Conditional upon strong labeling to help minimize overuse or misuse, coupled with postmarket safety follow-up. (See Options Table in Section 7.8.2)
Recommended Indication(s)/Population(s) (if applicable)	Temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair and dander/adults and children 2 years of age and older (same as proposed by Applicant)

Table of Contents

Table of Tables

Table of Figures

Glossary

AC	allergic conjunctivitis
AE	adverse event
BAK	benzalkonium chloride
BZK	benzalkonium chloride
CAC	Conjunctival Allergen Challenge
CCDS	Core Company Data Sheet
CMC	chemistry, manufacturing, and controls
CR	Complete Response
DFL	Drug Facts Label
DM	diabetes mellitus
DNDP	Division of Non-Prescription Drug Product
DPVII	Division of Pharmacovigilance II
DTOP	Division of Transplant and Ophthalmology Products
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
IOP	intraocular pressure
ISS	integrated summary of safety
LDS	label discernment study
MedDRA	Medical Dictionary for Regulatory Activities
MRHOD	maximum recommended human ophthalmic dose
NDA	new drug application
NPDS	National Poison Data System
OSE	Office of Surveillance and Epidemiology
OTC	over the counter
PADER	Periodic Adverse Drug Experience Report
PAC	perennial allergic conjunctivitis
PSUR	Periodic Safety Update report

PT	preferred term
QA	quality assurance
SAE	serious adverse event
SAC	seasonal allergic conjunctivitis
SAR	seasonal allergic rhinitis
SOC	system organ class
TEAE	treatment-emergent adverse event
WHO	World Health Organization

1. Executive Summary

1.1. Product Introduction

On January 30, 2015, FDA approved NDA 206276, olopatadine hydrochloride ophthalmic solution 0.77% (or olopatadine 0.7%), with a proprietary name of Pazeo, for use as a prescription drug for the treatment of ocular itching associated with allergic conjunctivitis (AC). This NDA supplement is a full switch of Pazeo from prescription (Rx) to over the counter (OTC).

The Applicant proposes the OTC name of Pataday Once Daily Relief with the labeling descriptor "Extra Strength" and with the same indication and dosing as in the prescription labeling. The dosing instructions are adults and children 2 years of age and older: put one drop in the affected eye(s) once daily, (b) (4)

This review borrows information from the reviews of the Rx to OTC switches of olopatadine hydrochloride ophthalmic solution 0.22% (or olopatadine 0.2%, sNDA 021545) and olopatadine hydrochloride ophthalmic solution 0.11% (or olopatadine 0.1%, sNDA 020688) by Elizabeth Donohoe, MD, both dated January 21, 2020 in DARRTS.[1] On February 14, 2020, FDA approved the full switch of olopatadine 0.1% from Rx-to-OTC (sNDA 020688) with the OTC name of Pataday Twice Daily Relief (relief of itching and redness) and olopatadine 0.2% (sNDA021545) with the OTC name of Pataday Once Daily Relief (no descriptor, relief of itching). Also, for this application, the Applicant refers to the safety data for all olopatadine products it submitted for the switches of Patanol and Pataday.

Table 1 below shows the recently approved switches and current olopatadine application.

Table 1. Olopatadine HCl Ophthalmic Solutions With Successful or Planned Rx-to-OTC Switches

NDA# / (IND#)	Rx Product	Rx Approval Year / OTC Approval	OTC Names
020688 / (107178)	Patanol (olopatadine 0.1%)	1996 / Feb 14, 2020	Pataday Twice Daily Relief
021545 / (142363)	Pataday (olopatadine 0.2%)	2004 / Feb 14, 2020	Pataday Once Daily Relief
206276 (060991)	Pazeo (olopatadine 0.7%)	2015 / Pending	Pataday Once Daily Relief "Extra Strength" PDUFA July 13, 2020

Abbreviations: OTC, over-the-counter
Source: Current reviewer

Olopatadine Active Ingredient

Olopatadine is a topical antihistamine with selective H1 receptor antagonist activity and mast cell stabilizing effects. It is marketed as an ophthalmic agent for the prevention or treatment of ocular pruritus due to allergic conjunctivitis and as a nasal spray for the relief of the symptoms

[1] This review has wording borrowed and adapted from the review of sNDA 021545 (olopatadine hydrochloride ophthalmic solution 0.22%) by Elizabeth Donohoe, MD

of seasonal allergic rhinitis (SAR). Olopatadine exhibits two distinct mechanisms of action. It inhibits histamine release from mast cells and is a relatively selective antagonist of H1 receptors. As a result, olopatadine prevents type 1 immediate hypersensitivity reactions. Topical ocular administration relieves the ocular pruritus associated with allergic conjunctivitis. Intranasal administration relieves symptoms associated with SAR. Olopatadine does not act upon alpha-adrenergic, dopaminergic, type 1 or type 2 muscarinic, or serotonergic receptors. There is minimal systemic absorption with ophthalmic use. (Source: Rx full prescribing information)

FDA approved olopatadine hydrochloride ophthalmic solution 0.7%, marketed as Pazeo (NDA 206276), as a prescription drug in 2015. Previous approvals of olopatadine ophthalmic solutions include a 0.1% ophthalmic solution (Patanol, a prescription drug) in December 1996, and a 0.2% ophthalmic solution (Pataday, a prescription drug) in December 2004. On February 12, 2020, FDA approved the full switches Rx-to-OTC of both Patanol and Pataday under the proprietary names of Pataday Twice Daily Relief and Pataday Once Daily Relief, respectively (see section XYZ). The Applicant cross-references these additional olopatadine ophthalmic solutions (Patanol and Pataday) in its submission.

The proposed OTC indication for Pazeo is also "temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair and dander/adults and children 2 years of age and older." The recommended dose for olopatadine 0.7% is one drop in each affected eye once daily as needed for relief of eye itching. Safety and effectiveness have been established in patients two years and older, with no overall differences in safety and effectiveness between elderly and younger patients (Full Prescribing Information).

Reviewer Comments:

- *The Applicant has not requested 5-year or 3-year Waxman-Hatch exclusivity for olopatadine 0.7%.*
- *The Applicant, Alcon, provided a letter of authorization to FDA from Novartis for the right to switch Pazeo from Rx to OTC. Novartis spun off Alcon as an independent company on or about April 9, 2019.*
- *The names Pazeo, olopatadine 0.7%, and Pataday Once Daily Relief Extra Strength are used interchangeably in this review as they are used in different portions of the Applicant's submission and subsequent Clinical Information Amendments and teleconferences.*

1.2. Conclusions on the Substantial Evidence of Effectiveness

The efficacy of olopatadine ophthalmic solution 0.7% was established for the indication of allergic conjunctivitis in clinical trials reviewed by the Division of Transplant and Ophthalmology Products (DTOP) for the prescription approval in 2015. This indication translates to the OTC use of temporarily relieving itchy eyes due to pollen, ragweed, grass, animal hair and dander. Refer to the clinical review dated December 14, 2014 by Wiley Chambers, MD for a comprehensive assessment of efficacy.

1.3. Benefit-Risk Assessment

Allergic conjunctivitis (AC) in the USA is relatively common, affecting 15%-25% or more of the population in the USA (O'Brien 2013). AC is a mast-cell mediated hypersensitivity reaction that can manifest as seasonal allergic conjunctivitis (SAC) and/or perennial allergic conjunctivitis (PAC). Allergic conjunctivitis involves inflammation of the conjunctiva, sparing the cornea in the mild forms but in the more chronic forms possibly involving the cornea. SAC is characterized by multiple symptoms, including watery eyes (85%), itchy eyes (85%), red eyes (75%), sore eyes (75%), swollen eyes (70%), and stinging eyes (65%) (Bielory 2000). Accurate diagnosis of symptoms associated with allergic conjunctivitis is generally recognizable by the consumer, particularly with itchy eyes as a primary symptom.

Other types of ocular allergy (non-SAC or non- PAC) are more serious, and referral to an ophthalmologist is generally warranted. An example includes vernal keratoconjunctivitis, which is associated with conjunctival scarring, eyelid thickening, ptosis, corneal neovascularization, ulceration, thinning, infection, keratoconus, and vision loss.

Reviewer Comment: Consumers would likely be under the care of a physician for these more serious conditions such as vernal keratoconjunctivitis.

Potential Benefits

Although allergic conjunctivitis is not a serious condition, it has been associated with headache and fatigue, impaired concentration and learning, loss of sleep, and reduced productivity.

Multiple OTC products to treat eye allergy symptoms are marketed in the United States; some are approved through the NDA process or marketed via the monograph system. In particular, ophthalmic solutions as treatments can help avoid the systemic side effects from oral antihistamines. The Applicant developed olopatadine 0.7% ophthalmic solution to extend the duration of relief over a period of 24 hours with once daily dosing vs. the 16-hour duration of relief with the 0.2% olopatadine solution. (see Table 9 in section 9 of this review).

Potential Risks

The risks of the olopatadine ophthalmic solutions have been characterized through clinical trials and post-marketing experience.

Table 2 below lists potential safety issues identified by the Applicant and listed in the Rx labeling, followed by a discussion of these safety issues. (Pazeo Package Insert).

Table 2. Applicant's List of Potential Safety Concerns From the Rx Label and the PSUR From May 1, 2017 to April 30, 2018

Current Safety Concerns	Comment (Addressed in Latest PSUR)
Important identified risks*	
Hypersensitivity	Addressed in Sections 16.3.1.1 and 16.4.1.1
Important potential risks*	
Corneal damage	Addressed in Sections 16.3.2.1 and 16.4.2.1
Missing (unstudied) information**	
Use during pregnancy	Addressed in Sections 16.3.5.1 and 16.4.3.1
Use during breastfeeding	Addressed in Sections 16.3.5.2 and 16.4.3.2

Source: Applicant's Core Safety Risk Management Plan Version 1.0 dated Oct 27, 2015
* Important risks are those risks which could have an impact on the risk-benefit balance of the product.
** Low risk during pregnancy and breastfeeding with no need for a warning on the Drug Facts Label, addressed by Division of Pediatric and Maternal Health consult
Abbreviation: PSUR, periodic safety update report

In the two most recent Periodic Safety Update Reports (PSURs) submitted to the three olopatadine NDAs covering the periods of May 1, 2015 to April 30, 2018 and May 1, 2018 to April 20, 2019, the Applicant states that it made no updates to the Core Company Data Sheet (CCDS) as a result of the PSUR.

Important Identified Risk: Hypersensitivity

Hypersensitivity and eyelid edema are listed adverse events in the Rx label for olopatadine 0.1% and 0.2% eye drops. However, these events are not listed for olopatadine 0.7%. Of note, reports of hypersensitivity reactions may be confounded by the underlying condition for which the patient was receiving olopatadine eye drops.

Reviewer Comment: Apparently, hypersensitivity or eyelid edema were not observed in clinical *trials involving 428 subjects exposed to olopatadine 0.7%. However, the Applicant lists hypersensitivity as a contraindication in the CCDS covering all ophthalmic formulations of olopatadine.*

Hypersensitivity may occur either associated with olopatadine, with the preservative benzalkonium chloride (BAK), or with any of the excipients used in the formulation.

Important Potential Risk: Corneal Damage

Anti-allergic treatments are often administered for several months to manage symptoms. Adverse events occurring with longer-term exposure to any topical ocular drug may be associated with either the active component or the preservative.

Many ophthalmic topical agents, including olopatadine eye drops, contain the preservative BAK. Corneal toxicity appears to be related to the BAK (preservative) concentration, dosage, and duration of treatment. The chronic use of ophthalmic solutions containing this preservative can have a cumulative effect and can cause a higher incidence of inflammatory reactions, epithelial damage, edema, and bullous keratopathy in predisposed patients.

However, cytotoxic effects induced by the anti-allergic eye drop products may not be exclusively due to the preservatives, with an increased toxicity having been observed in vitro

when BAK was accompanied with ketotifen or olopatadine than with BAK vehicle alone (Guzman-Aranguez et al. 2014).

The corneal disorders of keratitis and punctate keratitis are potential adverse events per the current CCDS for olopatadine 0.1% and 0.2% eye drops, but not for 0.7% eye drops. Since olopatadine 0.7% eye drops solution contains the same preservative in similar concentration as the other ophthalmic formulations of olopatadine, the Applicant states they are monitoring this risk for olopatadine 0.7% eye drops.

Other Less-Serious Warnings or Nonserious Adverse Events

The FDA-approved product labeling for Pazeo includes Warnings and Precautions regarding topical use only, contamination of tip and solution, and contact lens use. In clinical trials, most commonly reported adverse reactions occurred in 2% to 5% of patients treated with either Pazeo or vehicle. These events were blurred vision, dry eye, superficial punctate keratitis, dysgeusia, and abnormal sensation in eye.

Benefit-Risk Integrated Assessment

The Applicant submitted its own Benefit-Risk assessment for Pazeo included with the applications for Patanol (0.1%) and Pataday (0.2%). The Benefit-Risk assessment by Dr. Donohoe for the switch of Patanol and Pataday also has pertinent information about risks for ocular exposure to olopatadine products. This review borrows, in part, from both assessments.

Background:

For a drug to be marketed OTC, it must have the following characteristics:

Can be adequately labeled such that:

- The consumer can self-diagnose, self-treat, and self-manage the condition being treated
- No health care practitioner is needed for the safe and effective use of the product
- Drug has low potential for misuse and abuse by the consumer
- Safety margin is such that the benefits of OTC availability outweigh the risks

Reviewer Comment
An additional consideration that can factor into the safety margin regards the dosage strength, such that the dose is high enough to be effective, but low enough to be safe in the OTC setting.

Assessment:

Allergic conjunctivitis is a common condition accompanying seasonal or perennial allergies, and consumers often look for relief of eye itchiness as the symptom and redness as a sign. Current therapies include ocular surface lubricants, topical decongestants (vasoconstrictors), oral antihistamines, mast cell stabilizers (inhibitors), NSAIDs, and corticosteroid eye drops.

Although the current therapies for AC are generally adequate, olopatadine offers another option as an antihistamine and mast cell stabilizer. Olopatadine ophthalmic solution has a track record of use in patients since 1996 for the 0.1% solution, although Pazeo (0.7%) has been marketed only for 4-5 years. Over ten thousand patients have been exposed to olopatadine in completed clinical trials to date. Over (b) (4) patient months have been exposed cumulatively as of December 31, 2018 (per NDA 020688/S-032, Module 5, integrated summary of safety (ISS)) to ophthalmic formulations of olopatadine in more than 100 countries. Of note, human exposure to olopatadine 0.7% in clinical trials was only in 561 subjects, with 330 of these receiving 1 drop each eye per day for 6 weeks.

The Applicant submitted the two most recent evaluations of the key safety topics e in the PSURs submitted together to the three olopatadine NDAs, covering the period of May 1, 2015 to April 30, 2018, and then May 1, 2018 to April 30, 2019. These data are consistent with previous findings and do not change the overall risk assessment. Overall, the Applicant assessed that olopatadine in the prescription market, in all strengths and dosage forms, is generally well-tolerated, with few serious adverse events (SAEs), for the approved indications and doses. No changes were made to the Core Company Data Sheet (CCDS).

The most common ocular adverse events (AEs) associated with olopatadine ophthalmic solutions across clinical studies included headache, blurred vision, dry eye (and other ocular effects commonly associated with dry eye, e.g., abnormal sensation in the eye, pruritus, hyperemia, and ocular discomfort), and events like the underlying disease being studied.

The Applicant states that a review of its internal database (Argus), FDA Adverse Event Reporting System (FAERS), World Health Organization (WHO), and National Poison Data System (NPDS) data revealed no evidence that adverse events associated with the use of olopatadine prescription drugs are changing. The Applicant stated that "The number of received adverse event reports remained low with very slight variations over the analysis period with a reporting rate of 9.4 adverse event reports/million units sold globally for Novartis (Alcon) products, when considered as a primary suspect drug. However, it must be noted that the comparison of the reporting frequency of adverse events is limited due to the overall small number of the yearly received reports. Additionally, it is generally recognized that no reliable estimation of true incidence or a comparison of yearly reporting rate of adverse events can be made from spontaneous reporting data due to numerous confounding factors. Overall, the number of cases remains low and Novartis (Alcon) has observed no change in the positive benefit-risk profile of olopatadine." This reviewer agrees with this assessment (prescription use).

The potentially serious safety issues with this application are the hypersensitivity and corneal damage outlined by the Applicant. However, the more pertinent potential safety issue may be related to intentional or unintentional misuse or overuse of Pazeo by a consumer. Pazeo (olopatadine 0.7%) is 7-fold and 3.5-fold stronger than Patanol (0.1%) and Pataday (0.2%), respectively. Each of those drugs have seen OTC use in other countries, although Pazeo with its shorter track record, has not been marketed OTC overseas. In clinical trials, the Applicant stated that it did not dose subjects at more than one drop each eye per day, nor were they aware of any data dosing higher than one drop each eye per day. Thus, safety has not been studied at any dose higher than the current prescription dose, which is the proposed OTC dose. It is not clear whether any adverse events might be seen in a higher frequency or severity if a consumer overuses the drug. Of note, one serious adverse event from FAERS (cataract, although unlikely related to Pazeo) included verbatim that the patient used Pazeo three or four times daily. Another involved twice daily use. *These SAEs are notable not so much for the actual adverse event (cannot infer causality from a postmarket adverse event report) but the stated overuse despite having been instructed either by the learned intermediary, the labeled directions for use, or both.*

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Allergic conjunctivitis is common Estimated frequency of allergic conjunctivitis ranges from 5% to 22% of the population depending on the area of the USA studied. Symptoms of eye itchiness with allergic conjunctivitis are common.	Relief of eye itchiness due to allergic conjunctivitis is important to consumers for physiologic reasons and for physical comfort. Relief of symptoms of allergic conjunctivitis improves quality of life for consumers.
Current Treatment Options	Multiple antihistamine eye drop solutions are currently marketed OTC to treat allergic conjunctivitis. Mechanism of action for OTC eye drops to treat allergies includes antihistamine action and mast cell stabilization.	Pharmacotherapy has been the mainstay of treatment for conjunctival irritation. Most sufferers self-treat for minor eye irritations, which highlights the importance of OTC treatments for control of some of the symptoms.
Benefit	Olopatadine is a topical antihistamine with selective H1 receptor antagonist activity and mast cell stabilizing effects. It has been marketed as an ophthalmic agent to treat symptoms of allergic conjunctivitis in the United States since 2015 (as Pazeo, 0.7%). The Applicant is relying on preclinical and toxicology data and clinical studies for the 2015 NDA Pazeo approval to support efficacy and safety.	The effectiveness of the product has been established to treat symptoms related to allergic conjunctivitis. This eye drop product provides an additional choice to consumers who experience such symptoms. This eye drop product has both antihistamine and mast cell stabilizing properties.
Risk and Risk Management	For a risk assessment in this application, the Applicant submitted a ISS for all olopatadine products and postmarket safety data from 2000-2018, supplemented by updates from PSURs, Periodic Adverse Drug Experience Reports (PADERs), and a 120-day safety update. The proposed OTC labeling has the essential warnings translated from the current Pazeo Rx label; additional warnings regarding pregnancy and breastfeeding are not warranted. Adverse events are predominantly non-serious, however a few, such as hypersensitivity and corneal damage are listed in the Rx full prescribing information . However, an unknown for this application is what will happen if a consumer does not follow the proposed Drug Facts Label and misuses (overuses) the drug. In this instance the potential for adverse events is unstudied since the Applicant has not studied, nor is it aware of any	Olopatadine hydrochloride has a satisfactory safety profile in the prescription environment based on 23 years of clinical use for all olopatadine products and approximately 4 years for Pazeo in the postmarketing experience in the United States. Adverse events associated with olopatadine hydrochloride and its use as an ophthalmic solution are most commonly identified as headaches and eye symptoms. Safety of olopatadine hydrochloride ophthalmic solution 0.7%, in the prescription environment, is supported by clinical trial data (zero SAEs) and generally by postmarket safety data (26 SAEs over approximately 4 years, none fatal).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	data, in which subjects were exposed to more than one drop in each affected eye per day. The longest duration for use was 6 weeks. This length of time may be adequate for seasonal allergic conjunctivitis, however not for perennial allergic conjunctivitis. Consumers may overuse by daily dose and by length of time of use.	Warnings provided in the proposed OTC labeling may help mitigate the risk of serious adverse events. Potential misuse of the 0.7% olopatadine eye drops exposes a consumer to a dose of olopatadine that, based on information submitted by the Applicant and in the literature, has not been studied.

1.4. Patient Experience Data

Patient experience data were not submitted with this application for Pazeo 0.7%.

2. Therapeutic Context

2.1. Analysis of Condition

Allergic conjunctivitis is common. The estimated frequency of allergic conjunctivitis ranges from 5% to 22% of the population depending on the area of the USA studied. Symptoms of eye itchiness with allergic conjunctivitis are common. Relief of eye itchiness due to allergic conjunctivitis is important to consumers for physiologic reasons and for physical comfort. Additionally, relief of symptoms of allergic conjunctivitis improves the quality of life for consumers. Treatment options are listed below.

2.2. Analysis of Current Treatment Options

Several classes of drugs that have been used to treat or manage symptoms of allergic conjunctivitis including, but not limited to:

- Ocular surface lubricants
- Topical decongestants (vasoconstrictors)
- Systemic antihistamines
- Mast cell stabilizers (inhibitors of mast cell release)

Ocular surface lubricants such as isotonic saline, artificial tears, and ointments help to rinse antigens from the eye. However, these agents do not have direct efficacy on allergic mediators. These provide only temporary relief and have little or no effect on moderate-to-severe ocular allergy. They may also contain preservatives and when used excessively, can injure an already irritated ocular surface.

Topical decongestants (vasoconstrictors) are α-agonists that act to reduce redness and edema. Overuse of these agents, however, can cause mydriasis (pupil dilation) and lead to rebound hyperemia of the conjunctiva. Overall, vasoconstrictors are not recommended for treating ocular allergies, as the topical antihistamines are safer and more effective.

In recent years, topical antihistamines have become the mainstay of management for allergic conjunctivitis. The benefits of these agents are that they block histamine, stabilize the mast cell, and inhibit eosinophil activation and migration, thereby addressing the signs and symptoms of ocular allergy, particularly itching.

Systemic antihistamines can be used, in some cases, but these medications tend to dry the ocular surface (O'Brien 2013).

Mast cell stabilizers (inhibitors) prevent degranulation of mast cells. These agents are particularly effective in seasonal allergic conjunctivitis and perennial allergic conjunctivitis in which the predominant cell types are the mast cell and eosinophil. Ketotifen and olopatadine are examples of mast cell stabilizers.

Table 3 below lists some of the current OTC products that treat ocular itching, redness, or both.

Table 3. Examples of OTC Ophthalmic Drops Treatment Armamentarium for Allergic Conjunctivitis

Product(s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Zatidor NDA 021066	Ocular itching alone	2007 OTC 1999 Rx	Ophthalmic route	Effective relief of itching	Safe and tolerable	ketotifen 0.025% "Temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair and dander"
Alaway NDA 021996	Ocular itching alone	2007 2007	Ophthalmic route	Effective relief of itching	Safe and tolerable	ketotifen 0.025% Same Use on DFL as Zatidor
Patanol olopatadine HCL 0.1% NDA 020688	Ocular itching alone	1996	Ophthalmic route, twice daily		Safe and tolerable	Approved OTC February 2020 Similar Use to Zatidor
Pataday Olopatadine HCl 0.2% NDA 021545	Ocular itching alone	2008	Ophthalmic route, once daily		Safe and tolerable	Approved OTC February 2020 Similar Use to Zatidor
Other treatments						
Opcon-A NDA 020065	Ocular itching and redness	1994	Ophthalmic route			0.02675% naphazoline HCL and 0.315% pheniramine "Temporarily relieves itching and redness caused by pollen, ragweed, grass, animal hair and dander"
Visine A NDA 020485	Ocular itching and redness	1996	Ophthalmic route	Effective relief of redness due to minor eye irritations	Safe and tolerable, overuse can lead to rebound redness	0.025% naphazoline HCl and 0.3% pheniramine maleate

Abbreviations: DFL, drug facts label; NDA, new drug application; OTC, over-the-counter
Source: Current reviewer

Reviewer Comments:

- *In 2006-2007, ketotifen-containing ophthalmic drugs (Zatidor, Alaway) moved to the OTC market via Rx-to-OTC switches. Patanol and Pataday were switched to OTC in February 2020.*

- *Drugs containing an active ingredient such as naphazoline or oxymetazoline, alpha blockers used to relieve redness, can lead to rebound ocular irritation and redness. Rebound typically does not occur with antihistamines or antihistamine-mast cell stabilizers like ketotifen and olopatadine.*

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Until February 14, 2020, olopatadine ophthalmic solutions were marketed as prescription drugs in the United States under the trade names Patanol (olopatadine 0.1%), Pataday (olopatadine 0.2%), and Pazeo (olopatadine 0.7%), as listed below.

- Patanol (olopatadine 0.1%) was approved on December 18, 1996 under NDA 20688 for the treatment of signs and symptoms associated with allergic conjunctivitis (itching and redness relief) dosed twice a day. Patanol was switched to OTC on February 14, 2020 under the trade name Pataday Twice Daily Relief (itching and redness relief).
- Pataday was approved on December 22, 2004, under NDA 21545, for the treatment of ocular itching associated with allergic conjunctivitis dosed once a day. Pataday was switched to OTC on February 14, 2020 under the trade name Pataday Once Daily Relief (itching relief).
- Pazeo was approved on January 30, 2015, under NDA 206276, for the treatment of ocular itching associated with allergic conjunctivitis dosed once a day. Pazeo is the subject of the current switch application.

Reviewer Comment:

In this sNDA 206276, the Applicant references information related to all three ophthalmic products containing olopatadine hydrochloride (Patanol (0.1%), Pataday (0.2%) and Pazeo (0.7%). However, this review provides analysis and recommendations related only to Pazeo.

3.2. Summary of Presubmission/Submission Regulatory Activity

Regulatory Background

Three teleconferences listed below, and no face-to-face meetings, or pre-NDA meetings were held for this sNDA 206276.

Teleconference on April 3, 2019 Under PIND 142363 (sNDA 021545; Olopatadine 0.2%)

Meeting notes indicated that:

- FDA's DTOP noted that there are no significant differences in the safety and efficacy profiles for olopatadine 0.1%, 0.2%, and 0.7% and the distinction in the indications is based on the frequency of dosing (twice daily versus once daily) and not on concentration.
- Twice daily dosing is indicated for itching and redness relief, while the once daily dosing is only indicated for itching relief. Redness relief was not supported with once a day dosing for any of the concentrations.
- Alcon stated it had only considered switching olopatadine 0.1% and 0.2% from Rx-to-OTC marketing status, and that for business reasons it had not aimed to switch olopatadine 0.7%.
- FDA noted the Applicant will need to address the differences in indications in its submission(s).
- FDA agreed that additional clinical efficacy data would not be required to switch the 0.1% and 0.2% solutions.
- The Applicant stated it would like to market both olopatadine 0.1% and 0.2% under the same name, Pataday, as Pataday Twice Daily Relief (0.1%) and Pataday Once Daily Relief (0.2%). FDA expressed concerns that consumers may not be able to differentiate between the two olopatadine products. If the Applicant decides to market more than one olopatadine concentration, a label discernment study will likely be needed to distinguish between multiple olopatadine products.
- Alcon stated it had some market research data demonstrating consumers were able to distinguish between the different olopatadine products and would share this information with the FDA.

Reviewer Comment:

- *Upon further internal discussion after the April 3, 2019 teleconference, FDA determined that there were no safety concerns with the Applicant's proposed names for olopatadine ophthalmic drops 0.1% and 0.2%. Even if consumers interchanged the two products and dosed olopatadine 0.2% incorrectly at twice daily, the drug exposure would still be safe as it would be lower than with Rx Pazeo.*
- *In section 1.6.3 of its submission of sNDA 206276, the Applicant states that it met with FDA (teleconference) on April 3, 2019 in a Type B-Pre-sNDA meeting regarding the Rx-to-OTC switch of Pazeo. However, in that meeting, although FDA recommended Alcon consider switching Pazeo (0.7%), in addition to Patanol (0.1%) and Pataday (0.2%), Alcon stated that Novartis had not granted the Pazeo switch rights, so Alcon did not submit the Pazeo sNDA. Therefore, the April 3, 2019 meeting was held as a pre-NDA meeting for the 0.1% and 0.2% olopatadine hydrochloride ophthalmic products, not for a switch of*

Pazeo. FDA and the Applicant did not hold a pre-NDA meeting for Pazeo before the Applicant submitted a switch application on September 13, 2019.

Teleconference on September 10, 2019 Under PIND 060991 (sNDA 206276, Olopatadine Hydrochloride 0.7%)

Meeting minutes indicated that:

- Alcon stated that Novartis had now granted switch rights, so Alcon now plans to submit a sNDA for the Rx to OTC switch of Pazeo on September 16, 2019.
- Alcon stated the data they will submit are identical to those submitted for the Rx to OTC switch of Patanol and Pataday. They stated the only differences between the supplement for Pazeo and the other olopatadine supplements currently under review will be labeling and a request for the proprietary name, (b) (4) as the OTC version for Rx Pazeo.
- Alcon stated that they may submit a request for a different proprietary name for olopatadine 0.2%, conditionally approved as Pataday Once Daily Relief, namely, (b) (4) (b) (4), which should help consumers distinguish the olopatadine 0.7% from the 0.2% products. FDA did not comment on the acceptability of the proposed proprietary names.
- FDA asked if the manufacturing sites for all three olopatadine products are the same and Alcon confirmed they are the same. FDA then agreed that no additional Chemistry Manufacturing and Controls (CMC) or nonclinical safety studies need to be conducted to support the approval of a Rx-to-OTC switch of Pazeo. The Agency would rely on the findings of safety of the nonclinical program that were reviewed and approved under the original NDA submission for the Rx Pazeo NDA 206276
- FDA noted that the Applicant should submit the same safety data as required for the olopatadine 0.1% and 0.2% Rx-to-OTC switches, namely:
  - The NDA application should contain a summary of postmarket safety information for olopatadine from the following databases (worldwide):
  - Applicant's pharmacovigilance database
  - FAERS
  - WHO's International Drug Monitoring Program
  - NPDS from American Association of Poison Control Centers
  - A review of medical literature relevant to the clinical safety of olopatadine. Include a table listing the references with the type of study, objectives, population and principal results.
  - A list of countries where olopatadine is marketed either as an Rx or OTC product. Include certified English translations of any foreign nonprescription labels.
  - Whether olopatadine has been withdrawn from any foreign markets due to safety or regulatory reasons.

- Worldwide distribution data for both prescription and nonprescription use.
- Summary protocols, narratives and analyses of SAEs, deaths and discontinuations due to AEs from all clinical trials. Stratify data by age (3 years old to < 12, 12-65, and >65). Provide comparative analysis of AEs reported by subjects in the placebo groups.

Reviewer Comment:

The Applicant noted it does not market Pazeo as a nonprescription drug in any country, thus its submission will reflect nonprescription distribution and any safety data available for its other olopatadine products (not for Pazeo).

Teleconference November 13, 2019 Under sNDA 206276

Meeting notes indicated that:

- The Applicant's label discernment study was conducted with names of the three products that are not names that FDA is comfortable with; namely, (b) (4), (b) (4), and (b) (4). (b) (4) (olopatadine 0,2%, one drop each eye once daily). This presents an issue with FDA's precedent of not allowing a specific number of hours of relief except possibly (b) (4) drug. In addition, consumers might dose (b) (4)
- The Applicant agreed to reconsider the names of the three olopatadine ophthalmic products.

Letter From DTOP to Alcon on May 9, 2019 Asking Whether Pazeo Has Any Safety Issues That Could Preclude It From Being OTC

"We have reviewed the referenced material and request that you identify whether Pazeo has any toxicity or other potentiality for harmful effect, method of use, or collateral measures necessary for its use that would make Pazeo not safe for use without the supervision of a practitioner licensed by law to administer the product."

Letter From Alcon to FDA DTOP Submitted on July 19, 2019

The Applicant submitted a response to the Advice Letter from DTOP on May 9, 2019. Novartis stated that it "considers Pazeo to be safe when used under the supervision of a healthcare professional and has no intention to switch Pazeo to nonprescription status at this time."

sNDA 206276 Submitted on September 13, 2019

The Applicant submitted sNDA 206276 requesting the Rx-to-OTC full switch of Pazeo and the proprietary name of (b) (4).

Reviewer Comment

The Applicant reversed course after its letter on July 19, 2020 wherein it stated it had no intention to switch Pazeo from Rx-to-OTC.

Information Request Sent to Applicant on October 8, 2019 Requesting the Following Information (Summarized)

- Now that there could be a third over-the-counter (OTC) olopatadine HCl ophthalmic solution (0.7%) drug for ocular itching due to allergic conjunctivitis, the potential for confusion with consumers is heightened.
- Provide any data that you have showing how consumers will effectively distinguish the three products with similar indications, directions for use and potentially similar names.

Amendment to sNDA 206276 Submitted on October 22, 2019 (SDN 467)

The Applicant submitted a Clinical Information Amendment to address the Information Request of October 8, 2019(summarized):

- The Applicant noted it had conducted a pre-test for a "label discernment study". A summary of the study was submitted and according to the Applicant's analysis, results were generally supportive of the proposed OTC labeling for Twice Daily Relief (Patanol), (b) (4), and (b) (4), and supportive of the ability of consumers to distinguish between the three olopatadine eye drop products for proposed OTC use.

A Reviewer Comments:

- *A label discernment study (LDS) evaluates the ability of a consumer subject to detect differences in the Drug Facts Label and Principal Display Panel between products in a line extension with the same or similar active ingredient, naming, or indication. This review does not address the label discernment study in further detail.*
- *The Division of Non-Prescription Drug Product's (DNDP's) social scientist (Barbara Cohen) noted that the Applicant did not submit the protocol, questionnaire, or dataset. An Information Request was sent to the Applicant to provide additional information; this study was later reviewed by DNDP's social scientist.*

Amendment to sNDA 206276 Submitted on November 4, 2019 (SDN 470)

The Applicant submitted a Clinical Information Amendment to address the Information Request sent on October 29, 2019 (SDN 470) requesting the following (summarized):

- Clarify why the Applicant performed a pre-test for a label discernment study (LDS) rather than a pivotal study. FDA also asked for the complete study details for the pre-test LDS, including the complete data collection instrument (coding of responses, screening questions, cross-tabulations, and electronic dataset.
- The Applicant provided details, which will be discussed by the DNDP social scientist, Ms. Barbara Cohen, in her review. The Applicant noted it is now conducting a pivotal LDS, termed a "Project Judo ACE Discernment Study" in male and female subjects 15 years of age and older, with a final report available on December 20, 2019. The goal is to assess whether subjects can discern the indication and dosing directions for the 0.1%, 0.2%,

and 0.7% solutions with names/products [redacted], [redacted], and [redacted].

FDA Filed the sNDA 206276 Application for Review on November 21, 2019

FDA filed the sNDA 206276 application with no filing issues identified. However, FDA sent the following Information Request to facilitate the application review in correspondence to the Applicant:

- "Submit any clinical data you are aware of in which olopatadine HCl ophthalmic solution 0.7% is dosed more than one drop in each affected eye(s) per day. These data, if available, could help address safety for any overuse or misuse by a consumer. Provide this information by December 20, 2019".
- We note your plan to submit the final report of the pivotal Label Discernment Study, called "Project Judo" on December 20, 2019. Clarify the product names you are using in this pivotal consumer behavior study, that is, have any product names been modified in your Label Discernment Study since your submission dated November 4, 2019"?

Withdrawal of Proprietary Name Request (SDN 472)

On November 22, 2019, the Applicant withdrew their name request of "[redacted]" and planned to formally submit a new request for Pataday Once Daily Relief with the descriptor "Extra Strength."

Amendment to sNDA 206276 Submitted on November 25, 2019 (SDN 473)

Submission of new proprietary name request:

- On November 25, 2019, the Applicant submitted a name request of "Pataday Once Daily Relief" with a descriptor of "Extra Strength." The Applicant noted this led to a line extension of three olopatadine ophthalmic solutions with Pataday in the name, as shown in Table 4 below, comparing the previous Proprietary Names Under Review (used in the pivotal label discernment study) with the New Proprietary Names for Review:

Table 4. Comparison of Pivotal Study Proprietary Names With FDA Newly Proposed Proprietary Names

Rx Product	Pivotal Study Proprietary Names*	Agency-Proposed Proprietary Names**
Patanol (olopatadine 0.1%)	Pataday Twice Daily Relief (0.1%)	Pataday Twice Daily Relief (0.1%)
Pataday (olopatadine 0.2%)	[redacted] (0.2%)	Pataday Once Daily Relief (0.2%)
Pazeo (olopatadine 0.7%)	[redacted] (0.7%)	Pataday Once Daily Relief with labeling descriptor Extra Strength (0.7%)

*Study completed prior to November 4, 2019 submission –pending final Report
Alcon accepted new name on November 14, 2019 submitted for review
Source: Applicant's submission of November 25, 2019

- On November 14, 2019, Alcon accepted the new names proposed by the Agency. Alcon then formally submitted the proposed proprietary names for review on November 25, 2019. Pataday Twice Daily Relief (itching relief and redness relief) remained the same.

- On or about December 2, 2019, the proposed product names for the 0.2%, and 0.7% respectively, were adjusted to Pataday Once Daily Relief and Pataday Once Daily Relief (with labeling descriptor Extra Strength).

Amendment to sNDA Submitted December 4, 2019 (SDN 476)

The Applicant submitted a Clinical Information Amendment to address the Information Request sent on November 22, 2019 requesting the following (summarized):

- Clarify whether the Applicant studied or is aware of data for a dose of Pazeo greater than one drop per eye per day. Specifically: "Submit any clinical data you are aware of in which olopatadine HCl ophthalmic solution 0.7% is dosed more than one drop in each affected eye(s) per day. These data, if available, could help address safety for any overuse or misuse by a consumer. Provide this information by December 20, 2019."
- Clarify the names used in the "Project Judo ACE Discernment Study" versus any updated names the Applicant will use for marketing if the sNDAs for Patanol, Pataday, or Pazeo are approved.
- The Applicant replied that "Alcon has never generated nor are we aware of any clinical data in which olopatadine HCl ophthalmic solution 0.7% was dosed more than one drop in each affected eye(s) per day. That said, we note that the established safety profiles of Patanol, Pataday, and Pazeo are very similar and post-market data continue to support positive benefit/risk for the three products. The majority of adverse events reported for these products are ocular in nature, easily detectable by the patient, and non-serious."
- Alcon then provided further discussions of preclinical and post-market safety data, noting 10 reports of incorrect dose administered or inappropriate schedule of product administration, however, with only one SAE.
- Regarding preclinical safety data, Alcon stated, "Likewise, olopatadine demonstrated no significant ocular effects following chronic topical administration to the eyes of rabbits and monkeys delivered 4 times a day at concentration up to 1.0% and 0.5%, respectively. (Patanol NDA 020688). And, there were no observed adverse effect levels for rats and dogs after chronic oral administration of olopatadine were 10 and 5 mg/kg/day, respectively. This is approximately 2000-fold greater than the predicted human exposure. (Patanol NDA 020688)."
- Regarding Post-Market Safety Data, Alcon stated, "The post-market safety data for Pazeo was reviewed for cases associated with the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms of 'Incorrect dose administered' and 'Inappropriate schedule of product administration,' cumulative to October 31, 2019. A total of 10 cases were found, 6 of which were associated with other AEs. The other AEs reported among these cases were 2 reports each of eye pain and drug ineffective and one report each of back pain, cataract, concomitant disease aggravated, dry eye, erythema, seasonal allergy, tremor, and vision blurred. Only one serious event was reported (cataract). The narrative for this case is presented below. Overall, the low number of cases in the safety database do not suggest a pattern of dosing of Pazeo more than the labeled posology. In

addition, all but one of the adverse events reported in these cases are nonserious and demonstrate no link to any safety issue when considering the very low number of associated adverse events reported."

- Alcon then summarized: "In summary, if a patient were to dose Pazeo twice daily (worst case scenario among the 3 products), the systemic exposure due to accumulation would not be expected to be markedly higher than on-label dosing as the mean elimination half-life is 3.4 hours. In addition, pre-clinical toxicology demonstrates an adequate margin of safety at exaggerated dosing. Though local ocular adverse events may be more frequent with twice daily dosing of Pazeo, as mentioned above, these events are easily detectable by the patient and non-serious in nature."

Reviewer Comment:

The Applicant states that if Pazeo were used twice daily, then "…these events are easily detectable by the patient and non-serious in nature." Although it is important that a consumer can detect an ocular adverse event, if that adverse event is distinctly more common with overuse than with labeled use, an adequate warning should be provided to not overuse the drug. Also, if the adverse event is simply eye irritation, that is a non-serious adverse event. The risk factors for punctate keratitis are unclear to this reviewer except that use of the drug is presumably one of the risk factors.

- Regarding the proposed names used in the pivotal LDS (Pataday Twice Daily Relief, (b) (4) and (b) (4)), the Applicant stated that "the recruitment and interviews for the pivotal Study were completed prior to the 04- Nov-2019 submission and before Agency's informal teleconference on November 13, 2019, (see teleconference above) in which the Agency proposed new proprietary names, which were subsequently accepted by Alcon (see summary Table 4 above)."
- Alcon stated: Since Alcon has accepted the Agency's proposal for the new proprietary names, the assumption is that the completed pivotal Study is no longer relevant to discernment since the proprietary names ((b) (4) & (b) (4) (b) (4)) used in the study have been withdrawn. Therefore, Alcon is no longer planning the submission of the final report on December 20, 2019, based on the recent development and Alcon acceptance of FDA's proposed proprietary names."

Amendment to sNDA Submitted on December 6, 2019 (SDN 477)

The Applicant submitted a Clinical Information Amendment to address the Information Request sent on November 12, 2019 requesting the following (summarized):

- Submit a 120-day safety update for sNDA 206276.
- The Applicant noted it had already submitted safety data from November 1, 2019 to November 30, 2019 and, in addition, had provided safety data on November 20, 2019 for all three olopatadine ophthalmic drugs (0.1%, 0.2%, 0.7%) for the period January 1, 2019 to October 31, 2019 in a 120-day safety update for NDA 020688 (Patanol, 0.1%). The Applicant's submission(s) therefore covered the period FDA requested (May 1, 2019 to November 30, 2019) for Pazeo (olopatadine 0.7%).

Amendment to sNDA 206276 Submitted on December 20, 2019 (SDN 478)

The Applicant submitted a Clinical Information Amendment to address the Information Request sent on December 16, 2019 requesting the following (summarized):

- Submit the actual data from the pivotal Label Discernment Study, even though it was completed using the withdrawn proposed proprietary names of [redacted] (0.1%), [redacted] (0.2%), and [redacted] (0.7%).
- The Applicant submitted the labeling discernment pivotal study report and Table 5 below comparing the names it used in this study versus the new Agency-proposed proprietary names.

Table 5. Agency-Proposed Proprietary Names of Olopatadine Ophthalmic Solutions Used in Applicant's Label Discernment Study

Label Discernment Pivotal Study Proprietary Names: • The PN review request was withdrawn on 22-Nov-2019, SN # 0048	**Agency Proposed Proprietary Names** • Alcon accepted Agency's proposal for PN on 14-Nov-2019, with subsequent amendment on 25-Nov-2019, SN# 0049
Pataday Twice Daily Relief (0.1%)	**Pataday Twice Daily Relief** (0.1%)
[redacted] 0.2%)	**Pataday Once Daily Relief** (0.2%)
[redacted] 0.7%)	**Pataday Once Daily Relief** with labeling descriptor **Extra Strength** (0.7%)

Source: Applicant's submission of December 20, 2019
Abbreviations: PN, proprietary names

Reviewer Comments:

- *For analysis of this LDS data, and an assessment as to how it might apply even with the new proposed names, see Barbara Cohen's social science review.*
- *The new proposed OTC name for Pazeo, as of December 2019, is "Pataday Once Daily Relief, Extra Strength." The descriptor "Extra Strength" is meant to distinguish olopatadine 0.7% from olopatadine 0.2% product that is named Pataday Once Daily Relief. Note that each of the three olopatadine-containing eye drops have "Pataday" in the name.*

Summary of Issues and Actions

The Applicant has submitted a supplemental NDA for the Rx-to-OTC switch of olopatadine 0.7% eye drop solution, currently marketed as Pazeo. Review of Pazeo as a proposed OTC product does not pose an efficacy issue; however, there is a potential for name and dosing confusion with the other OTC olopatadine eye drop solutions. In addition, a potential safety issue could arise if consumers overuse Pazeo, which would automatically lead to an ocular dose of olopatadine unstudied in humans.

Although separate DNDP clinical reviews were conducted for each olopatadine eye drop product, reference is made to the other products in this review. The indication for Patanol (relief of itching and redness) differs from Pataday and Pazeo (relief of itching) as does the

dosing regimen. The dose is one drop in each affected eye twice a day for Patanol versus one drop in each affected eye once a day for Pataday and Pazeo.

3.3. Foreign Regulatory Actions and Marketing History

Olopatadine ophthalmic solution 0.7% is marketed as a prescription drug product in five countries, however it is not marketed as a nonprescription drug in any country.[2]

Distribution[3]

The cumulative number of units of all olopatadine products sold from 2000 through April 30, 2018 was (b) (4). Cumulative exposure by units, with distribution among regions, was:

- Japan: (b) (4)
- USA/Canada: (b) (4)
- European Economic Area (Europe): (b) (4)
- Rest of the World: (b) (4)

The Applicant provided the table below showing units sold, by brand, from 2000 to the end of 2018.

Table 6. Estimated Sales of Olopatadine Ophthalmic Solution, Cumulative by Brand From 2000 Through December 31, 2018

Brand	Units Sold
Patanol (olopatadine 0.1% eye drops, solution) Pataday (olopatadine 0.2% eye drops, solution) Pazeo (olopatadine 0.7% eye drops, solution)	(b) (4)
Total	

Source: Applicant submission of September 27, 2019, Clinical Information Amendment, 1.11.3, p.1/3.

Table 7 below shows worldwide distribution data for nonprescription olopatadine ophthalmic use (global manufacturers and generics). During the same timeframe March 2013 to December 2018, the total Rx units sold were (b) (4).

The Applicant noted that OTC use during the reporting period was restricted to just a few countries with limited sales, amounting to approximately (b) (4) units over the 5-year period, as shown in Table 7 below.

[2] Source: Applicant submission of 4/15/2019 Module 5.3.5.3, Appendix 14.
[3] Source: Applicant submission of 4/15/2019 Module 5.3.5.3 ISS, p. 14/66

Table 7. Worldwide Nonprescription (OTC) Sales of All Olopatadine Ophthalmic Solutions From March 2013 Through December 2018

Country	Units Sold
Amer. Central and Carib.	(b) (4)
Hong Kong	
Italy	
Malaysia	
Singapore	
South Africa	
Total	

Abbreviations: OTC, over-the-counter
Source: Applicant's submission Module 5.5.5.3, Appendix 14, Table 4 for Patanol and Pataday switch

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

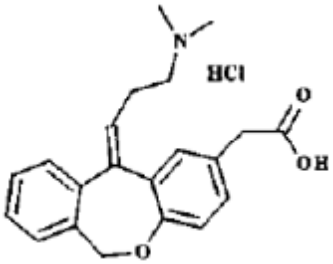
4.1. Office of Scientific Investigations (OSI)

An Office of Scientific Investigations request was not submitted for this review, since no clinical studies were conducted for this submission.

4.2. Product Quality

The Applicant is relying on FDA's previous findings under NDA 206276 (Pazeo 0.7%) regarding CMC. There are no drug substance or drug product changes from the current Rx NDA, and therefore no additional CMC work or review is required for this Rx-to-OTC switch application. The chemical structure in Figure 1 is presented below for olopatadine HCl.

Figure 1. Chemical Structure of Olopatadine



The ingredients of Pazeo are shown below:

- Pazeo (olopatadine 0.7%)

  Each mL of Pazeo solution contains an active ingredient [7.76 mg of olopatadine hydrochloride (7 mg olopatadine)] and the following inactive ingredients: povidone; hydroxypropyl-gamma-cyclodextrin; polyethylene glycol 400; (b) (4); boric acid; mannitol; benzalkonium chloride 0.015% (preservative); hydrochloric acid/sodium

hydroxide (to adjust pH); and purified water. Pazeo solution has a pH of approximately 7.2 and an osmolality of approximately 300 mOsm/kg.

Reviewer Comment:

- *As shown above, an inactive ingredient is benzalkonium chloride (BZK), used as a preservative. BZK can be an eye irritant and can also be absorbed by soft contact lenses.*
- *At the mid-cycle meeting on February 12, 2020, Dr. William Boyd from DTOP noted that BZK is used in higher total exposure in other ophthalmic drops and stated that even if a consumer used extra Pazeo or combined it with other olopatadine eyedrops concurrently or simultaneously, it would be unlikely to lead to a SAE due to the BZK component itself.*

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

To support the nonclinical safety of olopatadine 0.7%, the Applicant is relying on FDA's previous findings of nonclinical safety for olopatadine 0.1% and 0.2%. The Applicant did not conduct nonclinical safety studies for the Rx approval of Pazeo.

There is no additional review of nonclinical safety for this supplemental efficacy application.

4.5. Clinical Pharmacology

The Applicant refers to the data presented in the Rx full prescribing information and notes that:

- The mean elimination half-life of olopatadine in humans is approximately 8–12 hours.
- Olopatadine does not appear to have a significant potential for drug - drug interactions.
- Interactions involving cytochrome P-450 enzymes do not appear likely.
- Toxicokinetic studies demonstrated a satisfactory margin of safety for olopatadine. Plasma levels of olopatadine in oral toxicokinetic studies at the no-observed effect levels were 2- to 3- orders of magnitude higher than plasma levels found following topical ocular administration of 0.15% olopatadine ophthalmic solution in clinical studies
- No adjustment of Pazeo is warranted in elderly subjects, or subjects with renal or hepatic impairment.

4.6. Table of Clinical Studies

Table 8 below lists the clinical trials conducted for the Rx approval in 2015 to illustrate the point that the highest dose studied in humans in clinical trials is one drop each eye per day for 6 weeks.

Briefly, from Dr. Chambers’ review of Pazeo for the prescription approval in 2015, a total of five studies were conducted (C-10-127, C-11-036, C-10-126, C-12-053, and C-12-028) with 1125 subjects, ages 2-65. Of these 1125 subjects, 428 received olopatadine 0.7%, including 330 subjects age 2 and older who received olopatadine 0.7%, one drop in each eye once daily for 6 weeks.

Table 8. Safety and Efficacy Studies in Patients With Allergic Conjunctivitis for Rx Approval of Pazeo in 2015

Study Number	Design	Ages	Arms	Number of Subjects	Dosing	Duration
C-10-127 Phase 1 Safety and comfort	Randomized, double-masked, crossover, active- and vehicle-controlled study	≥18 years	Olopatadine HCl, 0.7% Vehicle Zaditor	43	1 drop per eye	Single dose
C-11-036 Phase 1 Safety and PK	Randomized, double-masked, parallel-group, vehicle-controlled study	18 to 65 years	Olopatadine HCl, 0.7% Vehicle	24 12	1 drop per eye once daily	7 days
C-10-126 Phase 3 Efficacy CAC	Randomized, double-masked, parallel-group, active- and vehicle-controlled study	≥18 years	Olopatadine HCl, 0.7% Olopatadine HCl, 0.2% Vehicle	66 68 68	1 drop per eye	3 non-consecutive doses over 3 weeks
C-12-053 Phase 3 Efficacy CAC	Randomized, double-masked, parallel-group, active- and vehicle-controlled study	≥18 years	Olopatadine HCl, 0.7% Olopatadine HCl, 0.2% Olopatadine HCl, 0.1% Vehicle	98 99 99 49	1 drop per eye	2 non-consecutive doses over 2 weeks
C-12-028 Phase 3 Safety	Randomized, double-masked, parallel-group, vehicle-controlled study	≥2 years	Olopatadine HCl, 0.7% Vehicle	330 169	1 drop per eye once daily	6 weeks

* Source: Dr. Chambers' 2015 NDA 206276 review for Rx olopatadine 0.7%, p.13
Abbreviations: CAC, Conjunctival Allergen Challenge; PK, pharmacokinetics

Reviewer Comments:

- *Table 8 above illustrates that the clinical studies performed for the approval of the prescription Pazeo do not include any dosing higher than one drop in each eye once daily. The Applicant confirmed it is also unaware of any study or report of higher dosing.*
- *In addition, for the approval of Patanol 0.1% in 1996, the Applicant studied a maximum dose in humans of 1-2 drops in both eyes three times daily for 6 weeks (Source: medical officer review of NDA 020688 dated July 23, 1996 by Jonca Bull, MD). Two drops maximum of a 0.1% solution three times daily is less drug than 1 drop of a 0.7% solution once daily (2 x 3 x 0.1% = "6" is less than 1 x 0.7% = "7"). Similarly, for the approval of Pataday 0.2% in 2004, the Applicant studied a maximum dose in humans of olopatadine 0.2%, 1 drop in each eye once daily for 6-12 weeks, backed up by a dose ranging study of olopatadine 0.15%, 2 drops in each eye twice daily for 15 days (Source: medical officer review of NDA 021545 dated December 13, 2003 by William Boyd, MD and Wiley Chambers, MD). Two drops of a of a 0.15% solution twice daily is less drug than 1 drop of a 0.7% solution once daily (2 x 2 x 0.15% = "6" is less than 1 x 0.7% ="7"). Thus, these total daily doses studied for the 0.1% solution and 0.2% solution are still below the prescription and proposed OTC dose of Pazeo by 14%-28% (the actual olopatadine 0.2% solution was only studied at 1 drop each eye daily).*

4.7. Review Strategy

The overall approach to this review is as follows:

- This review covers postmarket safety data submitted by the Applicant to sNDA 206276, sNDA 201245, and sNDA 020688. The Applicant submitted identical, or nearly identical safety data for all three sNDAs. Therefore, this review references information related to all three ophthalmic products containing olopatadine hydrochloride [Patanol (0.1%), Pataday (0.2%), and Pazeo (0.7%)] for ease of presenting information.
- The DTOP team will review the efficacy and safety data from the clinical trials submitted in support of this application.
- The clinical information under Modules 5.2 and 5.3.5.3 including appendices as well as the Benefit-Risk Summary are the same for all three sNDAs, except for minor differences in the Rx Full Prescribing Information.
- However, this review provides analysis and recommendations related only to the 0.7% product, "Pataday Once Daily Relief, Extra Strength."
- The following NDA document submissions are included in this safety review:
  - SDN 482, March 27, 2020, Clinical Information Amendment

  - Annual Report
- SDN 482, February 26, 2020, Clinical Information Amendment
  - PADER
- SDN 478, December 20, 2019, Clinical Information Amendment
  - Completed Label Discernment Study using withdrawn proprietary names
- SDN 477, December 6, 2019, Clinical Information Amendment
  - 4-month safety update submitted to correct sNDA 206276
- SDN 476, 12/04//2019, Clinical Information Amendment
  - No additional safety data to cover overuse
- SDN 473, November 25, 2019, Clinical Information Amendment
  - New Proprietary Name Request
- SDN 470, November 4, 2019, Clinical Information Amendment
  - Label Discernment Study overview
- SDN 458, September 13, 2019 sNDA submission and Proprietary Name Request

5. Review of Relevant Individual Trials Used to Support Efficacy

These data are reviewed by DTOP in their review of this sNDA. Briefly, the pivotal efficacy studies for the 2015 approval of Pazeo, studies C-10-126 and C-12-053, were controlled trials that used the validated Conjunctival Allergen Challenge (CAC) model and evaluated the efficacy endpoints of relief of itching and redness. Ocular itching is a patient reported outcome on a scale of 0-4 (none to severe) and redness is a clinically observed outcome. Table 9 below shows the comparison of itching scores from both studies versus placebo. Study 10-126 (study 1 in Table 9) measured at onset, 16 hours and 24 hours, and Study 12-053 (study 2 in Table 9) measured at onset and 24 hours. The 3-minute, 5-minute and 7-minute are itching assessments for each subject after antigen challenge at onset, 16 hours, and/or 24 hours. Redness relief is not shown as it did not consistently meet the endpoint for inclusion as a claim when used once daily.

Table 9. Comparison of Itching Scores* Between Pazeo (Olopatadine 0.7%), Pataday (Olopatadine 0.2%), and Vehicle

	Pazeo	Pataday		Vehicle	
Time Point	**Mean**	**Mean**	**Difference (95% CI)**	**Mean**	**Difference (95% CI)**
Study 1	**N=66**	**N=68**		**N=68**	
Onset					
3 mins	0.36	0.39	-0.02 (-0.31, 0.26)	1.9	-1.54 (-1.82, -1.25)
5 mins	0.53	0.61	-0.08 (-0.39, 0.22)	2.06	-1.53 (-1.84, -1.22)
7 mins	0.48	0.61	-0.13 (-0.44, 0.17)	1.97	-1.49 (-1.80, -1.18)
16h					
3 mins	0.7	0.87	-0.17 (-0.44, 0.11)	2.2	-1.5 (-1.77, -1.23)
5 mins	0.79	1.04	-0.24 (-0.55, 0.07)	2.27	-1.48 (-1.79, -1.16)
7 mins	0.75	0.98	-0.23 (-0.54, 0.08)	2.13	-1.38 (-1.69, -1.07)
24h					
3 mins	0.93	1.41	-0.48 (-0.76, -0.20)	2.54	-1.61 (-1.88, -1.33)
5 mins	1.1	1.52	-0.42 (-0.72, -0.12)	2.62	-1.51 (-1.81, -1.21)
7 mins	1.09	1.5	-0.41 (-0.72, -0.10)	2.5	-1.41 (-1.72, -1.11)
Study 2	**N=98**	**N=99**		**N=49**	
Onset					
3 mins	0.38	0.47	-0.09 (-0.28, 0.09)	1.91	-1.53 (-1.76, -1.30)
5 mins	0.53	0.61	-0.08 (-0.29, 0.12)	1.99	-1.46 (-1.71, -1.22)
7 mins	0.65	0.61	0.04 (-0.18, 0.26)	1.82	-1.17 (-1.45, -0.90)
24h					
3 mins	1.01	1.33	-0.31 (-0.57, -0.06)	2.3	-1.29 (-1.60, -0.97)
5 mins	1.22	1.48	-0.26 (-0.51, -0.01)	2.37	-1.15 (-1.46, -0.84)
7 mins	1.25	1.41	-0.16 (-0.42, 0.11)	2.14	-0.89 (-1.22, -0.57)

*Mean score estimates, treatment differences and corresponding 95% confidence intervals (CIs) were based on analysis of repeated measures using a mixed model with itching scores from each eye (left or right) as the dependent variable and fixed effect terms for investigator, treatment, eye-type (left or right), time, and treatment-by-time interaction;
The ocular itching score range is 0-4, where 0 is none and 4 is incapacitating itch.
Source: Rx Full Prescribing information (Rx Labeling)
Abbreviations: CI, confidence interval

Reviewer Comments:

No Added Clinical Benefit of Olopatadine 0.7% Beyond Olopatadine 0.2%

- *For pivotal study 10-126 endpoint itching*
  - *Dr. Chambers' NDA review of Pazeo lists a Reviewer's Comment: "Efficacy over vehicle for itching has been demonstrated 30 minutes after administration and continued for a duration of at least 24 hours after administration. The effectiveness of Olopatadine 0.7% is relatively similar to Olopatadine 0.2% (Pataday) at the onset of action, but slightly more evident at 24 hours." (overall -0.03--0.47 favoring Pazeo)*
- *For pivotal study* 12-053 endpoint itching
  - *Dr. Chambers' NDA review of Pazeo lists a Reviewer's Comment: "Efficacy over vehicle for itching has been demonstrated 30 minutes after administration and continued for a duration of at least 24 hours after administration. The effectiveness of Olopatadine 0.7% is relatively similar to Olopatadine 0.2% (Pataday) and Olopatadine 0.1% (Patanol) at the onset of action, but slightly more evident at 24 hours." (overall -0.16 Pataday and —0.52 Patanol). The Patanol comparator arm is not shown in Table 9 from the Rx label.*
- *Dr. Chambers noted in his July 30, 2014 NDA review of Pazeo, that itch relief score differences of 0.9 to 1 unit between test product and vehicle observed in most time points (two out of three in case of these studies) has been considered clinically significant ["In past CAC Studies, differences of 0.9-1 unit between test product and vehicle observed in the majority of time points (two out of three in the case of these studies) has been considered clinically significant".] However, Table 9 above and Dr. Chambers' accompanying reviewer comments (p.14 of NDA review of Pazeo) state that Pazeo (olopatadine 0.7%) does not show a clinically significant difference in itching scores compared with Pataday (olopatadine 0.2%) at the 16-hour or 24-hour time points.*
- *This point makes it clear that olopatadine 0.7% is an additional option for the OTC market; however, there is no added clinical benefit of itching relief over olopatadine 0.2%.*

6. Integrated Review of Effectiveness

This review focuses on postmarket safety; therefore, this section is not applicable. See DTOP review for information about effectiveness.

7. Review of Safety

7.1. Safety Review Approach

This review evaluates safety from postmarket data submitted by the Applicant and published literature. See section 7.8 below (Safety in the Postmarket Setting).

In addition to postmarket safety data, the Applicant's ISS included premarket safety data from nonclinical and clinical trials prior to the NDA approval. For a review of these data, see the current DTOP clinical review by William Boyd, MD, in which he summarizes safety findings from the five clinical trials in Table 9 above. Dr. Boyd's assessment mirrors that of Wiley Chambers, MD, who conducted the original clinical review for the Rx approval in 2015.

Reviewer Comment: The ISS is dated April 15, 2019 and covered the period from May 1, 2015 to April 30, 2018, which the Applicant updated from May 1, 2019 to December 31, 2019 following the sNDA 206276 submission.

7.2. Review of the Safety Database

7.2.1. Overall Exposure

Over ten thousand patients, accounting for (b) (4) patient-months, have been exposed to olopatadine in clinical trials and postmarketing as of December 31, 2018 (NDA 020688/S-032, Module 5, ISS). Ophthalmic formulations of olopatadine are available in 129 countries, including OTC in five countries for the lower strengths; however, there is no overseas OTC marketing for olopatadine 0.7%.

The clinical trials with all the Applicant's olopatadine products are shown in Table 10 below:

Table 10. Summary of Completed Clinical Trials With Each Olopatadine Product (Includes Intranasal Spray, Patanase 0.6% Olopatadine)

Formulation	Phase I	Phase II	Phase III	Phase IV	Total
Eye drops, solution	12	6	42	10	70
Intranasal Spray	7	8	9	1	25
Oral solution	3	0	0	0	3
Total	**22**	**14**	**51**	**11**	**98**

Source: Applicant's ISS p. 12 of 66 for sNDA 020688 and sNDA 021545 (Patanol and Pataday switches)

In these studies of all olopatadine formulations in 10,814 healthy subjects ages 3-65, there were zero deaths and a relatively small number of SAEs.

Reviewer Comment:

Although over 10,000 subjects have been exposed to olopatadine in clinical trials, only 428 subjects were exposed to olopatadine 0.7%. It is not clear that a total of 428 subjects exposed to olopatadine, of which 330 were exposed to olopatadine 0.7% for 6 weeks, is enough to infer that the drug will be safe for an OTC population of potentially millions of consumers.

To assess postmarket safety, an estimate of total exposure is helpful. In Table 11 below, the Applicant lists exposure in patient-months, based on sales data across all formulations of olopatadine (0.1%, 0.2%, 0.7% eyedrops and 0.6% nasal) from May 1, 2012 through April 30, 2018.

Table 11. Estimated Postmarketing (Nonclinical Trial) Exposure

Olopatadine Formulation	Units Sold	Estimated Exposure*	Units Sold	Estimated Exposure*	Units Sold	Estimated Exposure*
Eye drops						(b) (4)
IN spray						
Total						

Source: Applicant's ISS p.14 of 66 for sNDA 020688 and sNDA 021545 (Patanol and Pataday switches)
This table includes cumulative and interval exposure data obtained from Novartis Pharma (Jan 2000 to Apr 2018), Sandoz (Oct 2006 to Apr 2018).
* Estimated exposure = number of patient months, with each Unit Sold intended for use over 1 month
Abbreviations: IN, intranasal

Of note, as of December 31, 2018, the total units sold in the postmarket setting for olopatadine eyedrops, all formulations, was (b) (4). Assuming full use of each 30-day unit sold, the exposure to any olopatadine product in patient-months is also (b) (4).

The estimate of sales of all olopatadine ophthalmic products (0.1%, 0.2%, 0.7%) through December 2018 is shown in Table 12 below.

Table 12. Estimated Postmarketing Exposure by Olopatadine Ophthalmic Solution (Eye Drops) Brands Through December 31, 2018

Brand	Cumulative Sales
Patanol (olopatadine 0.1%)	(b) (4)
Pataday (olopatadine 0.2%)	
Pazeo (olopatadine 0.7%)	
Total	

Source: Applicant's ISS for sNDA 020688 and sNDA 021545 (Patanol and Pataday switches)

Reviewer Comment:

The actual number of people exposed is unknown since one person may have purchase multiple units of olopatadine.

7.3. Adequacy of Applicant's Clinical Safety Assessments

Not applicable.

7.4. Safety Results

7.4.1. Deaths

There were no deaths reported in clinical trials. See section 7.8 for deaths reported in the postmarket setting.

7.4.2. Serious Adverse Events

There were no SAEs reported in clinical trials with 428 subjects exposed to Pazeo.

7.5. Analysis of Submission-Specific Safety Issues

Not applicable.

7.6. Safety Analyses by Demographic Subgroups

Not applicable.

7.7. Additional Safety Explorations

7.7.1. Human Carcinogenicity or Tumor Development

Not applicable.

7.7.2. Human Reproduction and Pregnancy

The Division of Pediatrics and Maternal Health evaluated olopatadine ophthalmic solution during the reviews of the 0.1% and 0.2% Rx-to-OTC switch applications and determined there was insignificant risk to a fetus from use by a mother and no need to insert a warning on the proposed Drug Facts label for any of the ophthalmic strengths.

7.7.3. Pediatrics and Assessment of Effects on Growth

This application does not trigger the Pediatric Research Equity Act.

7.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There are no reports of drug abuse potential, withdrawal reactions, or rebound with this antihistamine drug product.

7.8. Safety in the Postmarket Setting

Risks Identified in Prescription Labeling

Although this review is focused on postmarket safety, mention of some safety issues noted in the prescription labeling is warranted. For example, prescription labeling for Pazeo states the following:

In a randomized, double-masked, vehicle-controlled trial, patients at risk for developing allergic conjunctivitis received one drop of either Pazeo (N=330) or vehicle (N=169) in both eyes for 6 weeks. The mean age of the population was 32 years (range 2 to 74 years). Thirty-five percent were male. Fifty-three percent had brown iris color and 23% had blue iris color. The most commonly reported adverse reactions occurred in 2-5% of patients treated with either Pazeo or vehicle. These events were blurred vision, dry eye, superficial punctate keratitis, dysgeusia, and abnormal sensation in eye.

Reviewer Comment: Some of these adverse events are symptoms found in the underlying disease being studied, allergic conjunctivitis.

Risks Identified in Applicant's Benefit/Risk Conclusions

The Applicant provided the summarized risks below; this mirrors information submitted previously in the Applicant's Safety Reports. The noted categories correspond to those used in the CCDS.

Important identified risks: Hypersensitivity.

Important potential risks: Corneal damage

Corneal disorders, keratitis, and punctate keratitis are listed adverse events as per the current CCDS for olopatadine eye drops, whether 0.1%, 0.2%, or 0.7%. Only a few serious cases of corneal disorders have been reported through Post-Marketing Surveillance. Upon review of cases, a causal relationship is difficult to establish due to different confounders such as the allergic disease itself. Corneal events due to use of preservatives (e.g. benzalkonium chloride) rarely result in hospitalization.

7.8.1. Safety Concerns Identified Through Postmarket Experience

Postmarket Data Submitted by Applicant in the Integrated Summary of Safety (ISS)

The Applicant submitted postmarket data in the ISS for all three olopatadine ophthalmic drug products from the following sources:

- Alcon's / Novartis' pharmacovigilance database, "Argus"
- FAERS
- WHO International Drug Monitoring Program
- NPDS from American Association of Poison Control Centers (AAPCC)
- Literature Review
- FDA requested the Applicant also provide the following information:
  - List of countries where olopatadine is marketed either as an Rx or OTC product; including certified English translations of foreign nonprescription labels
  - Whether olopatadine has been withdrawn from any foreign markets due to safety or regulatory reasons
  - Worldwide distribution data for both prescription and nonprescription use

Post-market AEs were coded with MedDRA Version 21.1. In all data presentations, events were grouped by SOC first, and then by the preferred term (PT) within SOC. All SOCs and PTs were listed in alphabetical order." (Source ISS, p.24 of 66)

In this application for sNDA 206276, the Applicant refers to the safety data submitted in NDA 020688 (olopatadine 0.1%) and NDA 021545 (olopatadine 0.2%) for all olopatadine ophthalmic solution drug products (0.1%, 0.2%, and 0.7%). In some instances, the data in sNDA 020688 and sNDA 021545 are lumped together with sNDA 206276, when it is not clear which adverse event reported relates to which strength. In other areas, the Applicant has been able to separate AEs for Pazeo only. In particular, the Applicant's ISS and Benefit-Risk assessment are identical for all

three sNDAs. For example, information under Modules 5.2 and 5.3.5.3 including appendices as well as the Benefit-Risk Summary are the same for all three sNDAs.

Overall, as shown in Table 13, As can be seen in Table 13 above, Pazeo has not been marketed OTC. Only Patanol and Pataday have been marketed as nonprescription drugs (OTC), with use to date restricted to just a few countries with limited sales of approximately (b) (4) units over the 5-year period.

Patanol was marketed as an OTC product in five countries (Italy, Myanmar, Namibia, South Africa, and Zimbabwe), and Pataday was marketed as an OTC product in one country (Hong Kong). There are 54 post-market AEs associated with OTC Patanol usage in the 5 countries and 4 post-market AEs with Pataday in Hong Kong.

Reviewer Comment:

It is not clear that about 58 AEs reported from OTC marketing in six countries for Pataday plus Patanol combined over about 5 years, or an average of 12 AEs per year will be indicative of AEs for Pazeo, which is 3.5-7 times stronger than Pataday and Patanol, respectively. Also, the OTC market in the US could be multiples of the OTC market in any of the six countries above.

Table 14, and Table 15 below, the Applicant used Novartis's Argus database (1996-2018) and identified 4,072 AEs for Patanol, 2,050 for Pataday, 763 for Pazeo (includes 21 SAEs), and 672 for Patanase.

Reviewer Comments

There are limitations of post-marketing adverse drug event reporting since repost are submitted voluntarily and the magnitude of underreporting is unknown. In addition, the total numbers for AE reports for any one product between databases also vary as do the respective dates included in queries. The raw numbers of reports or cases also vary widely. Detailed comparisons between databases are not appropriate, although general impressions of safety findings are similar.

Alcon's/Novartis' Pharmacovigilance Database, "Argus" (January 1, 2019 to October 31, 2019)

The Applicant submitted three tables of data, shown below, for postmarket adverse events reported to its Argus database. They stratified these data by marketing status (Rx vs. OTC, Table 13), by year of reporting (1996 to 2018, As can be seen in Table 13 above, Pazeo has not been marketed OTC. Only Patanol and Pataday have been marketed as nonprescription drugs (OTC), with use to date restricted to just a few countries with limited sales of approximately (b) (4) units over the 5-year period.

Patanol was marketed as an OTC product in five countries (Italy, Myanmar, Namibia, South Africa, and Zimbabwe), and Pataday was marketed as an OTC product in one country (Hong Kong). There are 54 post-market AEs associated with OTC Patanol usage in the 5 countries and 4 post-market AEs with Pataday in Hong Kong.

Reviewer Comment:

It is not clear that about 58 AEs reported from OTC marketing in six countries for Pataday plus Patanol combined over about 5 years, or an average of 12 AEs per year will be indicative of AEs for Pazeo, which is 3.5-7 times stronger than Pataday and Patanol, respectively. Also, the OTC market in the US could be multiples of the OTC market in any of the six countries above.

Table 14) and by duration of use (1 day-1 year+, Table 15). These tables summarize how many SAEs and non-serious AEs were reported to Novartis' safety database (Argus) from initial marketing of each product through December 31, 2018.

Table 13. Frequency of Postmarket AEs for Olopatadine-Containing Products, Stratified by Marketing Status Through December 21, 2018 - Data From Applicant's Internal Database (Argus)

	Market Status		
Dosage Strength	**Prescription**	**OTC**	**Total**
Patanol (olopatadine 0.1%)*, n			
Serious adverse events	154	6	160
Non-serious adverse events	3864	48	3,912
Total adverse events (serious + non-serious)	4018	54	4,072
Pataday (olopatadine 0.2%), n			
Serious adverse events	55	0	55
Non-serious adverse events	1991	4	1,995
Total adverse events (serious + non-serious)	2046	4	2,050
Patanase (olopatadine 0.6%), n			
Serious adverse events	30	0	30
Non-serious adverse events	672	0	672
Total adverse events (serious + non-serious)	702	0	702
Pazeo (olopatadine 0.7%), n			
Serious adverse events	21	0	21
Non-serious adverse events	742	0	742
Total adverse events (serious + non-serious)	763	0	763

Source: Applicant's ISS p. 26 of 66 for sNDA 020688 and sNDA 021545 (Patanol and Pataday switch)
* Includes generic olopatadine 0.1%
Patanase (olopatadine 0.6%) is a nasal product and not a subject of this review. It appears in the table to inform about olopatadine in general
MedDRA Version 21.1
Abbreviation: AE, adverse event; n, number of adverse events; OTC, over-the-counter

As can be seen in Table 13 above, Pazeo has not been marketed OTC. Only Patanol and Pataday have been marketed as nonprescription drugs (OTC), with use to date restricted to just a few countries with limited sales of approximately (b) (4) units over the 5-year period.

Patanol was marketed as an OTC product in five countries (Italy, Myanmar, Namibia, South Africa, and Zimbabwe), and Pataday was marketed as an OTC product in one country (Hong Kong). There are 54 post-market AEs associated with OTC Patanol usage in the 5 countries and 4 post-market AEs with Pataday in Hong Kong.

Reviewer Comment:

It is not clear that about 58 AEs reported from OTC marketing in six countries for Pataday plus Patanol combined over about 5 years, or an average of 12 AEs per year will be indicative of AEs for Pazeo, which is 3.5-7 times stronger than Pataday and Patanol, respectively. Also, the OTC market in the US could be multiples of the OTC market in any of the six countries above.

Table 14. Frequency of Postmarket AEs for Olopatadine-Containing Products, Stratified by Year of Reporting Through December 21, 2018 - Data From Applicant's Internal Database (Argus)

Dosage Strength	Year of Reporting					
AEs	1996-2000	2001-2005	2006-2010	2011-2015	2016-2018	Total
Patanol, n						
SAEs	2	7	31	65	55	160
Non-SAEs	453	846	961	893	759	3912
Total AEs*	455	853	992	958	814	4072
Pataday, n						
SAEs	0	0	2	18	35	55
Non-SAEs	0	0	389	1164	442	1995
Total AEs*	0	0	391	1182	477	2050
Patanase, n						
SAEs	0	0	11	18	1	30
Non-SAEs	0	0	252	398	22	672
Total AEs*	0	0	263	416	23	702
Pazeo, n						
SAEs	0	0	0	0	21	21
Non-SAEs	0	0	0	110	632	742
Total AEs*	0	0	0	110	653	763

Source: Applicant's ISS p. 30 of 66 for sNDA 020688 and sNDA 021545 (Patanol and Pataday switch)
Patanol (olopatadine 0.1%), includes generic olopatadine 0.1%
Pataday (olopatadine 0.2%)
Patanase (olopatadine 0.6%)
Pazeo (olopatadine 0.7%)
MedDRA Version 21.1
* Total AEs = serious AEs + non-serious AEs
Abbreviations: AE, adverse event; n, number of adverse events, SAE, serious adverse event

Table 15. Frequency of Postmarket AEs for Olopatadine-Containing Products, Stratified by Duration of Use Through December 21, 2018 - Data From Applicant's Internal Database (Argus)

Dosage Strength	Duration of Use					
Type of AE	1d to 7d	>7d to 30d	>1m to 1y	>1y	Other*	Total
Patanol, n						
SAEs	50	6	15	0	89	160
Non-SAEs	1001	417	118	21	2355	3912
Total AEs†	1051	423	133	21	2444	4072
Pataday, n						
SAEs	3	0	0	0	52	55
Non-SAEs	367	113	54	5	1456	1995
Total AEs†	370	113	54	5	1508	2050
Patanase, n						
SAEs	9	3	0	0	18	30
Non-SAEs	168	45	24	2	433	672
Total AEs†	177	48	24	2	451	702
Pazeo, n						
SAEs	0	2	0	0	19	21
Non-SAEs	102	33	7	0	600	742
Total AEs†	102	35	7	0	619	763

Source: Applicant's ISS p. 28 of 66 for sNDA 020688 and sNDA 021545 (Patanol and Pataday switch)
*Value missing or not determinable
Patanol (olopatadine 0.1%) includes generic olopatadine 0.1%
Pataday (olopatadine 0.2%)
Pazeo (olopatadine 0.7%)
Patanase (olopatadine 0.6%)
MedDRA Version 21.1

† Total AE = serious AE + non-serious AE
Abbreviations: AE, adverse event; n, number of adverse events, SAE, serious adverse event

Reviewer Comment:

Table 13, As can be seen in Table 13 above, Pazeo has not been marketed OTC. Only Patanol and Pataday have been marketed as nonprescription drugs (OTC), with use to date restricted to just a few countries with limited sales of approximately (b) (4) *units over the 5-year period.*

Patanol was marketed as an OTC product in five countries (Italy, Myanmar, Namibia, South Africa, and Zimbabwe), and Pataday was marketed as an OTC product in one country (Hong Kong). There are 54 post-market AEs associated with OTC Patanol usage in the 5 countries and 4 post-market AEs with Pataday in Hong Kong.

Reviewer Comment:

It is not clear that about 58 AEs reported from OTC marketing in six countries for Pataday plus Patanol combined over about 5 years, or an average of 12 AEs per year will be indicative of AEs for Pazeo, which is 3.5-7 times stronger than Pataday and Patanol, respectively. Also, the OTC market in the US could be multiples of the OTC market in any of the six countries above.

Table 14, and Table 15 above show that most nonserious AEs with Pazeo (742 of 763 total AEs) are reported in the first 1-7 days of use. The Applicant's data do not show when 19 of the 21 SAEs with Pazeo occurred (e.g. first 7 days of use or sometime during marketing from 2015 to 2018.

Separately, and with some overlap between databases, the Applicant identified AEs from the external databases for all olopatadine products together, not broken down by brand; FAERS (1997-2018): 7,390 cases, WHO (1968-2019): 3,427 cases, and NPDS (2000-2019): 512 exposures. There have been no drug withdrawals for safety or regulatory reasons. The data regarding total AEs from all olopatadine brands may be helpful since the 0.1% and 0.2% ophthalmic products have been on the market longer than Pazeo.

Deaths in the Postmarket Setting (Summarized in Office of Surveillance and Epidemiology Consult)

There are six deaths reported for olopatadine ophthalmic solution products in the postmarket setting. Dr. Donohoe reviewed five of these in her review of olopatadine ophthalmic drops 0.1% and 0.2%. None could be attributed to olopatadine. The sixth death reported in FAERS in a patient who used Pazeo amongst other medication, is discussed below.

Sixth FAERS Death Case #16921599, USA, Expedited 2019

This is an initial report received from a consumer on October 8, 2019 via a Patient Oriented Program: POP20150553. This report refers to a 77- year-old male patient (Patient Oriented Program Pat ID: (b) (6)). Details regarding medical history were unknown. Concomitant medication was not reported, except the patient received Sandostatin LAR Depot (octreotide) for the treatment of an unknown indication from an unknown start date at an unknown dose (route: unknown). The patient received Pazeo (olopatadine) for the treatment of an unknown

indication from an unknown start date at an unknown dose (route: unknown). On (b) (6) (b) (6), the patient died. It was unknown if an autopsy was performed. The causality of death with Sandostatin LAR Depot was reported as not assessable. The causality of death with Pazeo was reported as not assessable.

Reviewer Comment:

Whether Pazeo contributed to the patient's death cannot be determined due to a lack of information about a temporal association with use of Pazeo, past medical history, concomitant medications (except octreotide), clinical course, and cause of death.

FAERS

The Applicant submitted a summary of FAERS reports from 2015-cutoff in 2018, and later supplemented the safety data from FAERS, WHO, and NPDS in the 120-day safety report and PADERs. The Applicant's data were consistent with the FAERS data analyzed by OSE, so these FAERS data are described best by the OSE-Division of Pharmacovigilance II (DPVII) consult discussed below. For completeness, the Applicant's assessment of FAERS reports shown in Table 16 below list olopatadine (from any drug containing olopatadine) as the primary suspect.

Table 16. FAERS AE Report Summary With Olopatadine Reported as the Primary Suspect

Drug	Death n (%)	Serious* n (%)	Non-Serious n (%)	Overall Total N
Olopatadine	0 (0)	18 (20.69)	69 (79.31)	87
Patanol/Patanol S	0 (0)	37 (11.71)	279 (88.29)	316
Opatanol	0 (10)	10 (100)	0 (0)	10
Patanase	2 (3.92)	26 (50.98)	25 (49.02)	51
Pazeo	1 (0.29)	17 (4.89)	331 (95.11)	348
Pataday	2 (0.49)	29 (7.16)	376 (92.84)	405
Allelock	0 (0)	0 (0)	0 (0)	0
Olopat	0 (0)	0 (0)	0 (0)	0

* Includes death
Source: Applicant's ISS page 36 of 66 for sNDA 020688 and sNDA 021545 (Patanol and Pataday switch)
Note: Allelock is an olopatadine tablet 5 mg for oral administration marketed overseas.
Olopat is an olopatadine ophthalmic solution 0.2% marketed OTC and overseas by Ajanta Pharma Ltd.
Abbreviations: AE, adverse event; FAERS, FDA Adverse Event Reporting System

WHO

Postmarket data from the WHO Database Search by Brand from 1997 to March 2019 are shown in Table 17 below. There are 3427 reports or cases, with potentially multiple MedDRA terms generated by each report.

Table 17. Numbers of Adverse Drug Reactions for Olopatadine, by Brand, WHO Database, January 1997-March 2019

	Olopatadine Brands									
MedDRA	**Unknown Brand**	**Pataday**	**Patanase**	**Patanol**	**Pazeo**	**Opatanol**	**Olopat**	**Allelock**	**Other**	**All Cases**
Total number of cases										3427
Blood and lymphatic system disorders	7	1	0	1	0	0	3	47	527	586
Cardiac disorders	6	3	4	1	1	7	0	31	330	383
Congenital, familial and genetic disorders	17	0	0	1	0	0	0	2	277	297
Ear and labyrinth disorders	1	9	2	3	5	0	0	4	75	99
Endocrine disorders	0	0	0	0	0	0	0	1	11	12
Eye disorders	126	218	9	170	382	92	0	20	1661	2678
Gastrointestinal disorders	45	32	14	13	5	8	13	435	3339	3904
General disorders and administration site conditions	81	307	26	276	75	17	2	205	2393	3382
Hepatobiliary disorders	23	0	0	0	0	0	0	135	1227	1385
Immune system disorders	15	19	3	22	18	5	0	23	370	475
Infections and infestations	18	24	4	12	9	7	0	11	646	731
Injury, poisoning and procedural complications	27	50	10	26	41	5	0	25	642	826
Investigations	12	18	13	4	8	5	2	130	1052	1244
Metabolism and nutrition disorders	3	6	2	1	0	0	0	28	273	313
Musculoskeletal and connective tissue disorders	13	19	6	10	6	0	0	26	769	849
Neoplasms benign, malignant and unspecified	3	1	0	1	0	0	0	4	111	120
Nervous system disorders	57	53	26	56	31	26	9	982	6866	8106
Null	0	0	0	4	0	0	0	0	4	8
Pregnancy, puerperium, and perinatal conditions	0	0	0	3	0	1	0	2	33	39
Product issues	19	9	2	5	33	4	0	0	68	140
Psychiatric disorders	25	10	14	10	4	1	6	83	1040	1193
Renal and urinary disorders	16	2	0	1	1	0	1	36	335	392
Reproductive system and breast disorders	3	0	0	1	0	0	0	7	35	46

	Olopatadine Brands									
MedDRA	**Unknown Brand**	**Pataday**	**Patanase**	**Patanol**	**Pazeo**	**Opatanol**	**Olopat**	**Allelock**	**Other**	**All Cases**
Respiratory, thoracic, and mediastinal disorders	42	31	28	14	14	23	3	72	1283	1510
Skin and subcutaneous tissue disorders	57	21	7	32	16	27	2	151	1569	1882
Social circumstances	1	1	3	1	1	0	0	0	4	11
Surgical and medical procedures	1	2	0	1	0	0	0	0	24	28
Vascular disorders	1	2	3	11	1	6	0	20	248	292

Abbreviations: ADRs, adverse drug reactions; MedDRA, Medical Dictionary for Regulatory Activities; SOC, system organ class
Source: Applicant's ISS p. 51 of 66 for sNDA 020688 and sNDA 021545 (Patanol and Pataday switch)

Reviewer Comment:

In the WHO database, the category "Other" has the largest number of reports for most of the various AEs. Even so, it is notable when the brand is identified, that there are 382 reports of eye disorders for Pazeo versus 218 for Pataday and 170 for Patanol. Also, there are 33 "product issues" for Pazeo versus 9 for Pataday and 5 for Patanol. Pazeo has been approved (2015) only a fraction of the time that Patanol (1996) and Pataday (2004) have been approved. At a minimum, from the WHO database, the rate of reporting for eye disorders and product issues for Pazeo is higher.

National Poison Data System

Total reports by year:

- 2000-2004: 122
- 2005-2009: 191
- 2010-2014: 159
- 2015-2019 (partial): 77

The five top SOCs were:

- Ocular: 262 (48%)
- Miscellaneous: 91 (17%)
- Neurological: 82 (15%)
- Gastrointestinal: 59 (11%)
- Dermal: 38 (7%)

Note: Data broken down by brand (i.e., concentration) not available.

Reviewer Comment

It is not clear that these reports involve "poisoning" since they have ocular and dermal categories. Of note, the ocular category has the most reports (262).

120-Day Safety Update

The Applicant submitted the 120-day safety update report for the three NDAs on November 20, 2019. As a Summary of Clinical Safety for Olopatadine Hydrochloride Ophthalmic Solution 0.1%, 0.2%, and 0.7% covering the period January 1, 2019 to October 31, 2019. Alcon reported no new clinical studies, and included data from its Argus database, FAERS, WHO, and the literature. For Pazeo alone, the following data were reported:

Pazeo

- Argus database: 173 AEs, of which 5 are SAEs (2 eye disorders, 2 nervous system disorders, and 1 immune system disorder).
- FAERS: 73 AEs, of which 5 are SAEs.
- WHO: (April 1-October 31, 2019): 152 AEs, and SAEs were not listed.
- Literature:
  - Jagarlamudi et al. (Jagarlamudi et al. 2019) compared the effects of 0.7% [Pazeo] olopatadine hydrochloride eye drops to a fixed dose combination of 0.1% [Patanol] olopatadine hydrochloride plus 0.4% ketorolac tromethamine solution eye drop for the treatment of allergic conjunctivitis over a 14-day treatment period. The most frequently reported treatment-emergent adverse event (TEAE) in both regimens was headache.

Based on the data in this 120-day safety update, the Applicant states that "A review of Alcon's internal database as well as the FAERS and WHO data for the olopatadine eye drop solutions Patanol [olopatadine 0.1%], Pataday [olopatadine 0.2%], and Pazeo [olopatadine 0.7%] for the period of January 1, 2019 to October 31, 2019…continues to support the favorable safety profile of these products as demonstrated in clinical trials, as well as previously reported post-market data."

Reviewer Comments:

- *The adverse events reported in Argus, FAERS and WHO databases often are duplicated in each database, so the total AEs are 173 with 5 being SAEs.*

- *This reviewer concurs that the data from the 120-day safety update supports the safety of Pazeo in the prescription environment. There were two deaths reported with use of Pataday (0.2%), not Pazeo, in all three databases. These deaths did not appear to be related to Pataday use. In addition, the 5 SAEs in this 120-Day Safety Update, added to the 21 SAEs in the sNDA submission, yield a total of 26 SAEs for Pazeo. This is the number (26) evaluated in the OSE-DPVII consult.*

Additional Sources of Data Reported About Pazeo Outside of the Integrated Summary of Safety and 120-day Safety Update

- FDAAA Section 915 Analysis January 2017
- PSUR (May 1, 2015 to April 30, 2018)
- PSUR (May 1, 2019 to April 30, 2019)
- PSUR (May 1, 2019 to April 30, 2020)
- Annual Report February 2020
- PADER 2019 (January 30, 2018 to January 29, 2019)
- PADER 2020 (January 30, 2019 to January 29, 2020)
- OSE-DPVII Consult February 2020

FDAAA Section 915 Non-New Molecular Entity Postmarket Safety Summary Analysis

OSE performed a Section 915 Review dated January 9, 2017 which summarized postmarket safety from U.S. approval from January 30, 2015 through the first 18 months post approval to December 31, 2016 (the rule states 18 months or 10,000 patients, whichever is later). Dr. Ronald Wassel from OSE determined that there were 134 reports (5 SAEs, all labeled in the Rx labeling, or inadequate information to make an assessment), although none revealed potential or ongoing safety issues that needed to be addressed. A summary of relevant findings is shown in Table 18 below:

Table 18. Most Frequently Reported MedDRA PTs With N≥5 for Pazeo, Received by FDA From January 30, 2015 Through December 31, 2016

MedDRA PT	Number of FAERS Reports	Labeled (Yes/No), Location or Other Category
Vision blurred	38	Yes, AR
Drug ineffective	25	U
Eye irritation	16	Yes, AR (as abnormal sensation); also, IR
Eye pain	10	No; see section 3.4
Eyelid margin crusting	9	IR
Dry eye	8	Yes, AR; also, IR
Eye swelling	8	IR
Ocular hyperemia	8	IR
Abnormal sensation in eye	7	Yes, AR
Eye discharge	6	IR
Eyelid edema	6	IR
Dysgeusia	5	Yes, AR
Medication residue present	5	U

* A report may contain more than one preferred term.
Abbreviations: AR, Adverse Reactions; FAERS, FDA Adverse Event Reporting System; IR, Indication-related; MedDRA, Medical Dictionary for Regulatory Activities; PTs, preferred terms; U, Uninformative
Source: OSE 915 review

OSE reiterated the limitations of FAERs reports:

"FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population."

Periodic Safety Update Report (PSUR) (May 1, 2015 to April 30, 2018)

This PSUR has been previously reviewed by Dr. Donohoe for olopatadine 0.1% and 0.2%, with some data for 0.7%, too. In the current review of Pazeo, this reviewer selectively revisits only the safety of olopatadine in pregnancy and breast-feeding because Pazeo is 3.5-7-fold stronger than the olopatadine 0.2% and 0.1% ophthalmic solutions, it could have a larger risk, and the Applicant notes there is "missing information" for the effects in pregnancy and breastfeeding with olopatadine as an active ingredient. Dr. Donohoe, in the Rx-to-OTC switch reviews for Patanol and Pataday also assessed the available data on the safety of olopatadine ophthalmic solution 0.1% and 0.2% in pregnant and breastfeeding women. The prescription labeling for olopatadine products instructs providers that the eye drops should be used in pregnant women only if the "potential benefit to the mother justifies the potential risk to the embryo or fetus" and "caution should be exercised when administered to a nursing mother."

Dr. Donohoe's finding are summarized and quoted or paraphrased below:

This PSUR, covering 3 years from May 1, 2015 to April 30, 2018, listed five cases of pregnancy associated with olopatadine eye drops. All five cases were prospective pregnancy cases.

Analysis of the data did not reveal any new safety information regarding use of olopatadine during pregnancy.

During that same time period, a total of six cases related to breastfeeding were retrieved. Analysis of these cases did not reveal any new safety information regarding use of olopatadine during breast-feeding.

Current OTC antihistamine eye drops include no pregnancy/breastfeeding statement. DNDP asked colleagues in DTOP to make recommendations regarding labeling issues including use of language to address pregnancy or breastfeeding safety concerns as the prescription labeling for Patanol and Pataday instructs providers that the eye drops should be used in pregnant women only if the "potential benefit to the mother justifies the potential risk to the embryo or fetus" and "caution should be exercised when administered to a nursing mother"; DTOP did not recommend including related warning language in the OTC Drug Facts Label (see Section 10.1 Nonprescription Drug Labeling). In Dr. Donohoe's review of Patanol, she noted that another OTC eye drop (Lumify, NDA 208144) state in the Drug Facts Label: If pregnant or breast-feeding, ask a health professional before use. However, she notes that the active ingredient in Lumify is brimonidine, a selective alpha-adrenergic receptor agonist (redness reliever), not an anti-histamine.

Dr. Donohoe also noted that although labeling used outside the United States may not impact the agency's decision-making, the following language was used in submitted labeling for olopatadine eye drops marketed in Namibia, South Africa, and Zimbabwe where Patanol is OTC:

- "Use of Patanol in pregnancy is not recommended"
- "Patanol is not recommended for breastfeeding mothers"

Dr. Donohoe conducted a literature search with the terms: 'foetal exposure during pregnancy', 'exposure during pregnancy' and 'maternal exposure during pregnancy' and review of published literature did not reveal any new significant safety findings (updated terms in 2017 included "Pregnancy and neonatal topics"; PTs "Forceps delivery", "Failed forceps delivery", "Vacuum extractor delivery", "Exposure via body fluid", and "Ectopic pregnancy under hormonal contraception"). In 2016, four cases of pregnancy (one non-medically confirmed) were reported, all non-serious; in 2017, there were no pregnancy cases and two cases of "exposure during breast-feeding", both non-serious.

The safety reports (PSUR /PADER) submitted in 2018 noted a cumulative total of 31 cases concerning use of olopatadine during pregnancy [presumably since 2000]. "Of the 31 cases, three cases were not associated with pregnancy and were retrieved due to broad search criteria. In 10 cases exposure via lactation were reported, these cases are included [under] 'Use in breastfeeding'. There was no evidence of harm to children who are breastfed in mothers exposed to olopatadine. During the reporting interval, a search using the criteria mentioned above retrieved a total of 13 cases. Of these 13 cases, two cases were not associated with pregnancy and were retrieved due to broad search criteria." The remaining 11 cases (all non-serious, five pregnancy and six breastfeeding) are mentioned above.

The 2019 Safety Report identified one adverse event from one case report which was identified under the SOC including "Pregnancy", which was a serious unlisted event. The serious unlisted event identified was abortion. In that case (PHHY2018MX190661), the event of interest 'abortion', was presented under the SOC related to 'Nervous system disorders' based on its lead event 'brain edema.'

Based on these data, OTC consulted the Division of Pediatrics and Maternal Health, and they recommended, because systemic exposure is very low, that no specific language needed to be added to the proposed Drug Facts Label (DFL) for any of the three strengths of olopatadine if they were to switch to OTC marketing.

Reviewer Comment:

Based on the research conducted by Dr. Donohoe for Patanol and Pataday, and the OSE consult, this reviewer (Steven Osborne) agrees that no specific language needs to be added to the Pazeo proposed DFL to warn about use during pregnancy or breastfeeding, and this will then mirror labeling for other OTC antihistamines, which also do not carry a warning for pregnancy or breastfeeding.

PSUR 2019 and PSUR 2020

These two reports did not reveal safety data not already covered or that in the PADERs of 2019 and 2020, discussed below.

Annual Report 2020

On February 26, 2020 the Applicant (under Novartis) submitted an Annual Report covering the period from January 1, 2019 to December 31, 2019. This Annual Report included sections on Labeling, Manufacturing, and Regulatory Business, and no new safety data. The Applicant submitted proposed labeling changes under Pregnancy and Lactation Labeling Rule, stating:

(b) (4)

the proposed labeling changes to comply Pregnancy and Lactation Labeling Rule (PLLR). Agency approval is still pending."

Reviewer Comment

The submission of a prior approval supplement with proposed labeling to comply with the PLLR is a routine submission and does not connote a new safety concern.

PADER 2019

On March 27, 2019, the Applicant submitted a PADER summarizing postmarket safety data received by Novartis Pharmaceuticals Corporation for the period January 30, 2018 to January 29, 2019 for Pazeo. Table 19 below shows a summary of the various SOCs for the SAEs and AEs. The Applicant stated: "The review of the data did not reveal any unusual cluster or pattern of unlisted adverse events. During this reporting period, there were no cases with fatal outcome."

Table 19. Summary by SOC for All Events Reported as Lead Diagnosis or Lead Symptom

System Organ Class	Serious Unlisted	Serious Listed	Non-Serious Unlisted	Non-Serious Listed	Total Events
Ear and labyrinth disorders	0	0	4	0	4
Eye disorders	0	0	81	49	130
Gastrointestinal disorders	0	0	3	0	3
General disorders and administration site conditions	0	0	19	153	172
Immune system disorders	0	1	14	10	25
Infections and infestations	0	0	4	1	5
Injury, poisoning and procedural complications	0	0	48	0	48
Musculoskeletal and connective tissue disorders	0	0	2	0	2
Nervous system disorders	0	0	3	4	7
Product issues	0	0	22	0	22
Psychiatric disorders	1	0	5	0	6
Respiratory, thoracic and mediastinal disorders	0	0	8	1	9
Skin and subcutaneous tissue disorders	0	0	4	0	4

Abbreviations: SOC = system organ class
Source: Applicant's PADER 2019

Reviewer Comment:

Table 19 above shows two SAEs, which included one psychiatric disorder (unlisted) and one immune system disorder (listed), and 130 nonserious eye disorder events. These events are included in the AEs reported in the 120-day safety report above. It is not clear whether any of these reports can be attributed (causal) to use of Pazeo. Also, although misuse is not a category listed, there are 22 "Product Issue" reports and overall approximately 400 total events (sum of Total Events column) received. Each adverse event report might have multiple events reported.

PADER 2020

On March 27, 2020, the Applicant submitted a PADER summarizing postmarket safety data for Pazeo received by Novartis Pharmaceuticals Corporation for the period January 30, 2019 to January 29, 2020.

These data were mostly covered in the 120-day Safety Update discussed above (which covered January 1, 2019-October 31, 2019). There were two deaths reported and one case of blindness. This PADER was not available yet for the OSE-DPVII review, however these reports are discussed in the OSE-DPVII review as they were also picked up in FAERs.

Reviewer Comment:

These data did not change the safety assessment.

OSE-DPVII Consult

On February 18, 2020, Regina Lee, PharmD from the OSE, (OSE-DPVII, or DVPII) completed a consult cleared through DPVII that the DNDP requested to help assess all SAEs reported to FAERS for olopatadine 0.7% since its approval in 2015.

Dr. Lee reviewed adverse events reported to the FAERS through December 22, 2019, the Applicant's Summary of Clinical Safety, the 120-day Safety Update Report, and most recent PADER, January 30, 2018 to January 29, 2019).

Dr. Lee focused on the following SAEs of interest: misuse, death, blindness, corneal abrasion, and hypersensitivity. To capture all SAEs associated with Pazeo, DPVII broadened and categorized these adverse events as misuse, death, and ocular and non-ocular events.

The consult identified 26 FAERS cases associated with Pazeo that reported misuse (n=2), death (n=1), ocular SAEs (n=19), and non-ocular SAEs (n=4). The descriptive characteristics of FAERS reports are shown in Table 20 below, followed by the MedDRA PTs in Table 21. The top five reported PTs were Eye irritation, Hypersensitivity, Ocular hyperemia, Glaucoma, and Vision blurred.

Table 20. Descriptive Characteristics of FAERS Cases Reporting SAEs or Misuse With Pazeo, Received by FDA from 2015 Approval Through December 22, 2019

Characteristics Details	No. of Cases (N=26)
Sex	
Female	19
Male	6
Not reported	1
Age (years)	
17 – 64	12
≥65	2
"Elderly"	1
Not reported	11
Country	
United States	25
Foreign	1
Report type	
Expedited	17
Non-expedited	3
Direct	6
Serious outcomes (n=25)*	
Death	1
Hospitalization	2
Other serious	24
All SAEs	
Death	1
Ocular SAEs†	19
Blindness	2
Blindness transient	1
Corneal abrasion	2
Hypersensitivity‡	3
Drug hypersensitivity	1
Eye irritation	3
Glaucoma	3
IOP increased	1
Iridocyclitis	1
Ocular hypertension	1
Periorbital swelling	1
Vision blurred	2

Characteristics Details	No. of Cases (N=26)
Misuse§	2
Intentional product misuse	1
Incorrect dose administered	1
Non-ocular SAEs	4
Lung disorder	1
Metal poisoning	1
Migraine	1
Tachycardia	1

Source: DPVII consult page 6
* The following outcomes qualify as serious: death, hospitalization (initial or prolonged), and other serious important medical events. A report may have one or more outcome.
† There were 19 cases involving ocular SAEs that reported multiple PTs. A case may contain one or more PTs.
‡ One of the cases reported hypersensitivity related to the eye. The remaining two cases did not provide sufficient detail to determine whether the hypersensitivity was related to the eye.
§ One case of misuse, which did not report serious outcomes, was captured under the PT Intentional Product Misuse (n=1). The second case was not coded for misuse and was captured under the PT Incorrect Dose Administered (n=1).
Abbreviations: FAERS, FDA Adverse Event Reporting System; IOP, intraocular pressure, SAE, serious adverse event

Table 21. MedDRA PTs of High Importance and Ocular PTs Associated With Pazeo Through December 22, 2019*

MedDRA PT	Number of FAERS Reports
Eye irritation	3
Hypersensitivity	3
Ocular hyperemia	3
Glaucoma	3
Eye pain	3
Vision blurred	2
Lacrimation increased	2
Blindness	2
Visual impairment	2
Corneal abrasion	2
Swelling of eyelid	2
Eye pruritus	1
Periorbital swelling	1
Erythema of eyelid	1
Visual acuity reduced	1
Eye discharge	1
Ocular hypertension	1
Eye inflammation	1
Punctate keratitis	1
Uveitis	1
Ciliary hyperaemia	1
Blindness transient	1
Eye swelling	1
Eyelids pruritus	1
Periorbital pain	1
Death	1
Conjunctivochalasis	1
Blepharospasm	1
Instillation site pain	1
Intraocular pressure decreased	1

MedDRA PT	Number of FAERS Reports
Drug hypersensitivity	1
Intraocular pressure increased	1
Iridocyclitis	1
Cataract	1
Intentional product misuse	1

Source: DPVII consult page 8
* A report may contain more than one MedDRA PT. The PTs in bold are the PTs of interest.

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; FAERS, FDA Adverse Event Reporting System; PTs, preferred terms

DPVII made the following assessments of the FAERS data:

- In the misuse cases (n=2), the contributory role of Pazeo could not be excluded in one case of corneal abrasion associated with the concomitant use of Pazeo and contact lens. The second case did not provide enough information for assessment.
- In the death case (n=1), the contributory role of Pazeo was indeterminate due to the lack of clinical information provided.
- In the ocular SAEs cases (n=19), the contributory role of Pazeo could not be excluded in eight cases; the PTs described in these cases include *Blindness* (n=1), *Corneal abrasion* (n=2), *Hypersensitivity* (n=2), *Eye irritation* (n=1), intraocular pressure *(IOP) increased* (n=1), and *Periorbital swelling* (n=1). We note that exposure to benzalkonium chloride in Pazeo solution has been associated with allergic contact sensitivity and corneal neurotoxicity and inflammation; although the extent of its contribution to the ocular events is unclear. The contributory role of Pazeo was indeterminate in 11 cases due to the lack of clinical information provided.
- In the non-ocular SAEs cases (n=4), which include *Tachycardia* (n=1)*, Metal poisoning* (n=1)*, Migraine* (n=1)*, and Lung disorder* (n=1), the contributory role of Pazeo was indeterminate given the lack of clinical information, including temporal association, past medical history, concomitant medications, and clinical outcome.

The OSE-DPVII review of the Applicant's data confirms that the SAEs reported in the PADERs and Summary of Clinical Safety are consistent with those reported in FAERS.

Dr. Lee opined that the limited FAERS cases identified are not enough to predict the misuse potential of Pazeo. Therefore, if a concern for potential misuse remains, "DPV recommends that ONDP consider requesting the Applicant provide in their annual periodic reports a summary of worldwide experience of all misuse cases."

A summary of the FAERS reports for Misuse (2), Death (1), Ocular SAEs (3 of 19 total), Drug hypersensitivity (4), Iridocyclitis (1) and Glaucoma or increased Intraocular Pressure (4) is shown below for completeness. The reviewer comments are those, or guided by those, of Dr. Lee from DPVII.

7.8.1.1. Summary of Misuse Adverse Events (N=2)

FAERS Case # 12126628, USA, Non-Expedited, 2016

PTs: Corneal abrasion, device physical property issue, intentional product misuse, scleral disorder

A 38-year-old male with allergic rhinitis and conjunctivitis received Pazeo for atopic conjunctivitis at a dose of one drop once daily. On an unknown date, he used Pazeo "with his contact lens" (intentional product misuse), which caused damage to the contact lens (lenses fragmented) and led to a corneal abrasion from the fragmented contact lens. On an unknown date within two months of starting Pazeo the patient developed "ulcerations" of the sclera (scleral disorder). Treatment with Pazeo was discontinued after 51 days. Concomitant medications were not reported. The events resolved on an unknown date. The physician states that the event was related to the use of Pazeo.

DPVII Reviewer's Comments:

- *The contributory role of Pazeo cannot be excluded given that the corneal abrasion occurred with the misuse of Pazeo while wearing contact lens.*
- *The product label advises against the concomitant use of soft contact lens under Warnings and Precautions and Patient Counseling Information.*

FAERS Case # 15596279, Foreign, Expedited, 2018

PTs: Cataract, concomitant disease aggravated, drug ineffective, eye pain, incorrect dose administered, vision blurred

A female of unspecified age with pre-existing eye pain received Pazeo eye drops twice daily for the treatment of itchy eyes from an unknown date at an unknown dose. Past medical history and concomitant medications were not reported. She instilled Pazeo "three or four times a day" and felt it was not working. She stopped taking the product for three weeks but still complained of blurry vision. She believes she was "using it too much/too many times" (incorrect dose administered). She was told that itchiness and blurred vision were expected side effects of Pazeo and that if she stopped the product, the side effects should subside with time. Pazeo was discontinued on an unknown date. The outcomes of the events, incorrect dose administered, eye pain, concomitant disease aggravated, drug ineffective, and cataract were not reported. The outcome of the event vision blurred was reported as unchanged. Further investigation yielded no manufacturing-related cause for the reported lack of efficacy of the Pazeo product.

DPVII Reviewer's Comments:

- *The contributory role of Pazeo cannot be determined given the lack of information on temporal association, past medical history, concomitant medications, and clinical outcome. Additionally, it is unknown to what extent the overuse of Pazeo contributed to the ocular symptoms.*
- *Although misuse was not included in the MedDRA coding, this case described the misuse of Pazeo eye drops at a frequency of three to four times the recommended frequency.*

7.8.1.2. Summary of Deaths

Death

FAERS Case # 16921599, USA, Expedited, 2019

PTs: Death

A 77-year-old male received octreotide and Pazeo for an unknown indication from an unknown date. Past medical history and concomitant medications were not reported. The patient died. It was unknown if an autopsy was performed. No additional information was provided.

DPVII Reviewer's Comment:

The contributory role of Pazeo cannot be determined given the lack of information on temporal association, past medical history, concomitant medications, clinical course, and cause of death.

7.8.1.3. Ocular Serious Adverse Events (3 of 19 Total)

Blindness, Blindness Transient

FAERS Case #13333654, USA, Expedited, 2017

PTs: Blindness, drug ineffective, erythema, eye irritation, eye pruritus, ocular hyperaemia, periorbital pain, vision blurred, visual acuity reduced

A 57-year-old male received Pazeo eye drops for an unknown indication from an unknown date at a dose of one drop twice daily for 14 days. On an unknown date, Pazeo alleviated the redness and irritation in his eyes with the morning dose but a few hours later, the eye became cloudy (vision blurred) and irritated (eye irritation) again. The night dose alleviated the symptoms but his eye became red (ocular hyperaemia), irritated, painful, and itchy in the morning. It was also painful behind the eye socket. The patient stated he was considered legally blind and could see shapes only but could not focus on anything (visual acuity reduced). Treatment with Pazeo was stopped on an unknown date and switched to a new medication (unspecified). The outcome of the events was not reported. Past medical history and concomitant medications were not reported.

DPVII Reviewer's Comments:

- *The contributory role of Pazeo cannot be excluded based on a temporal association of "a few hours" from Pazeo exposure to the onset of the ocular symptoms. However, the time to onset from Pazeo exposure to the onset of visual acuity reduced and blindness is unclear.*
- *Several of the reported ocular symptoms are commonly associated with allergic conjunctivitis.*

FAERS Case # 14119738, USA, Expedited, 2017

PTs: Blindness, product quality issue

An 83-year-old male with the concurrent conditions of unspecified “vision problems”, hypertension , diabetes mellitus (DM), and hypercholesterolemia received Pazeo (lot number 247048F) for the treatment of itchy eyes. Concomitant medications included “blood thinners and multiple medications for hypertension, DM, and hypercholesterolemia.” He administered Pazeo for about 4-5 days, at which time the Pazeo solution looked clear. Because he wanted to ensure easy access to the eye drops, he stored the bottle upside down with the top tightly sealed, after which the appearance of the eye drops became milky white in color (product quality issue). The patient reported that he “was blind”, stating that he “has had vision problems.” The outcome of the event blindness and action taken with Pazeo were not reported. The Pazeo sample was provided to the manufacturer’s quality assurance (QA) department for analysis; however, because the sample was open and did not contain any ophthalmic solution, a conclusive root cause could not be determined. Additionally, no manufacturing-related root causes were found during the investigation. The QA department noted that consumer perception and consumer mishandling could not be eliminated as a potential root cause for this complaint. Review of the complaint history and chemical/microbial release data found no issues which could have contributed to this complaint. A total of one complaint was identified for lot 267048F reporting an issue with the color of the solution.

DPVII Reviewer’s Comment:

The contributory role of Pazeo cannot be determined given the lack of information on temporal association, clinical course, concomitant medications, clinical outcome, the action taken, the Pazeo, and contact lens use or presence of trauma. The case narrative describes a change in the color of the Pazeo solution, which alludes to the possibility of contamination, which is a labeled event under the Warnings and Precautions section (in the Full Prescribing Information). Additionally, further assessment by the Applicant’s QA department did not identify a root cause and could not exclude mishandling of the product.

FAERS Case # 12416649, USA, Expedited, 2016

PTs: Blindness transient

Two patients of unspecified age and gender received Pazeo (batch/lot number unknown) for an unknown indication and experienced "lost vision for a short period of time" (blindness transient). Past medical history and concomitant medications were not reported. No other information was provided.

DPVII Reviewer’s Comment:

The contributory role of Pazeo cannot be determined given the lack of information on temporal association, past medical history, concomitant medications, clinical course, clinical outcome, the action taken with Pazeo, and contact lens use or presence of trauma.

7.8.1.4. Drug Hypersensitivity, Hypersensitivity

FAERS Case # 16018100, USA, Direct, 2019

PTs: Drug hypersensitivity, erythema of eyelid, eyelids pruritus, swelling of eyelid

A 35-year-old female instilled one drop of Pazeo in each eye for "pollen allergy." On the second day, within 15 minutes of Pazeo instillation, both eyelids became swollen, red, and itchy. Past medical history includes environmental and drug allergies to pollen, trees, mold, dust mites, tetracycline, blue dye, and acetaminophen/tramadol (Ultracet), and sensitivities to wheat, corn, soy, sodium metabisulfite, kale, avocado, bananas, cow's milk, barley, cane sugar, cantaloupe, blue #1, blue #2, yellow #5, lentils, monosodium glutamate, pecan, pistachio, and cucumber. Concomitant medications, outcome of the aforementioned adverse events, and action taken with Pazeo were not reported.

*DPVII Re*viewer's *Comments*:

- *The contributory role of Pazeo cannot be excluded based on a temporal association of 15 minutes from Pazeo exposure to the onset of drug hypersensitivity, described as eyelid swelling, erythema, and pruritis.*
- *Exposure to benzalkonium chloride in Pazeo solution has been associated with allergic contact sensitivity.*
- *Other potential etiologies are possible related to environmental factors, concomitant medications, contamination of the Pazeo solution, contact lens use, or the presence of trauma, as this information was not provided.*

FAERS Case # 11246237, USA, Direct, 2015

PTs: Blepharospasm, hypersensitivity, swelling of eyelid, urticaria, visual impairment

A 59-year-old healthy female with no known drug allergies or concomitant medications received Pazeo eye drops from a nurse practitioner (the reporter) for allergic conjunctivitis (day 0). On day 1, within one minute of Pazeo self-instillation, the patient experienced swelling of the bilateral lower eyelids with twitching of the lower eye muscles and one large welt on the outer aspect of her right eye without pruritis. These symptoms improved throughout the day but did not resolve. Pazeo was discontinued. On day 2, the patient complained of slightly swollen lower eyelids and continuous twitching of the left lower eyelid, which were also observed at her follow-up appointment on day 3. She described her vision to be "like a film over her left eye." She did not experience any shortness of breath. The nurse practitioner advised her not to use this product again in the setting of a new allergic reaction. No information was provided on the treatment of the adverse event or the clinical outcome.

DPVII Reviewer's Comments:

- *The contributory role of Pazeo cannot be excluded based on the temporal association of one minute from Pazeo exposure to the onset of blepharospasm, hypersensitivity, and visual impairment.*

- *Exposure to benzalkonium chloride in Pazeo solution has been associated with allergic contact sensitivity and corneal neurotoxicity and inflammation. This case does not describe any potential alternate etiologies given the absence of comorbid conditions or concomitant medications. The presence or absence of contact lens use was not reported.*

FAERS Case # 15515654, USA, Expedited, 2018

PTs: Asthma, hypersensitivity

A 38-year-old female received Pazeo for an unknown indication from an unknown date at an unknown dose and frequency. Past medical history and concomitant medications were not reported. On an unknown date, the patient had allergies (hypersensitivity) and asthma. The outcome of the events asthma and hypersensitivity and the action taken with Pazeo were not reported. No additional information was provided. This case was lost to follow-up.

DPVII Reviewer's Comments:

- *The contributory role of Pazeo cannot be determined given the lack of information on temporal association, past medical history, concomitant medications, clinical course, clinical outcome, and the action taken with Pazeo.*
- *It is also unclear whether the eye was affected by the hypersensitivity. Exposure to benzalkonium chloride in Pazeo solution has been associated with allergic contact sensitivity.*

FAERS Case # 16244604, USA, Expedited, 2019

PTs: Hypersensitivity, syncope

An adult female of unspecified age received Pazeo for the treatment of an unknown indication on an unknown date at an unknown dose and frequency. Past medical history and concomitant medications were not reported. On an unknown date, the patient reported "being on the medication and recently hospitalized due to bad allergies (hypersensitivity)" and also said she fainted (syncope). The action taken with Pazeo was not reported. The outcome of the events hypersensitivity and syncope was not reported. No additional information was provided.

DPVII Reviewe'sr Comments:

- *The contributory role of Pazeo cannot be determined given the lack of information on temporal association, past medical history, concomitant medications, clinical course, clinical outcome, and the action taken with Pazeo.*
- *It is unclear whether the eye was affected by the hypersensitivity. Exposure to benzalkonium chloride in Pazeo solution, has been associated with allergic contact sensitivity (Applicant's ISS) .*

7.8.1.5. Iridocyclitis

FAERS Case # 16475926, USA, Expedited, 2019

PTs: Iridocyclitis

A female in her mid-50’s (exact age unspecified) received Pazeo for the treatment of ocular itch associated with allergic conjunctivitis from an unknown date at a dose of one drop once daily. Past medical history and concomitant medications were not reported. On an unknown date, she developed bilateral anterior uveitis (iridocyclitis). It was reported that she discontinued Pazeo and was started on a steroid for inflammation. The outcome of the event iridocyclitis was not reported.

DPVII Reviewer’s Comments:

- *The contributory role of Pazeo cannot be determined given the lack of information on temporal association, past medical history, concomitant medications, clinical course, clinical outcome, and contact lens use or presence of trauma.*
- *Exposure to benzalkonium hydrochloride in Pazeo solution has been associated with allergic contact sensitivity and corneal neurotoxicity and inflammation.*

7.8.1.6. Glaucoma, Increased Intraocular Pressure (IOP), and Ocular Hypertension

FAERS Case # 15427233, USA, Expedited, 2018

PTs: Glaucoma

An elderly female patient (age unspecified) received Pazeo, travoprost (Travatan Z), and betaxolol (Betoptic S) for an unknown indication from an unknown date. Past medical history and concomitant medications were not reported. On an unknown date, the patient developed "glaucoma.” The outcome of the event glaucoma and the action taken with Pazeo, travoprost, and betaxolol were not reported.

DPVII Reviewer’s Comment: The contributory role of Pazeo cannot be determined given the lack of information on temporal association, past medical history, concomitant medications, clinical course, clinical outcome, and the action taken with Pazeo.

FAERS Case # 15728796, USA, Expedited, 2018

PTs: Eye irritation, glaucoma

An adult female of unspecified age received Pazeo and brinzolamide/brimonidine (Simbrinza) for an unknown indication from an unknown date. On an unknown date, she had glaucoma and burned eyes (eye irritation). On an unknown date, she underwent cataract surgery. Past medical history and concomitant medications were not reported. The outcomes of the events glaucoma and eye irritation and the action taken with brinzolamide/brimonidine and Pazeo were not reported. No additional information was provided.

*DPVII Reviewe*r’s *Comments*:

- *The contributory role of Pazeo cannot be determined given the lack of information on temporal association, past medical history, concomitant medications, clinical course, clinical outcome, the action taken with Pazeo, contact lens use, and presence of trauma.*
- *Exposure to benzalkonium hydrochloride in Pazeo solution has been associated with allergic contact sensitivity and corneal neurotoxicity and inflammation.*
- *This case is confounded by the concomitant use of brinzolamide/brimonidine, which is indicated for the treatment of glaucoma and labeled for eye irritation under Adverse Reactions.*

FAERS Case # 12439878, USA, Expedited, 2016

PTs: Intraocular pressure increased

A 64-year-old male received Pazeo (lot number 257359F) one drop in each eye once daily for the treatment of itchy eyes. Past medical history and concomitant medications were not reported. Nine days later, during a follow up appointment, he discovered his IOP increased from 22 to 28 in his left eye, at which time he was instructed to discontinue Pazeo. The IOP reading was not reported for his right eye. The patient stated that he was instilling unspecified steroid drops in his right eye only, which could have contributed to the increased IOP in his right eye. He was prescribed brimonidine/timolol (Combigan) for the treatment of IOP increased. The outcome of the event IOP increased was not reported. Further information requested, but not received.

DPVII Reviewer’s Comment: The contributory role of Pazeo cannot be excluded based on a temporal association of within nine days of initial Pazeo exposure to the onset of IOP increased. However, the potential alternate etiologies cannot be excluded, as information on past medical history, baseline IOP, and concomitant medications is lacking.

FAERS Case # 16283267, USA, Non-Expedited, 2019

PTs: Ocular hypertension

An adult female of unspecified age received Pazeo for the treatment of chronic allergic conjunctivitis from an unknown date. Past medical history was not reported. Concomitant medications included ketotifen fumarate (Alaway), loteprednol etabonate (Lotemax), and hydrocortisone cream (Cortisone). On an unknown date, she developed "ocular hypertension due to OTC steroid cream.” The outcome of the event ocular hypertension and the action taken with Pazeo and hydrocortisone were not reported. No additional information was provided.

DPVII Reviewer’s Comment:

- *The contributory role of Pazeo cannot be determined given the lack of information on temporal association, past medical history, clinical course, clinical outcome, the action taken with Pazeo, and the presence of trauma.*
- *In addition, this case is confounded by the concomitant use of ophthalmic and topical steroids, including loteprednol, which is labeled for increased IOP under Warnings and Precautions. The patient also reported “ocular hypertension due to OTC steroid cream”,*

which is not typically applied to the eye. Of note, the drug facts label for hydrocortisone cream contains a warning to "avoid contact with eyes."

7.8.2. Expectations on Safety in the Postmarket Setting

The relative safety of olopatadine 0.7% is established in the prescription setting for patients age 2 and older including geriatric patients, providing they adhere to the approved indication and a dose of no more than one drop in each affected eye per day, and do not use olopatadine 0.7% with any other olopatadine ophthalmic solutions. However, the Applicant's Argus database plus supplemental safety reports (PADERS, FAERS PSUR, 120-day safety update) and the OSE-DPVII consult still yielded 26 SAEs, 2 of which involved misuse (Pazeo not excluded in one report), and overall 19 ocular SAEs (Pazeo not excluded in eight case reports). It is likely OTC use will lead to SAEs.

Meanwhile, all use of Pazeo is from the prescription environment in the USA. Thus, there are no data for USA consumers or any consumers for the 0.7% solution. This reviewer has not located any clinical trial data or literature information for any of the three concentrations for use in humans of more olopatadine than one drop of the 0.7% solution in each eye per day. Based on the clinical reviews, the 0.1% and 0.2% strengths were also not studied in humans at doses that exceeded the equivalent drug amount of the 0.7% solution. The medical consequences of overuse of the 0.7% solution are therefore unstudied.

The systemic safety of the 0.7% solution was studied in animals, reaching a systemic exposure about 60-80 times, or more, than expected in a human administered an ophthalmic dose of one drop. In the Patanol development program, two humans were given a 80mg dose of olopatadine with no adverse consequences, and multiple subjects received a 5 mg oral tablet in the Pazeo development program. This is much more systemic exposure than the amount of olopatadine that would be absorbed from an eye drop containing about 0.3 mg of olopatadine, only a small fraction of which would be absorbed into the systemic circulation. There are no concerns about systemic safety. However, such a comparison is not relevant given the adverse events in humans are ophthalmic, not systemic. In the Patanol development program, monkeys received four drops daily of a 0.5% solution for months with no apparent serious problems. The maximum amount of drug instilled daily in the eyes of monkeys without allergic conjunctivitis is just below the amount of drug in 3 drops of Pazeo (4 drops x 0.5% ="2" vs 3 drops x 0.7% = "2.1"). No animal studies were conducted with Pataday or Pazeo, so this study in monkeys is the only potential study comparator for Pazeo in an overuse situation.

Reviewer Comment

Extrapolating or interpolating a dose of drug used in an animal model to then use in humans is part of a normal development program. It is not clear that the safety in normal monkey eyes at a high dose (4 drops of 0.5%) will translate to an overuse situation in humans with the same high dose (about 2-2.9 drops).

The section below outlines some possible approaches to mitigating the unknown risk(s) if the labeled dose is exceeded.

What are some Options to Address the Safety of Olopatadine Hydrochloride Ophthalmic Solution 0.7% in the OTC Market?

Background

- This product is proposed for the Rx-to-OTC switch of Pazeo under the proposed Proprietary Name of Pataday Once Daily Relief, Extra Strength. The directions for use state one drop in each affected eye once per day.
- The highest dose of olopatadine ophthalmic solution studied by the Applicant in humans, or found in the literature, is one drop of the 0.7% in each eye per day for 6 weeks. The Applicant studied a higher systemic dose in animals than would be achieved by the ophthalmic dose in humans (so there is at least a 60-80-fold margin of systemic safety, likely much higher).
- There are no Phase 1, Phase 2, or Phase 3 studies for any of the olopatadine ophthalmic solution products that dosed higher than the proposed dose in the eyes for OTC consumers. The Applicant agreed in their response to an Information Request.
- In the postmarket safety reporting, 26 SAEs have been reported, although only 2 with misuse (one death, unrelated, and one blindness, neither likely related). In the one SAE reporting a cataract the consumer reported using Pazeo (olopatadine 0.7%) 3 or 4 times per day, which is itself concerning.

What is the Concern?

- The main concern is that consumers might overuse Pataday Once Daily Relief, Extra Strength either by mistake, or intentionally, with unknown and unstudied safety consequences.
- For example, consumers might confuse the dosing of Pataday Once Daily Relief, Extra Strength with the twice daily dosing of the already approved Pataday Twice Daily Relief (olopatadine 0.1%, one drop in each affected eye twice daily), and then overuse Pataday Once Daily Relief, Extra Strength.
- Or, consumers may intentionally use Pataday Once Daily Relief, Extra Strength with either of the other two approved OTC olopatadine ophthalmic solutions.

Table 22. Possible Approaches (in No Particular Order) to Evaluating the Safety Under OTC Conditions of Overuse of Olopatadine Ophthalmic Solution 0.7%

Intervention	Pros	Cons	Comments
(1) Issue a CR for the application and require a Safety Study with a higher dose	Safety related to an overuse condition would be studied prior to OTC approval	CR may be viewed as an overly strong measure given that the drug looks relatively safe in the Rx environment	CR for an OTC drug may not have a precedent when the reason for the CR is a hypothetical safety risk that only occurs if consumers fail to follow the Directions for Use.
(2) Require a safety study (phase 1, of adequate size) with a higher dose prior to PDUFA date.	Avoids a CR, extends clock with a major amendment	Delays approval date	May be reasonable to Applicant, however timing may be rushed
(3) Approve application with strong labeling (e.g., "Do not use more than 1 drop per eye per day" and "Do not use with other Pataday products"	Easiest approach, and justifiable based on submitted safety data (e.g. if we don't go down the path of worrying about the unknown)	May require a quick Label Comprehension Study for new DFL, possibly a targeted Self-selection study Consumers may not follow the Directions (how to Use the drug) Possibly no precedent for Do Not Use on DFL with another specific OTC product	There are always some SAEs with Rx drugs, however no deaths or irreversible SAEs with Rx Pazeo 0.7%. Social science input considered for this option
(4) Approve, strong labeling and a PMC for a safety study with a higher dose (phase 4 study designed like a phase 1)	Meet PDUFA date Still get safety data in a prospective clinical trial setting	Takes a chance that Applicant may not conduct the PMC promptly	If we see SAEs in the OTC environment, it is unclear whether we could require the PMC to be done immediately.
(5) Approve application and ask Applicant to include in their annual and periodic reports, a summary of all experience with misuse cases (and their consequences)	Meet PDUFA date Still get Safety Data	Safety data arrives months or longer after OTC approval and is retrospective	*This is a suggestion for our consideration from the OSE-DPV2 team which conducted the consult regarding FAERS data*

Intervention	Pros	Cons	Comments
(6) Issue a CR; however, then give Applicant the choice to: a) do safety study above OR b) do LCS/SS with strong DFL wording and if LCS/SS not supportive then Applicant needs to do safety study	Responsibility is on Applicant to decide best course	Delay potential approval date	*Suggestion from clinical reviewer (Dr. Donohoe) for other olopatadine switches.* Request for safety data for "potential overuse/misuse" may be difficult to get (via regulatory authority) without "proving" via LCS/SS that it is a legitimate concern. However, Applicant may choose to do safety study because it may be most efficient.
(7) Approve application with proposed labeling or closely like proposed labeling	Meet PDUFA date	Accepts possibility of overuse with unknown ocular effects	*Recommendation from DTOP*. Use vigilant review of subsequent AE reports and update labeling as needed

Abbreviation: CR, complete response; DFL, drug facts label; FAERS, FDA Adverse Event Reporting System; LCS/SS Label Comprehension study/Self-selection study; OSE-DPVII, Office of Surveillance and Epidemiology - Division of Pharmacovigilance II; OTC, over-the-counter; PMC, postmarket commitment; SAE, serious adverse event
Source: this reviewer

Reviewer Comments

- *The review team considered the unknown and unstudied safety with a higher than labeled dose of olopatadine 0.7% to be problematic. We can anticipate overuse by some consumers, with a drug as easy as an eyedrop to administer for a common symptom of ocular itching.*
- *Based on the postmarket safety data and the OSE review, it is likely some consumers will misuse the drug with a goal of more relief, so we need to try practical measures to at least explore the safety of Pazeo for consumers who do not follow the directions.*
- *In addition, because consumers typically overuse some OTC drugs(reference), a safety study using more than one drop per day for the proposed duration of dosing (e.g. 6 weeks) before consulting a doctor would add to the assurance that OTC marketing of Pazeo will be safe for consumers.*
- *On February 25, 2020, this reviewer met with the Cross-Discipline Team Leader for the application, Frank Becker MD and Karen Mahoney MD, FACE, deputy director of Office of Nonprescription Products, and the signatory for the application to discuss options from an earlier version of Table 22 above. No decisions were made at that time.*
- *On April 29, 2020, this reviewer, Frank Becker MD, Karen Mahoney, MD, FACE and regulatory project manager Jung Lee met. Our group leaned towards Option 6 from Table 22 above, issuing a CR and allowing the Applicant to address the CR by selecting whether to conduct a safety study first, or revise the DFL with strong statements and possibly bolding or highlighting, then conduct a targeted self-selection study (subjects with redness and itching). 6. Only if the label comprehension study (LCS) with a revised*

and stronger DFL and the targeted self-selection study failed to demonstrate a high degree of understanding of the DFL and appropriate self-selection, would the Applicant then need to conduct a clinical safety study demonstrating adequate safety with a higher dose than one drop each eye per day, prior to OTC approval.

- *At a review team meeting on May 21, 2020 Options 1-6 from Table 22 above were considered, particularly Options 1 and 2, with Option 1 issuing a CR and requiring a safety study, and Option 2 requiring a safety study but avoiding an immediate CR via a clock extension and a major amendment. Following the meeting, this reviewer added a 7th Option per the recommendation of DTOP, an approval without further conditions.*
- *On June 2, 2020, the OTC clinical and social science team met with the DTOP clinical team and the respective office directors, Dr. Michele and Dr. Ganley to discuss a path forward. Slides and the Option Table above were presented by OTC. Dr. Ganley expressed reasonable comfort that based on the mechanism of action for an antihistamine and mast cell stabilizer drug, wide use and likely overuse of already OTC or OTC-eligible eye drops for itching and redness relief, it would be unlikely that consumers would be harmed by overuse of olopatadine 0.7%. Dr. Ganley considered Option 5 (postmarket adverse event reporting) above to be reasonable Dr. Mahoney opened a discussion of whether a precedent might be set for other drugs if OTC approved a drug with no data about the potential effects (harm) of overuse, since OTC drugs have typically been studied and often used Rx at higher doses than the dose approved for OTC. Dr. Michele commented that it might be possible to frame reasoning for approval of olopatadine 0.7% without additional safety data, and not opening a door for other drugs that might be riskier. No decisions were made yet.*
- *Also at the June 2, 2020 a few examples of stronger labeling were considered, such as bolding the warning "Do not use more than 1 drop in each eye per day", or "Do not use more than 1 drop in each eye per day: safety has not been studied above 1 drop in each eye per day", and "If you need to use more than 1 drop in each eye per day, contact your doctor; you may need additional medical care". DTOP expressed concern with any labeling other than what has previously been used with similar OTC eye drops. The team made a comparison with drug facts labeling on the February 2020 approvals of the 0.1% and 0.2% olopatadine eye drops, and with the 2017 approval of Lumify (brimonidine tartrate), indicated for ocular redness relief. To this reviewer, Option 6 in Table 22 above appears to be the best choice for safety plus practicality (issue a CR and give the Applicant a choice of a safety study or consumer behavior studies with an optimized label, and a safety study required for approval only if the consumer behavior studies fail). Option 1, (issuing a CR and requiring a safety study,regardless of any consumer behavior studies, is the most conservative and safest approach although it limits options for the Applicant. Option 2 (extend the PDUFA clock and conduct a safety study now) is probably too late in the cycle at the date of this review. Option 3 (Approval with strong labeling in Directions and Warnings) is practical, although it is unclear whether strong labeling will be understood by the consumer, unless it has been previously tested in an OTC DFL. Option 4 (Approval with a required postmarket safety study) is a potentially reasonable approach, although it risks a period of unstudied safety*

if consumers overuse the drug. Option 5 (Approval and require a breakout of misuse-related adverse events in postmarket reports) is reasonable though riskier due to delays in receiving and reporting adverse event reports). Option 7 (approval without conditions, meaning no required studies and no major changes from the proposed labeling by the Applicant) is inconsistent with previous OTC approvals, which have typically required an understanding of safety in humans at a dose higher than the proposed OTC dose, to cover potential overuse/misuse by consumers.

7.8.3. Additional Safety Issues From Other Disciplines

There were no other safety issues from other disciplines as the proposed OTC drug product is the same as the current prescription drug product.

7.9. Integrated Assessment of Safety

The Applicant did not conduct any new clinical studies to support this review. Therefore, this safety review analyzes postmarket data and is discussed above. Overall there have been 26 serious adverse events reported for olopatadine 0.7% since approval in 2015 and no fatalities. The number of adverse events reported (per year) are close between the three olopatadine ophthalmic products in Table 14 (Applicant's Argus database), however there may be a trend towards more total AEs (not necessarily SAEs) for olopatadine 0.7% (763 total and 21 SAEs in about 4 years or 190 AEs and 5 SAEs per year) than for olopatadine 0.1% (4072 total and 160 SAEs in about 23 years or 177 AEs and 7 SAEs per year) or 0.2% (2050 total and 55 SAEs in about 15 years or 137 total and 3-4 SAEs per year).

Literature Review

In addition to the articles in the ISS and noted earlier in this review, the Applicant submitted an updated literature review from PubMed and Google Scholar for the period January 1, 2019 to March 31, 2019 using the search terms: olopatadine; olopatadine hydrochloride; Patanol; Pataday; Opatanol; Pazeo; Patanase. Of these four articles, only two pertained to ophthalmic olopatadine. They are outlined below:

Nakatani H et al. (Nakatani et al. 2019) examined the effectiveness of olopatadine and alcaftadine ophthalmic solutions to placebo in allergy-sensitive individuals at 3, 5, 7, 15, and 20 minutes after an allergen challenge (4 or 8 hours after dose). Overall, TEAEs occurred in 12.2% of the individuals who received olopatadine alone. The most commonly reported adverse event was oropharyngeal discomfort (6.1%), and no adverse event led to study discontinuation. No ocular adverse events occurred in olopatadine-treated eyes.

Patel et al. (Patel et al. 2018) investigated topical olopatadine and ketotifen in terms of effectiveness and safety for the management of allergic conjunctivitis. Individuals were evaluated after the 4th, 15th, and 30th days of treatment. A total of 10% of patients reported TEAEs after olopatadine treatment. The most common adverse event was headache (7%) followed by a burning sensation of the eyes (3%).

In addition, this reviewer conducted an additional targeted literature search in February 2020 and repeated in April 2020, on PubMed and Google with the search terms:

- Olopatadine overuse
- Olopatadine misuse
- Olopatadine serious adverse events
- Pazeo overuse
- Pazeo misuse
- Pazeo serious adverse events

This search did not reveal any references citing overuse / misuse of olopatadine 0.7% (or any olopatadine drug), nor any references suggesting the drug in the prescription environment posed a significant risk to patients.

8. Advisory Committee Meeting and Other External Consultations

FDA did not convene an advisory committee meeting for this application.

9. Labeling Recommendations

9.1. Prescription Drug Labeling

9.2. The main warnings in the Rx label are hypersensitivity and corneal damage. Nonprescription Drug Labeling

See Section 12.4 for the proposed Drug Facts Label. The Applicant translated the main warnings from the Rx label to the proposed Drug Facts Label. The Warnings section of the DFL outlines what the consumer should do before using the drug and when to stop the drug and seek medical help if certain symptoms develop (adverse events). A key element is the Directions for Use, which states one drop in each affected eye per day.

Key elements of the Rx Full Prescribing Information that were important, besides the (b) (4) and Directions, in the development of the proposed DFL are:

- Contraindications: None
- Warnings and Precautions: For topical use only. Not for injection or oral use
- The Rx full prescribing information also states:

  "There are no adequate or well-controlled studies with PAZEO in pregnant women. Olopatadine caused maternal toxicity and embryofetal toxicity in rats at levels 1,080 to 14,400 times the maximum recommended human ophthalmic dose (MRHOD). There

was no toxicity in rat offspring at exposures estimated to be 45 to 150 times that at MRHOD. Olopatadine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

"Contact Lens Use Patients should not wear a contact lens if their eye is red. The preservative in PAZEO solution, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses and whose eyes are not red, should be instructed to wait at least five minutes after instilling PAZEO before they insert their contact lenses."

Reviewer Comments

1) *This reviewer defers to the IDS labeling team and the social scientist for the best way to strengthen the DFL in a manner to best guide the consumer to use the drug only as directed in the DFL and not overuse or misuse.*
2) *Some ideas for strengthening the Drug Facts label are adding 3 statements under Directions, When using this product, and Do not use. Of key import is that these statements were tested for OTC drugs, however, in the DFL in which they appear, not in the proposed DFL for olopatadine 0.7%.*
    - *Directions (example from OTC Differin Gel): "Do not use more than one drop per eye, per day. Using more than directed will not provide faster or better results*
    - *When using this product (example from OTC Rogaine): "Do not use more than directed". And then under "Directions" we said "Using more or more often will not improve results"*
    - *Do not use (example from OTC acetaminophen): "Do not use with any other drug containing olopatadine"*

10. Risk Evaluation and Mitigation Strategies (REMS)

Not applicable for an Rx-to-OTC switch application.

11. Postmarketing Requirements and Commitments

Any postmarket requirements an commitments are pending further discussion. It is unclear whether any risk from potential overuse by a consumer, which would necessarily involve an ocular dose of an unstudied amount of drug, could be minimized by an optimized Drug Facts label. Or, can thisunstudied safety concern from potential overuse only be addressed with a clinical safety study or close monitoring of postmarket safety reporting.

12. Appendices

12.1. References

Bielory, L, 2000, Allergic and immunologic disorders of the eye. Part II: ocular allergy, J Allergy Clin Immunol, 106(6):1019-1032.

Guzman-Aranguez, A, P Calvo, I Ropero, and J Pintor, 2014, In vitro effects of preserved and unpreserved anti-allergic drugs on human corneal epithelial cells, J Ocul Pharmacol Ther, 30(9):790-798.

Jagarlamudi, A, E Anushree, S Harika, K Kavya Sri, and C Rohit, 2019, A simple randomized comparative study to evaluate the efficacy of 0.7% w/v Olopatadine hydrochloride ophthalmic solution and the Fixed Dose Combination of 0.1% w/v Olopatadine hydrochloride and 0.4% w/v Ketorolac tromethamine ophthalmic solution for the treatment of allergic conjunctivitis, J Drug Deliv Ther, 9(3):279-285.

Nakatani, H, P Gomes, R Bradford, Q Guo, E Safyan, and DA Hollander, 2018, Alcaftadine 0.25% versus Olopatadine 0.1% in Preventing Cedar Pollen Allergic Conjunctivitis in Japan: A Randomized Study, Ocul Immunol Inflamm, 27(4):622-631.

O'Brien, TP, 2013, Allergic conjunctivitis: an update on diagnosis and management, Curr Opin Allergy Clin Immunol, 13(5):543-549.

Patel, D, N Sarala, and NP Datti, 2018, Topical Olopatadine Hydrochloride versus Ketotifen Fumarate for Allergic Conjunctivitis, J Ophthalmic Vis Res, 13(2):119-123.

12.2. References/Applicant Submitted Literature for Safety

The Applicant cited two of the references listed above (Nakatami et al 2018 and Patel et al 2018) as recent support for the safety of olopatadine. These are shown in the table below with a brief listing the objectives and results.

Table 23. Two Recent Studies Supporting Safety of Olopatadine Ophthalmic Solution

REFERENCE	STUDY TYPE	SAMPLE	OBJECTIVES	RESULTS
Nakatani et al. Alcaftadine 0.25% versus Olopatadine 0.1% in preventing cedar pollen allergic conjunctivitis in Japan: A randomized study. Ocul Immunol Inflamm. 2018 Mar 15: 1-10.	Phase 3, single-center, randomized, double-blinded, vehicle- and active-controlled trial	Japanese adults (N = 240) with a history of allergic conjunctivitis and positive skin test to Japanese cedar pollen-specific allergen.	To assess the safety and efficacy of alcaftadine 0.25% ophthalmic solution versus vehicle and olopatadine 0.1% ophthalmic solution.	• TEAEs occurred in 12.2% of the individuals who received olopatadine alone. • The most commonly reported adverse event was oropharyngeal discomfort (6.1%) • No adverse event led to study discontinuation. • No ocular adverse events occurred in olopatadine-treated eyes.
Patel et al. Topical olopatadine hydrochloride versus ketotifen fumarate for allergic conjunctivitis. J Ophthalmic Vis Res. 2018 Apr-Jun; 13(2): 119-123.	Randomized study	Patients of either gender ages 8 or older (N = 120) , clinically diagnosed with seasonal allergic conjunctivitis.	To compare the safety and efficacy of olopatadine HCl 0.1% and ketotifen fumarate 0.025% for allergic conjunctivitis.	• A total of 10% of patients reported TEAEs after olopatadine treatment. • The most common adverse event was headache (7%) followed by a burning sensation of the eyes (3%).

Source: Applicant's ISS p. 57 of 66 for sNDA 020688 and sNDA 021545 (Patanol and Pataday switch)

Additional References listed in Module 2 of sNDA 206276)

1. Gomes, PJ, 2014, Trends in prevalence and treatment of ocular allergy, Curr Opin Allergy Clin Immunol, 14(5):451-456.
2. O'Brien, TP, 2013, Allergic conjunctivitis: an update on diagnosis and management, Curr Opin Allergy Clin Immunol, 13(5):543-549.
3. Singh, K, S Axelrod, and L Bielory, 2010, The epidemiology of ocular and nasal allergy in the United States, 1988-1994, J Allergy Clin Immunol, 126(4):778-783 e776.
4. Leonardi, A, F Piliego, A Castegnaro, D Lazzarini, A La Gloria Valerio, P Mattana, and I Fregona, 2015, Allergic conjunctivitis: a cross-sectional study, Clin Exp Allergy, 45(6):1118-1125.
5. Miraldi Utz, V and AR Kaufman, 2014, Allergic eye disease, Pediatr Clin North Am, 61(3):607-620.
6. Ventocilla, M, M Bloomenstein, and P Majmudar, 2014, Allergic Conjunctivitis, accessed October 13, 2015, https://emedicine.medscape.com/article/1191467-overview#showall.
7. Bielory, L, 2008, Ocular allergy overview, Immunol Allergy Clin North Am, 28(1):1-23, v.
8. Periodic Safety Update Report, *Olopatadine* (Novartis 2018)
9. Abelson, MB, PJ Gomes, T Pasquine, MR Edwards, RD Gross, and SM Robertson, 2007, Efficacy of olopatadine ophthalmic solution 0.2% in reducing signs and symptoms of allergic conjunctivitis, Allergy Asthma Proc, 28(4):427-433.
10. Vogelson, CT, MB Abelson, T Pasquine, DM Stephens, DA Gamache, RD Gross, SM Robertson, and JM Yanni, 2004, Preclinical and clinical antiallergic effect of olopatadine 0.2% solution 24 hours after topical ocular administration, Allergy Asthma Proc, 25(1):69-75.

11. Virchow, JC, S Kay, P Demoly, J Mullol, W Canonica, and V Higgins, 2011, Impact of ocular symptoms on quality of life (QoL), work productivity and resource utilisation in allergic rhinitis patients--an observational, cross sectional study in four countries in Europe, J Med Econ, 14(3):305-314.
12. Weeke, ER, 1987, Epidemiology of hay fever and perennial allergic rhinitis, Monogr Allergy, 21:1-20.
13. Canonica, GW, J Bousquet, J Mullol, GK Scadding, and JC Virchow, 2007, A survey of the burden of allergic rhinitis in Europe, Allergy, 62 Suppl 85:17-25.
14. Bilkhu, PS, JS Wolffsohn, and SA Naroo, 2012, A review of non-pharmacological and pharmacological management of seasonal and perennial allergic conjunctivitis, Cont Lens Anterior Eye, 35(1):9-16.
15. Internal Reference: Olopatadine Core Safety Risk Management Plan Version 1, data lock point: August 31, 2015, issued October 27, 2015.
16. Guzman-Aranguez, A, P Calvo, I Ropero, and J Pintor, 2014, In vitro effects of preserved and unpreserved anti-allergic drugs on human corneal epithelial cells, J Ocul Pharmacol Ther, 30(9):790-798.
17. Baudouin, C, A Labbe, H Liang, A Pauly, and F Brignole-Baudouin, 2010, Preservatives in eyedrops: the good, the bad and the ugly, Prog Retin Eye Res, 29(4):312-334.
18. Periodic Safety Update Report, *Novartis Core Company Data Sheet (CCDS; Version 1.0) for Olopatadine Eye Drops Solution and Olopatadine Nasal Spray* (Novartis 2015)
19. Church, DS and MK Church, 2011, Pharmacology of antihistamines, World Allergy Organ J, 4(3 Suppl):S22-27.
20. Simons, FE and KJ Simons, 1994, The pharmacology and use of H1-receptor-antagonist drugs, N Engl J Med, 330(23):1663-1670.

12.3. Financial Disclosure

Not applicable, as no clinical studies were conducted for this application.

12.4. Proposed OTC Labeling

Figure 2. Proposed OTC Labeling for Pataday Once Daily Relief: Principal Display Panel for Carton (Descriptor "Extra Strength" Shown in This Version, November 25, 2019)

(See drug facts on next page.)

Drug Facts

Active Ingredient ***Purpose***

Olopatadine (0.7%)……..Antihistamine (equivalent to olopatadine hydrochloride 0.776%)

(b) (4) Temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair and dander

Warnings

For external use only

Do not use

- if solution changes color or becomes cloudy
- if you are sensitive to any ingredient in this product
- to treat contact lens related irritation

When using this product

- do not touch tip of container to any surface to avoid contamination
- remove contact lenses before use
- wait at least 10 minutes before reinserting contact lenses after use
- (b) (4)

Stop use and ask a doctor if you experience (b) (4):

- eye pain
- changes in vision
- increased redness of the eye
- itching worsens or lasts for more than 72 hours

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Directions

- **Adults and children 2 years of age and older**. Put 1 drop in the affected eye(s) once daily, (b) (4) (b) (4).
- **Children under 2 years of age**. Consult a doctor.

SIDE PANEL (folded around container or box):

Drug Facts (continued)

Other information

- only for use in the eye
- store between 2°-25°C (36°-77°F)

(b) (4)

Questions?

In the U.S., call 1-800-757-9195 or email alcon.medinfo@alcon.com

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

STEVEN F OSBORNE
06/17/2020 07:57:53 AM
clinical review sNDA 206276 Pazeo Rx-to-OTC switch

FRANCIS E BECKER
06/17/2020 08:26:41 AM

Social Science Discussion: NDA 206276

Background

Social science has been asked to weigh in on the applicability of potential consumer studies in support of a regulatory decision on Pataday Extra Strength olopatadine 0.7% (NDA 206276). There were no consumer behavior studies submitted by the Applicant for this NDA other than a label discernment/targeted label comprehension study, which will be discussed below. The overarching ONPD clinical concern is that consumers may misuse Pataday Extra Strength and - unlike a typical Rx to OTC switch NDA reviewed by ONPD - there are no published studies on safety in dosing in excess of .7%, once a day.

General Role of Consumer Behavior Studies, and their Caveats

Before addressing the particulars of this NDA, a brief overview of the role of consumer behavior studies is helpful. Each Rx-to-OTC switch NDA presents its own set of unique issues. However, the approved Rx products have already been demonstrated to be safe and effective under controlled trials and subsequently prescribed under the watch of a healthcare professional. The issue is - within the context of the nonprescription environment, without the guardrails of healthcare professional involvement- how consumers will self-select and use the drug. The consumer behavior studies can offer valuable insights and data in this regard. These data in turn are factored into the benefit risk assessment that clinicians make when determining whether to recommend the drug.

However, it is important to keep in mind that label comprehension and (some) self-selection studies focus on assessment of cognitive understanding when consumers are asked to focus on a label. They cannot address what might happen if a consumer doesn't read the label prior to self-medicating. They also cannot address what might happen, even if the user has read the label correctly, if subsequently the product of concern is inadvertently mistaken for another product in the medicine cabinet due to a similar packaging look and feel. Moreover, comprehension and stated intention, respectively, can at times be markedly different from actual behavior.

Consumer Misuse in General

Consumer misuse overall can take many forms. Often in OTC consumer behavior studies we observe that pregnant and breastfeeding women assert that despite the standard Drug Facts label statements, they don't need to ask their doctor before use of topical products since topical products aren't perceived to be absorbed through the skin. We might note that consumers do not correctly understand how to correctly use or maintain a dosage administration device, with the result that too much product or too high a concentration of active ingredient could possibly be administered. We see consumers say that they intentionally take more than the maximum labeled amount of an analgesic product in order to "stay ahead of the pain". And, as noted above, consumers can use products found in the medicine cabinet (perhaps originally intended for someone else) without carefully reading the label. Finally, misuse can occur when a consumer simply does not read the label carefully enough before taking the product.

The general assumption – which is reflected by actual use study findings - is that there will always be some consumer misuse of a product once it is out on the marketplace. There is virtually never 100% correct comprehension, self-selection, and/or actual use of a product. If that were the bar for approval, no product would ever be approved. The key is to get misuse to the lowest possible minimum through research-based labeling, packaging, or other means, and then determine whether that level of risk is acceptable given the stated benefits.

Consumer Misuse from Umbrella Branding and Pataday-Specific Concerns

In contrast to some of the above more "dramatic" examples of misuse, the concern about Pataday Extra Strength in significant part involves specific nuances related in part to "umbrella branding" issues. Umbrella branding involves selling some or many related products under a single overall brand name and/or distinctive packaging look and feel. It can leverage a huge brand equity in support of each product while increasing shelf presence. It can also create a potential for misuse in that under the brand umbrella, different products have different indications, ingredients, dosing strengths, or dosing regimens that may go unnoticed by consumers who focus on the similarities of packaging visuals.

Although Pataday is not widely recognized as a brand name, some issue related to umbrella branding still apply. If Pataday 0.7% is approved in this review cycle, there would be three products with a similar packaging look and feel that arrived on the drugstore shelf approximately within six months to a year of each other. Two of the three are once a day; one of the three is extra strength; one of the three has a redness indication.

However, it's important to note that while potential misuse is compounded by the umbrella branding – it exists without it. That is why it is important to think through the path of potential solutions to assess whether they can address the problem(s) at hand.

To begin, with, the underlying assumption in this discussion is that potential misuse around Pataday Extra Strength could broadly fall into three different buckets:

1) Consumers who don't see/understand the labeling of *not more than* once a day, even if they have only the once a day extra strength product on hand and aren't confusing it with another Pataday product.

2) Consumers who correctly discern that the 0.1% alone has the indication for redness but deliberately decide to use that product along with Pataday Extra Strength, because they don't understand that the 0.7% should not be taken with another olopatadine product; there is nothing currently on the labeling that addresses that.

3) Consumers who have two or three of the products in the medicine cabinet (perhaps they previously purchased Pataday 0.1% but now that the 0.7% is available they want to use that), but they or someone else in the family inadvertently confuses them at the time of administration and mistakenly takes the 0.7% twice in a day.

Pataday Label Discernment and Targeted Label Comprehension Study

When FDA voices concerns about label confusion regarding similarly branded products which nonetheless may have different dosing regimens or active ingredients, thus presenting the potential for safety or efficacy issues, label discernment studies are sometimes submitted by a sponsor. Label discernment studies (LDS) appear to be the proprietary work of – and conducted by – only one of the consumer behavior study CROs; FDA has not authored a guidance to industry on LDS. Generally, consumers are placed in a simulated store environment with the products arrayed on a shelf, and they are asked a series of open-ended questions regarding differences and similarities between/among the products. Although in the past this reviewer has seen LDS of questionable methodology, over time FDA expectations for these studies appear to have been recognized to a degree. However, one issue that I still have with the LDS component of the study is that the data tables do not differentiate between the "top of mind" differentiating factors and all subsequently mentioned differentiating factors, which were elicited as the result of probes. This could have potentially shed further light on how quickly differences and similarities were recognized.

Study Background

In the Rx-to-OTC switch NDA, the Applicant originally submitted a "pre-test." Because pre-tests are not intended to be final studies for review, ONPD requested that the Applicant field a pivotal study and submit the report during the review cycle. The pivotal study focused on the three product names and packaging at the time of NDA submission: (b) (4) olopatadine 0.7% (b) (4) antihistamine – once a day dosing; (b) (4) olopatadine 0.2% (b) (4) antihistamine – once a day dosing; and (b) (4) olopatadine 0.1% (b) (4) antihistamine and redness reliever – twice a day dosing. However, after the study had begun and during the NDA review, DMEPA proposed that the names be revised to Pataday Once Daily Relief Extra Strength, Pataday Once Daily Relief, and Pataday Twice Daily Relief respectively, and ONPD and the Applicant agreed. This development, while undoubtedly improving clarity and therefore being overall a positive step, inadvertently negated a good deal of the potential usefulness of the study as the new PDPs were not the focus of the already-started research; therefore, the primary objective of ascertaining recognized PDP dosing frequency differences among the three products (see below) turned out to be no longer applicable. However, FDA advised that the sponsor continue with the fielding of the LDS as we anticipated that there still might be useful qualitative insights from the data that could speak to FDA's continuing concerns about potential consumer misuse due to consumer confusion. For this discussion paper, due to the above factors, I have read the 684-page study report (including data tables) but have not engaged an FDA statistician to confirm these data from the datasets, nor have I looked at the electronic datasets myself to confirm verbatims or run any independent analyses of the data. Therefore, I am conveying Applicant-reported results.

Objectives

The stated primary objective of this study was the percentage of participants who had a correct response for dosing discernment among the three products (defined as dosing frequency or hours of

relief) based on the descriptors on the Principal Display Panel (PDP). An a priori success threshold was established at 85% (lower bound) The first stated secondary objective was discernment of the indications (eye itch for Pataday 0.2% and 0.7% vs eye itch plus redness relief for Pataday 0.1%). The above primary objective and secondary objectives were assessed in the first part of the study – the label discernment.

The second stated secondary objective was comprehension of dosing instructions. This objective was assessed through a follow-on targeted label comprehension component that immediately followed the label discernment component. As comprehension of dosing instructions was a secondary objective, there were no a priori thresholds.

Methodology:

The study population consisted of a general population of 404 participants, ages 15 and older, which included subgroups for limited literacy (n=117), parents/caregivers of children ages 2-14 (n=103), adolescents ages 15-17 (n=67), and current users of OTC allergy eye drops (n=166). The study was conducted at eight market research sites around the United States. Qualified participants first viewed the packages of the three products on a store shelf; they were told to pick up and turn over the packages however they wished. They were also told that they could refer back to the products at any time during the study. First, there were open-ended label discernment questions about what differences and similarities they identified among the labeling. Next, participants were asked specifically to look at all sides of the packaging, which included the DFL. There were then two targeted label comprehension questions for each product – one asking about number of drops per day, and one asking about the dosing frequency.

Sponsor-Reported Relevant Results:

Comprehension of dosing frequency of (b) (4) product (label comprehension component):

- As Table 2 depicts, there was an excellent understanding of "once a day" for (b) (4) (olopatadine 0.7%) product (397/404, or 98.3%).

- However, Table 2 shows that only 94/404, or 23%, of study participants proactively stated that the products *should not be used more than* once a day. Looking at subgroups, this concept was more likely to be voiced by adults (vs adolescents), and by non-parents/caregivers (vs parents/caregivers). That doesn't mean that this concept wasn't understood by the others; people often express their ideas in shorthand. It is certainly possible that some or many others understood the concept but simply didn't voice it that way. However, we don't know one way or another what the reality of that comprehension was. And there is a difference between not needing to use a product any more than once a day for efficacy, and it being risky to use more than once a day.

  The comprehension of this "do not use more than" aspect does not appear to have been adequately assessed, either in question wording or in reporting of results. Although the

Applicant states that it was, (Table 1, from the study report) this assertion isn't supported by Table 2, in which responses of "once a day" were assessed as correct as those responses of "not more than once a day".

Indication (label discernment component):

- In the label discernment component of the study (Table 3), 310/404 or 76.7% mentioned "redness" as a differentiating factor for the 0.1%.

Packaging Look and Feel (label discernment component):

- In the label discernment component of the study, 206/404, 50.7% (Table 3) stated the packages (graphics, colors, etc.) were different in appearance, and 176/404, 43.5% (Table 4) stated they were similar.

Implications of Study Findings: Potential Misuse and Potential Solutions around Pataday 0.7%

1. Potential Misuse: Consumers who don't see/understand the labeling of *not more than* once a day, even if they just have the once a day extra strength product on hand and aren't confusing it with another Pataday product.

   Addressed by current LDS/LCS?: The targeted LCS did not adequately address this issue.

   Potential Consumer Behavior Study Path Forward: Improve labeling to highlight further "not more than once a day" and conduct another targeted LCS with relevant scenarios. However, even a very strong comprehension result from such a study doesn't negate the possibility that consumers won't read the label.

2. Potential Misuse: Consumers who correctly discern that the 0.1% alone has the indication for redness and deliberately decide to use that product along with Pataday Extra Strength, because they don't understand that it should not be taken with another olopatadine product.

   Addressed by current LDS/LCS?: The LDS showed that most consumers do see that only one of the products has a redness indication – theoretically providing more evidence for this possibility.

   Potential Consumer Behavior Study Path Forward: Improve labeling, through preliminary iterative testing, to address that it should not be taken with another olopatadine product. Note: this will be challenging because a) previous research shows that many consumers do not understand ingredients and b) the concept of "should not be taken with" can mean different things to different people (some may interpret, for instance, as referring to simply not at the exact same time, but it would be ok to take 30 minutes apart). Then assess in a targeted LCS with relevant scenarios. However, as noted above, even a very strong comprehension result from such a study doesn't negate the possibility that consumers won't read a label.

To address this, the Sponsor could conduct a follow-on targeted self-selection study which could be a bit more realistic. In such a study, allergy sufferers with redness in their eyes could be presented with the three products and asked to pick what they would purchase, without specifically directing them to read the labels. That would provide important insights into how these consumers would decide what if any combinations of products to use, including asking about whether they would think of using Pataday .1% along with Pataday Extra Strength, in the event that the latter product did not sufficiently relieve their redness. Although such findings would be conceptually useful and perhaps very helpful, FDA can consider whether asking the Applicant to conduct an additional (self-selection) study beyond targeted label comprehension is the best use of the Applicant's time and resources when this example of misuse might not involve more than 0.8-0.9% total olopatadine per day, and when a self-selection study would not address other examples of misuse with a potentially greater inherent risk.

3. Potential Misuse: Consumers who have two or three of the products in the medicine cabinet (perhaps they previously purchased Pataday 0.1% but now that the 0.7% is available they want to use that), and they or someone else in the family inadvertently confuses the products at the time of administration and mistakenly takes the 0.7% twice a day.

   Addressed by current LDS/LCS? The LDS showed that approximately 50% of consumers thought the products had a similar look and feel – theoretically providing more evidence for this possibility.

   Potential Consumer Behavior Study Path Forward: None. The Applicant would either have to change the look and feel of the 0.7% package to avoid confusion, or conduct a safety study.

Discussion

The lack of safety data is problematic because it means there is no objective information by which to weigh the impact of the above instances of misuse that will undoubtedly occur. Consumer behavior studies could provide research-based insights with which to minimize instances of misuse (such as in creating and assessing optimized labeling), as well as data to inform predictions of the likelihood of such instances under the circumstances of optimized labeling. However, as seen in potential misuse #3 above, there are no consumer behavior studies easily envisioned that could help to mitigate this occurrence. While it could be contended that this is always the case with umbrella branding, and yet we approve products that fall under this rubric, this situation appears to be different because theoretically here a one-time consumer mistake could have significant consequences. In the more typical umbrella branding situation, either a one-time mistake would not have significant consequences or alternatively we would have full safety information with which to weigh its impact.

We could ask the Applicant to conduct the consumer behavior studies outlined above, and if the resulting data merely underscores the above issues, at that point they would need to do a safety study. However, that is still problematic because if the resulting data implies less of a concern, we still know

that studies can't perfectly predict behavior, and in any case potential misuse #3 cannot be addressed by a study.

Another option could be to give the Applicant the choice of either changing the packaging design for Pataday 0.7%, and conducting targeted LCS and self-selection, or doing a safety study. If they opt for a safety study (which may be likely given the marketing strength of umbrella branding) and it turns out that there is no harm related to higher dosing, FDA could decide that there would be no need for further consumer studies. If there is some degree of harm, at that point the requisite studies could be conducted accordingly.

Yet another option could be to have the Applicant conduct an actual use study (AUS), where study participants take the products home and use as they ordinarily would. Actual use studies are the most time and resource intensive of the consumer behavior studies. While the findings would certainly be helpful, it would be very difficult for an AUS to sufficiently address the potential misuse scenario of a consumer having more than one Pataday product in the medicine cabinet, nor would it address the misuse scenario of purchasing and using Pataday 0.1% to relieve redness, along with use of Pataday 0.7%. A standard AUS focuses on one product only.

Ultimately, the role of consumer behavior studies is not to replace safety data, but to "partner' with it so that the medical officers have full context in making a benefit-risk approval decision.

Table 1: Label Comprehension - Depiction of Q8 as corresponding to objective of "once daily, [redacted]

Table 10.3-1 Secondary Analysis: Indication Discernment and Dosing Comprehension - % Correct (Total Population)

(Question #)	Secondary Objective	Total Study Population (N=404) n	%	(LB, UB)*
Discernment				
(Q.1/2)	**Discernment (Indication – Eye Itch vs. Eye Itch + Redness Relief)**	308	76.2	(71.78, 80.31)
Label Comprehension				
(Q.8)	[redacted] - Put 1 drop in the affected eye(s) **once daily,** [redacted]	395	97.8	(95.81, 98.98)
(Q.3)	[redacted] - **Put 1 drop in the affected eye(s)** once daily, [redacted]	387	95.8	(93.35, 97.53)
(Q.6)	**Twice Daily Relief** - Put 1 drop in the affected eye(s) **twice daily, every 6 to 8 hours. Do not use more than 2 drops per day**	386	95.5	(93.05, 97.34)
(Q.4)	[redacted] - Put 1 drop in the affected eye(s) **once daily,** [redacted]	383	94.8	(92.16, 96.75)
(Q.7)	[redacted] - **Put 1 drop in the affected eye(s)** once daily, [redacted]	378	93.6	(90.71, 95.75)
(Q.5)	**Twice Daily Relief - Put 1 drop in the affected eye(s) twice daily, every 6 to 8 hours.** Do not use more than 2 drops per day	345	85.4	(81.57, 88.69)

**Lower and upper two-sided 95% Exact confidence bounds.*
Source: Tabulated Data

Source: Page 33 of 41 of Study Report Synopsis

Table 2: Label Comprehension Study Component - Dosing Frequency

*Lucy's eye is itchy, and she is getting ready to use this product (HAND PARTICIPANT (b) (4)).
*She has never used it before.

Q8a. According to the packaging, how many times should Lucy use it today?

		LITERACY		PARENTS/ CAREGIVERS		TYPE		OTC USERS	
	TOTAL	NL	LL	YES	NO	ADULTS	ADOLESCENTS	YES	NO
		(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)
Base: Total Responding	404	287	117	103	234	337	67	166	238
Correct/Acceptable (Net)	397	285	112	101	229	330	67	163	234
	98.3	99.3b	95.7	98.1	97.9	97.9	100.0	98.2	98.3
Correct (Net)	397	285	112	101	229	330	67	163	234
	98.3	99.3b	95.7	98.1	97.9	97.9	100.0	98.2	98.3
(001) Once a day	112	81	31	27	65	92	20	51	61
	27.7	28.2	26.5	26.2	27.8	27.3	29.9	30.7	25.6
(002) One time	51	42	9	13	28	41	10	25	26
	12.6	14.6	7.7	12.6	12.0	12.2	14.9	15.1	10.9
(003) 1 drop in the affected eye(s) once daily, no more than once a day	94	66	28	25	60	85	9	33	61
	23.3	23.0	23.9	24.3	25.6	25.2f	13.4	19.9	25.6
(004) Once	137	94	43	36	73	109	28	53	84
	33.9	32.8	36.8	35.0	31.2	32.3	41.8	31.9	35.3
(801) One	3	2	1	-	3	3	-	1	2
	0.7	0.7	0.9	-	1.3	0.9	-	0.6	0.8
Incorrect (Net)	7	2	5	2	5	7	-	3	4
	1.7	0.7	4.3a	1.9	2.1	2.1	-	1.8	1.7
(005) Twice	4	-	4	2	2	4	-	1	3
	1.0	-	3.4a	1.9	0.9	1.2	-	0.6	1.3
(102) Ask a doctor	1	1	-	-	1	1	-	1	-
	0.2	0.3	-	-	0.4	0.3	-	0.6	-
(103) 3	1	-	1	-	1	1	-	-	1
	0.2	-	0.9	-	0.4	0.3	-	-	0.4
(802) One drop	1	1	-	-	1	1	-	1	-
	0.2	0.3	-	-	0.4	0.3	-	0.6	-
**total	404	287	117	103	234	337	67	166	238

Proportions/Means compared for statistically significant differences at the 95% level of confidence: - a/b - c/d - e/f - g/h
A lower case letter next to the percent indicates a value significantly greater than the value in the corresponding column.
**Minimum base for statistical testing is 30

Table 3: Label Discernment Component – Differences Among Product Packages

Q1a/Q2a. What, if anything, are the differences/similarities among these products?
Q1b/Q2b. Are there any other differences/similarities that you see?

		LITERACY		PARENTS/ CAREGIVERS		TYPE		OTC USERS	
	TOTAL	NL	LL	YES	NO	ADULTS	ADOLESCENTS	YES	NO
		(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)
Base: Total Responding	404	287	117	103	234	337	67	166	238
Differences (Net)	404	287	117	103	234	337	67	166	238
	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
(101) Dosing Frequency (b) (4)	366	264	102	92	210	302	64	149	217
(b) (4)	90.6	92.0	87.2	89.3	89.7	89.6	95.5	89.8	91.2
(102) Redness Relief (T)	310	224	86	78	176	254	56	120	190
	76.7	78.0	73.5	75.7	75.2	75.4	83.6	72.3	79.8
(103) 2.5 ml vs. 5 ml/ amount/bottle size/.085 oz vs. .17 oz	200	150	50	49	108	157	43	79	121
	49.5	52.3	42.7	47.6	46.2	46.6	64.2e	47.6	50.8
(104) Graphics (font, color, style, look, reading ease/ difficulty)	205	157	48	53	118	171	34	88	117
	50.7	54.7b	41.0	51.5	50.4	50.7	50.7	53.0	49.2
(105) Hydrochloride Solution (0.1%, 0.2%, 0.7%)/Strength of Ingredients	214	155	59	55	115	170	44	85	129
	53.0	54.0	50.4	53.4	49.1	50.4	65.7e	51.2	54.2
(106) Superior/Stronger Relief (W)	112	79	33	29	62	91	21	45	67
	27.7	27.5	28.2	28.2	26.5	27.0	31.3	27.1	28.2
(107) Indicates ages 2 and older/age restrictions	10	5	5	2	6	8	2	2	8
	2.5	1.7	4.3	1.9	2.6	2.4	3.0	1.2	3.4
(108) Relieves Common allergies	32	25	7	10	18	28	4	16	16
	7.9	8.7	6.0	9.7	7.7	8.3	6.0	9.6	6.7
(109) Has different ingredients/says antihistamine	31	25	6	9	19	28	3	15	16
	7.7	8.7	5.1	8.7	8.1	8.3	4.5	9.0	6.7
(110) Has more/less/ different information	11	10	1	1	7	8	3	4	7
	2.7	3.5	0.9	1.0	3.0	2.4	4.5	2.4	2.9
(111) Relieves itchy eyes/ eye itch relief/itch relief	16	10	6	8	7	15	1	8	8
	4.0	3.5	5.1	7.8	3.0	4.5	1.5	4.8	3.4
(112) Works with contacts	1	-	1	-	1	1	-	-	1
	0.2	-	0.9	-	0.4	0.3	-	-	0.4
(113) Relieves eye itch and allergies	1	-	1	-	1	1	-	1	-
	0.2	-	0.9	-	0.4	0.3	-	0.6	-

Proportions/Means compared for statistically significant differences at the 95% level of confidence: - a/b - c/d - e/f - g/h
A lower case letter next to the percent indicates a value significantly greater than the value in the corresponding column.
**Minimum base for statistical testing is 30

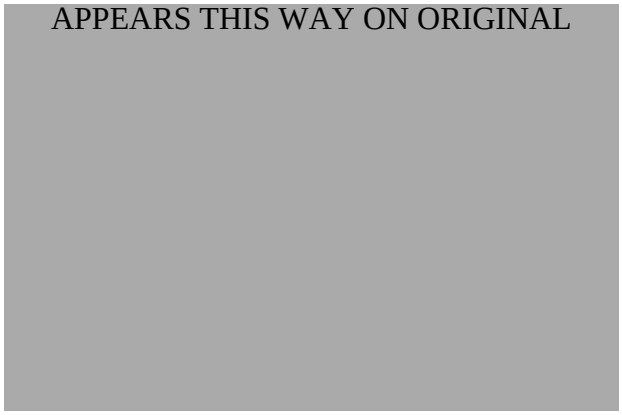
Table 4 – Label Discernment Component – Similarities Among Product Packages (Continued on following page)

	TOTAL	LITERACY		PARENTS/ CAREGIVERS		TYPE		OTC USERS	
		NL	LL	YES	NO	ADULTS	ADOLESCENTS	YES	NO
		(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)
Base: Total Responding	404	287	117	103	234	337	67	166	238
(114) Storage temps/phone #/ tamper evident info/inactive ingredients	3 0.7	3 1.0	- -	2 1.9d	- -	2 0.6	1 1.5	1 0.6	2 0.8
(115) The word eye	1 0.2	- -	1 0.9	- -	1 0.4	1 0.3	- -	- -	1 0.4
(116) Does not list allergens (S)	1 0.2	- -	1 0.9	- -	1 0.4	1 0.3	- -	- -	1 0.4
(117) More sterile (T)	2 0.5	- -	2 1.7a	- -	- -	- -	2 3.0e	- -	2 0.8
Similarities (Net)	404	287	117	103	234	337	67	166	238
	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
(201) Pataday	189 46.8	143 49.8	46 39.3	48 46.6	109 46.6	157 46.6	32 47.8	71 42.8	118 49.6
(202) Eye Itch / Eye Itch Relief	197 48.8	149 51.9b	48 41.0	50 48.5	113 48.3	163 48.4	34 50.7	82 49.4	115 48.3
(203) Works in Minutes	203 50.2	144 50.2	59 50.4	61 59.2d	110 47.0	171 50.7	32 47.8	74 44.6	129 54.2
(204) 30-day Supply	14 3.5	11 3.8	3 2.6	3 2.9	8 3.4	11 3.3	3 4.5	5 3.0	9 3.8
(205) For Ages 2 and older	10 2.5	8 2.8	2 1.7	3 2.9	5 2.1	8 2.4	2 3.0	4 2.4	6 2.5
(206) Alcon / Alcon Laboratories	114 28.2	90 31.4b	24 20.5	27 26.2	64 27.4	91 27.0	23 34.3	52 31.3	62 26.1
(207) Relief from common allergens: pet dander, pollen, grass, ragweed/ Treats the same issues/same purpose	259 64.1	187 65.2	72 61.5	70 68.0	139 59.4	209 62.0	50 74.6	106 63.9	153 64.3
(208) Tamper Evident information	2 0.5	1 0.3	1 0.9	- -	2 0.9	2 0.6	- -	1 0.6	1 0.4
(209) Trademark/Logo of Novartis	90 22.3	71 24.7	19 16.2	22 21.4	53 22.6	75 22.3	15 22.4	33 19.9	57 23.9

Table 4 cont'd – Label Discernment - Similarities

	TOTAL	LITERACY		PARENTS/ CAREGIVERS		TYPE		OTC USERS	
		NL	LL	YES	NO	ADULTS	ADOLESCENTS	YES	NO
		(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)
Base: Total Responding	404	287	117	103	234	337	67	166	238
(210) Available Without a Prescription/OTC	226 55.9	172 59.9b	54 46.2	62 60.2	124 53.0	186 55.2	40 59.7	98 59.0	128 53.8
(211) Sterile	50 12.4	42 14.6b	8 6.8	17 16.5d	21 9.0	38 11.3	12 17.9	15 9.0	35 14.7
(212) Has bottle actual size on box	1 0.2	1 0.3	- -	1 1.0	- -	1 0.3	- -	- -	1 0.4
(213) Olopatadine Hydrocloride Ophthalmic Solution/Olopatadine/ Hydrocloride Ophthalmic	38 9.4	26 9.1	12 10.3	8 7.8	19 8.1	27 8.0	11 16.4e	17 10.2	21 8.8
(214) Descriptions/writing/ instructions/directions	24 5.9	21 7.3	3 2.6	4 3.9	17 7.3	21 6.2	3 4.5	10 6.0	14 5.9
(215) Antihistamine	29 7.2	20 7.0	9 7.7	9 8.7	13 5.6	22 6.5	7 10.4	13 7.8	16 6.7
(216) They're drops	4 1.0	3 1.0	1 0.9	2 1.9	2 0.9	4 1.2	- -	3 1.8	1 0.4
(217) Layout/size of box/ graphics/colors	176 43.6	120 41.8	56 47.9	43 41.7	103 44.0	146 43.3	30 44.8	71 42.8	105 44.1
(218) Ingredients/solutions (ns)	95 23.5	74 25.8	21 17.9	24 23.3	56 23.9	80 23.7	15 22.4	37 22.3	58 24.4
(219) Volume ml/ounces amount is listed	11 2.7	8 2.8	3 2.6	5 4.9	5 2.1	10 3.0	1 1.5	7 4.2	4 1.7
(220) Provides dosage/length of relief	44 10.9	35 12.2	9 7.7	10 9.7	25 10.7	35 10.4	9 13.4	18 10.8	26 10.9
(221) Phone #	1 0.2	1 0.3	- -	- -	1 0.4	1 0.3	- -	- -	1 0.4
(222) Now available	3 0.7	3 1.0	- -	- -	3 1.3	3 0.9	- -	1 0.6	2 0.8
(223) Eyes/eye relief (ns) / itch (ns)/relief (ns)	20 5.0	11 3.8	9 7.7	2 1.9	16 6.8	18 5.3	2 3.0	8 4.8	12 5.0
(224) Label/drug facts	9 2.2	6 2.1	3 2.6	4 3.9	4 1.7	8 2.4	1 1.5	6 3.6	3 1.3

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page


APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BARBARA R COHEN
06/03/2020 04:00:47 PM

FRANCIS E BECKER
06/03/2020 04:16:50 PM

Ophthalmic Clinical Review
William M. Boyd, M.D.
NDA 20688/S-032 olopatadine hydrochloride ophthalmic solution, 0.1%
NDA 21545/S-022 olopatadine hydrochloride ophthalmic solution, 0.2%
NDA 206276/S-005 olopatadine hydrochloride ophthalmic solution, 0.7%

CLINICAL REVIEW

Application Type	Supplemental Efficacy Applications – OTC Switch
Application Number(s)	NDA 20688/S-032 PATANOL (olopatadine hydrochloride ophthalmic solution) 0.1% NDA 21545/S-022 PATADAY (olopatadine hydrochloride ophthalmic solution) 0.2% NDA 206276/S-005 PAZEO (olopatadine hydrochloride ophthalmic solution) 0.7%
Priority or Standard	Standard
Submit and Received Date(s)	4/15/2019 - NDA 20688/S-032 and NDA 21545/S-022 9/13/2019 - NDA 206276
Reviewer Name(s)	William M. Boyd, M.D. Division of Ophthalmology
Review Completion Date	1/8/2019
Applicant	Novartis Pharmaceuticals Corporation
Dosage Form(s)	Topical ophthalmic solutions
Recommendation on Regulatory Action	Recommend Approval for: • NDA 20688/S-032 olopatadine hydrochloride ophthalmic solution, 0.1%; • NDA 21545/S-022 olopatadine hydrochloride ophthalmic solution, 0.2%; and • NDA 206276/S-005 olopatadine hydrochloride ophthalmic solution, 0.7%

Table of Contents

Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Submitted are three supplemental new drug applications requesting an OTC switch for previously approved prescription products:

NDA 20688/S-032 PATANOL (olopatadine hydrochloride ophthalmic solution) 0.1%
NDA 21545/S-022 PATADAY (olopatadine hydrochloride ophthalmic solution) 0.2%
NDA 206276/S-005 PAZEO (olopatadine hydrochloride ophthalmic solution) 0.7%

The over the counter (OTC) products will have the same strength, dose, duration of use, dosage form, indication, and route of administration as the approved prescription (Rx) NDA product. There is no drug substance or drug product changes from the current NDAs.

Alcon, Inc. was a subsidiary of Novartis until April 9, 2019. These three supplements have been submitted by Alcon, acting as an Agent for Novartis. Novartis continues to own the applications.

Alcon has proposed new names for the products:

Olopatadine ophthalmic solution, 0.1%	Pataday Twice daily relief
Olopatadine ophthalmic solution, 0.2%	Pataday Once daily relief
Olopatadine ophthalmic solution, 0.7%	Pataday Once daily relief extra strength

Comparison of Formulations

Component	Pataday Twice Daily Relief	Pataday Once Daily Relief	Pataday Once Daily Relief Extra Strength
Olopatadine Hydrochloride	0.111	0.222	0.776
Benzalkonium Chloride	0.01	0.01	0.015
Hydroxypropyl-gamma-cyclodextrin	-	-	1.5
Edetate disodium	-	0.01	-
Povidone K29/32	-	1.8	4.0
PEG-400	-	-	4.0
Hypromellose	-	-	0.4
Sodium chloride	0.6	0.55	-
Mannitol	-	-	0.2
Boric Acid	-	-	0.3
Dibasic sodium phosphate, anhydrous	0.5	0.5	-
Sodium hydroxide	qs to pH 7.0	qs to pH 7.0	qs to pH 7.2
Hydrochloric acid	qs to pH 7.0	qs to pH 7.0	qs to pH 7.2
Purified water	qs to 100%	qs to 100%	qs to 100%

1.2. Conclusions on the Substantial Evidence of Effectiveness

NDA 20688 contains adequate and well controlled studies which support the safety and efficacy of olopatadine hydrochloride ophthalmic solution, 0.1% for the treatment of redness and itching when administered two times per day.

NDA 21545 contains adequate and well controlled studies which support the safety and efficacy of olopatadine hydrochloride ophthalmic solution, 0.2% for the treatment of itching when administered once or twice a day and for the treatment of itching and redness when administered twice a day.

NDA 206276 contains adequate and well controlled studies which support the safety and efficacy of olopatadine hydrochloride ophthalmic solution, 0.7% for the treatment of itching when administered once or twice a day and for the treatment of itching and redness when administered twice a day.

Table 1: Patanol Clinical Studies Summary

Parameters	C-94-10 (Pivotal #1)	C-94-58 (Pivotal #2)	C-94-39 (Pivotal#3)
Study Design	Randomized, double-masked, placebo-controlled, parallel-group study	Randomized, triple-masked, single center, crossover	Triple-masked, Placebo control
Objective	To compare safety and efficacy, onset and duration-of-action, and to determine the optimal concentration of AL04943A Ophthalmic Solution (0.01%, 0.05%, 0.10% and 0.15%) versus placebo in the treatment of allergen-mediated conjunctivitis using the provocation challenge test	To compare the efficacy of 0.05% and 0.10% AL04943A Ophthalmic Solution versus placebo in the treatment of allergen-mediated -conjunctivitis using the provocation challenge test and to demonstrate the onset-of-action and duration-of-action.	To compare the efficacy of 0.05% and 0.10% Olapatadine Ophthalmic Solution versus placebo in treatment of allergen-medicated conjunctivitis using the provocation challenge test and to demonstrate the onset of action and duration of action
Randomization	Contralateral Eye	Contralateral Eye	Contralateral Eye
Subjects	Normal, healthy male or female volunteers currently not using topical or systemic medications, with history Of symptoms of a clinical active allergic conjunctivitis, who had a positive allergen diagnostic test and a successful baseline challenge	Normal, healthy male and female volunteers, currently not using topical or systemic medications, with a history of symptoms of a clinically active allergic conjunctivitis, who had a positive allergen diagnostic test and a successful baseline challenge	Normal, healthy male and female volunteers, currently not using topical or systemic medications, with a history of symptoms of a clinically active allergic conjunctivitis, who had a positive allergen diagnostic test and a successful baseline challenge
Treatment Groups	AL04943A 0.15%=24 AL04943A 0.10% = 25 AL04943A 0.05%= 24 AL04943A 0.01% = 25 Placebo:98	AL04943A 0.05%=30 AL04943A 0.10%= 30 Placebo= 60	AL04943A 0.05%=60 AL04943A 0.10%= 60 Placebo=120
Study Visits	1=Screening 2=Confirmatory CAC 3=Onset-of-action (27 min before CAC) 4=Duration-of-action (8 hrs before CAC) 5=Duration-of-action (6 hrs before CAC)	1=Screening 2=Confirmatory CAC 3=Onset-of-action (8 hours before CAC) 4=Duration-of-action (27 mins before CAC)	1=Screening 2=Confirmatory CAC 3=Duration-of-action (27 minutes before CAC) 4=Onset-of-action (8 hours before CAC)
Dosing Regimen	1 drop at Visits 3, Visit 4 and Visit 5	1 drop at Visits 3 and Visit 4	1 drop Visit 3 and Visit 4
Post-CAC Assessment Time-points	3, 10, 20 minutes -- all parameters	3, 10, 20 minutes -- all parameters	3, 10, 20 minutes -- all parameters
Primary Efficacy	Itching and sum of scores for regional redness	Itching and sum of scores for regional redness	Itching and sum of scores for regional redness

Source: NDA 20688/S-032 Module 2.5

Table 1: Pataday Clinical Studies Summary

#	Protocol	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing Duration	Total # Subjects Exposed to Active Drug
1	C-00-36 (contralateral eye designed CAC study)	Prospective, contralateral eye randomized, placebo-controlled, double-masked	Subjects with history of allergic conjunctivitis and positive skin prick test	Pataday vs Placebo	1 drop 1 drop	Visit 3 (27 mins onset-of-action) Visit 4 (24hr duration-of-action) Visit 5 (16hr duration-of-action) (3 non-consecutive days)	45
2	C-01-18 (totally randomized by eye designed CAC study)	Prospective, randomized, placebo-controlled, double- masked	Subjects with history of allergic conjunctivitis and positive skin prick test	Pataday vs Placebo	1 drop 1 drop	Visit 3 (27 minutes onset-of-action) Visit 4 (16hr duration-of-action) (2 non-consecutive days)	24
3	C-01-100 (totally randomized by eye designed CAC study)	Prospective, randomized, placebo-controlled, double- masked	Subjects with history of allergic conjunctivitis and positive skin prick test	Pataday vs Placebo	1 drop 1 drop	Visit 3 (16hr duration-of-action) Visit 4 (onset-of-action) (2 non-consecutive days)	69
4	C-01-10 (environmental study)	Prospective, randomized, placebo-controlled, double- masked, parallel group	Patients > 10 years of age with history of allergic conjunctivitis, positive skin prick test, and positive CAC for fall (ragweed) allergens	Pataday vs Placebo	1 drop QD 1 drop QD	12 weeks	119
5	C-01-77 (6-week safety study)	Prospective, randomized, placebo-controlled, double- masked, parallel group	Subjects > 3 years of age with asymptomatic eyes	Pataday vs Placebo (2:1 randomization)	1 drop QD 1 drop QD	6 weeks	236
6	C-00-23 (PK/safety study)	Prospective, randomized, placebo-controlled, double-masked, two-way crossover	Subjects 18 to 75 years of age	5-mg orally dosed olopatadie Placebo	1 dose BID 1 dose BID	2.5 days (5 doses total)	(117)*
7	C-02-67 (environmental study)	Prospective, randomized, placebo-controlled, double-masked,	Patients > 10 years of age with history of allergic conjunctivitis, positive skin prick test, and positive CAC for spring (grass) allergens	Pataday vs Placebo	1 drop QD 1 drop QD	10 weeks	129
8	C-01-90 (environmental Study)	Prospective, randomized, placebo-controlled, double-masked,	Patients > 10 years of age with history of allergic conjunctivitis, positive skin prick test, and positive CAC for spring (grass) allergens	Pataday vs Placebo	1 drop QD 1 drop QD	12 weeks	119
						Total Subject Exposure to Pataday	**858**

*In this table, the subjects in C-00-23 are not included with the total number of subjects exposed to Pataday as these subjects were exposed to 5-mg, oral doses of olopatadine hydrochloride.

Source: NDA 21545/S-022 Module 2.5

Table 1: Summary of Completed Studies with Olopatadine HCl Solution, 0.77%*

Study Identifier/ Study Type	Study Design	Study Population	Treatment Groups	Number of Patients	Dosing Regimen	Dosing Duration
Safety and Efficacy Studies in Patients with Allergic Conjunctivitis						
C-10-126 Phase 3 Efficacy CAC	Randomized, double masked, parallel-group, active and vehicle controlled study	Seasonal or perennial allergic conjunctivitis patients 18 years of age or older	Olopatadine HCl, 0.77% Olopatadine, 0.2% Vehicle	66 68 68	1 drop per eye	3 non-consecutive doses over 3 weeks
C-12-053 Phase 3 Efficacy CAC	Randomized, double masked, parallel-group, active and vehicle controlled study	Seasonal or perennial allergic conjunctivitis patients 18 years of age or older	Olopatadine HCl, 0.77% Olopatadine HCl, 0.2% Olopatadine HCl, 0.1% Vehicle	98 99 99 49	1 drop per eye	2 non-consecutive doses over 2 weeks
Safety / Clinical Pharmacology Studies						
C-12-028 Phase 3 Safety	Randomized, double masked, parallel-group, vehicle controlled study	Healthy subjects 2 years of age or older with asymptomatic eyes	Olopatadine HCl, 0.77% Vehicle	330 169	1 drop per eye once daily	6 weeks
C-10-127 Phase 1 Safety and comfort	Randomized, double masked, crossover, active and vehicle controlled study	Healthy normal subjects 18 years of age or older	Olopatadine HCl, 0.77% Vehicle Zaditor	43	1 drop per eye	Single dose
C-11-036 Phase 1 Safety and PK	Randomized, double masked, parallel-group, vehicle controlled study	Healthy normal subjects, 18 to 65 years of age. At least 50% of subjects of Japanese ethnicity	Olopatadine HCl, 0.77% Vehicle	24 12	1 drop per eye once daily	7 days

* 4 clinical studies (C-10-126, C-11-036, C-12-028 and C-12-053) used the same, final formulation for Olopatadine HCl Solution, 0.77% (FID 119628) and it's Vehicle (FID 119717). A different initial formulation was used in the first clinical study C-10-127 for Olopatadine HCl Solution, 0.77% (FID 118622) and it's Vehicle (FID 118654). Two studies (C-10-126 and C-12-053) had PATADAY (Olopatadine, 0.2%) as an active comparator and used the same, marketed formulation for PATADAY (FID 101788).

Source: NDA 206276/S-005 Module 2.5

1.3. Benefit-Risk Assessment

Allergic conjunctivitis occurs when the conjunctiva becomes swollen or inflamed due to a reaction to various allergens: pollen, dander, mold, or other allergy-causing substances. Allergens cause release of histamine from mast cells, leading to hyperemia (redness) due to swelling of blood vessels and the eyes become itchy, red, puffy and teary. The mast cell's degranulation releases various preformed and newly formed mediators of the inflammatory cascade. Complications are very rare. Although allergic conjunctivitis may commonly reoccur, it rarely causes any visual loss.

There are a number of products, including H1 histamine receptor antagonists, mast cell stabilizers, an NSAID and a corticosteroid approved for the treatment of itching in the setting of conjunctivitis, or allergic conjunctivitis (redness and itching). There are a number of histamine receptor antagonists and combination vasoconstrictor/antihistamine receptor antagonists approved for the treatment of itching and/or redness without the requirement of a prescription.

As previously noted, adequate and well controlled trials for each original application demonstrated efficacy and safety for the original approvals.

There are no safety issues identified in this review that would preclude the safe administration of olopatadine 0.1%, 0.2% or 0.7% as an OTC product.

The Division of Ophthalmology recommends approval of these three supplemental applications for an OTC switch:

NDA 20688/S-032 olopatadine hydrochloride ophthalmic solution, 0.1%
NDA 21545/S-022 olopatadine hydrochloride ophthalmic solution, 0.2%
NDA 206276/S-005 olopatadine hydrochloride ophthalmic solution, 0.7%.

2. Review of Safety

2.1. Safety Review Approach

The Integrated Summary of Safety (ISS) was provided in the Rx to OTC switch sNDA for NDA 020688/S-032 and NDA 021545/S-022 submitted on April 15, 2019, and contained all available safety information for the 0.1%, 0.2% and 0.7% products. The same safety database was cross-referenced in the Rx to OTC switch for NDA206276/S-005 submitted on September 13, 2019. The ISS contains summaries and analyses of both clinical trial and post-marketing surveillance information of the currently marketed olopatadine products (including all adverse events).

This information was provided using the following sources of information:

- Sponsor's pharmacovigilance database
- FDA Adverse Event Reporting System (FAERS)
- World Health Organization (WHO) International Drug Monitoring Program
- National Poison Data System (NPDS) from American Association of Poison Control
- Centers (AAPCC), and
- Review of the medical literature relevant to the clinical safety of olopatadine; a table listing the reference, type of study, objectives, population, and principal results is provided.

The analysis population comprises subjects from clinical trials as well as post-marketing reports of patients experiencing AEs. The clinical trial portion of the analysis population includes healthy normal subjects and subjects with allergic conjunctivitis or rhinitis, ranging

in age from 3 years to >65 years of age. The post-marketing portion of the analysis population comprises real-world patients from the 129 countries where olopatadine is marketed.

A total of 98 completed clinical studies across all olopatadine formulations are included in the ISS. The majority of the completed clinical studies examined ophthalmic formulations of olopatadine (70 out of 98), and the majority of those were Phase 3 studies (42 out of 74). The following Table 1 contains a tabular summary of the completed clinical trials included in the ISS.

Table 1: Tabular Summary of Completed Clinical Trials

Formulation	Phase I	Phase II	Phase III	Phase IV*	
	N	n	n	n	Total
Eye drops, solution	12	6	42	10	**70**
Intranasal Spray	7	8	9	1	**25**
Oral solution	3	0	0	0	**3**
Total	**22**	**14**	**51**	**11**	**98**

*Includes non-IND study C-99-100

The 98 studies included in this ISS are: C-00-10, C-00-23, C-00-34, C-00-53, C-00-70, C-01-10, C-01-18, C-01-35, C-01-77, C-01-90, C-02-07, C-02-21, C-02-45, C-02-54, C- 02-65, C-02-67, C-03-11, C-03-49, C-03-52, C-04-20, C-04-45, C-04-70, C-05-33, C-05-64, C-07-01, C-08-32, C-09-039, C-09-050, C-10-126, C-11-013, C-12-028, C-93-75, C-93-83, C-94-37, C-94-52, C-94-61, C-94-75, C-94-100, C-95-12, C-95-73, C-96-46, C-96-79, C-96-82, C-98-04, C-98-40, C-99-100, EXC458-C001(C-12-10), M-12-047, SMA-10-13, C-06-34, C-07-02, C-09-034, C-09-044, C-10-002, C-10-127, C-11-036, C-12-053, C-93-79, C-94-10, C-94-102, C-94-39, C-94-58, C-94-65, C-94-80, C-95-18, C-96-15, C-96-76, C-96-81, C-97-59, C-98-37, C-98-44, C-99-94, RDG-10-278, 13-100-0009, C-00-16, C-00-33, C-00-36, C-00-58, C-01-05, C-01-100, C-01-32, C-01-41, C-01-83, C-01-92, C-02-10, C-02- 37, C-02-46, C-02-64, C-02-66, C-03-10, C-03-48, C-03-51, C-04-01, C-04-35, C-04-60, C-05-30, C- 05-61, C-05-69.

Source: NDA 20688/S-032 Module 5.3.5.3

2.2. Review of the Safety Database

2.2.1. Olopatadine Overall Exposure

Cumulative Subject Exposure in Clinical Trials: Approximately 10,814 patients received olopatadine treatment in marketing authorization holder sponsored investigational clinical trials cumulatively. Estimates of the cumulative patient exposure, based upon actual exposure data from completed interventional clinical trials is provided in the following Table 2. There

were no ongoing interventional trials during the reporting interval of the most recent PSUR, and no trials ongoing at the time of this submission.

Table 2: Cumulative subject exposure from completed clinical trials

Exposure (Number of subjects)	Olopatadine	Comparator(s)	Placebo
Completed studies*	10,814	1,958	6,888
Ongoing studies	0	0	0
Total	**10,814**	**1,958**	**6,888**

*Includes the total patients exposed in the completed clinical studies
C-00-10, C-00-23, C-00-34, C-00-53, C-00-70, C-01-10, C-01-18, C-01-35, C-01-77, C-01-90, C-02-07, C-02-21, C-02-45, C-02-54, C-02-65, C-02-67, C-03-11, C-03-49, C-03-52, C-04-20, C-04-45, C-04-70, C-05-33, C-05-64, C-07-01, C-08-32, C-09-039, C-09-050, C-10-126, C-11-013, C-12-028, C-93-75, C-93-83, C-94-37, C-94-52, C-94-61, C-94-75, C-94-100, C-95-12, C-95-73, C-96-46, C-96-79, C-96-82, C-98-04, C-98-40, C-99-100, EXC458-C001(C-12-10), M-12-047, SMA-10-13, C-06-34, C-07-02, C-09-034, C-09-044, C-10-002, C-10-127, C-11-036, C-12-053, C-93-79, C-94-10, C-94-102, C-94-39, C-94-58, C-94-65, C-94-80, C-95-18, C-96-15, C-96-76, C-96-81, C-97-59, C-98-37, C-98-44, C-99-94, RDG-10-278, 13-100-0009, C-00-16, C-00-33, C-00-36, C-00-58, C-01-05, C-01-100, C-01-32, C-01-41, C-01-83, C-01-92, C-02-10, C-02- 37, C-02-46, C-02-64, C-02-66, C-03-10, C-03-48, C-03-51, C-04-01, C-04-35, C-04-60, C-05-30, C-05-61, C-05-69.

Source: NDA 20688/S-032 Module 5.3.5.3

Post-Authorization (non-clinical trial) Exposure: An estimate of the patient exposure is calculated based on worldwide sales volume. One bottle of 5 mL eye drops contains sufficient volume to cover the patient's needs for one month when administered as indicated in the product information. Since the treatment with this product may be maintained for up to four months, the number of units used per patient could vary from one to four units / patient; and, therefore, it is difficult to give an exact number of patients exposed. Therefore, an estimation based on patient-months has been calculated.

No sales data since the first launch of the product are available. Cumulative sales could be obtained from 01 Jan 2000 onwards. Since then, the patient exposure is estimated to be approximately (b) (4) patient-months. Interval exposure [since data lock point (DLP) of previous PSUR] is estimated to be approximately (b) (4) patient-months. The estimated exposures are provided in Table 3, Table 4, and Table 5, below.

The patient exposure data are reflective of the last PSUR cutoff date. Patient exposure data through 31 Dec 2018 is estimated to be (b) (4) patient-months.

Table 3: Estimated Post-Marketing (non-clinical trial) Exposure

Formulation	Previous reporting interval 01 May 2012 to 30 Apr 2015		Current reporting interval 01 May 2015 to 30 Apr 2018		Cumulative Until 30 Apr 2018	
	Amount sold (units sold)	Estimated exposure (number of patient-months)	Amount sold (units sold)	Estimated exposure (number of patient months)	Amount sold (units sold)	Estimated exposure (number of patient months)
Eye drops, solution	(b) (4)					
Intranasal Spray						
Total						

This table includes cumulative and interval exposure data obtained from Novartis Pharma (Jan 2000 to Apr 2018), Sandoz (Oct 2006 to Apr 2018)

Source: NDA 20688/S-032 Module 5.3.5.3

Table 4: Interval Exposure from Marketing Experience

Formulation	EEA	USA and Canada	Japan	ROW
Eye drops, solution	(b) (4)			
Intranasal Spray				

EEA: European Economic Area; ROW: Rest of the World; USA: United States of America.

This table includes interval exposure data obtained from Novartis Pharma, and Sandoz (May 2015 to Apr 2018.) Source of data: Worldwide sales volume

Source: NDA 20688/S-032 Module 5.3.5.3

Table 5: Cumulative exposure from marketing experience

Formulation	EEA	USA and Canada	Japan	ROW
Eye drops, solution	(b) (4)			
Intranasal Spray				

EEA: European Economic Area; ROW: Rest of the World; USA: United States of America.

This table includes interval exposure data obtained from Novartis Pharma (Jan 2000 to Apr 2018), Sandoz (Oct 2006 to Apr 2018)

Source of data: Worldwide sales volume

Source: NDA 20688/S-032 Module 5.3.5.3

There were no non-interventional studies or registries designed to obtain information on special populations and no relevant information from other post-authorization sources during the reporting interval or cumulatively.

2.2.2. Relevant characteristics of the safety population:

The analysis population comprises subjects from clinical trials as well as post-marketing reports of patients experiencing AEs. The clinical trial portion of the analysis population includes healthy normal subjects and subjects with allergic conjunctivitis or rhinitis, ranging in age from 3 years to >65 years of age. The post-marketing portion of the analysis population comprises real-world patients from the 129 countries where olopatadine is marketed.

2.2.3. Adequacy of the safety database:

The safety database is adequate with respect to size, duration of exposure, duration of treatment, patient demographics, and disease characteristics.

2.3. Adequacy of Applicant's Clinical Safety Assessments

2.3.1. Issues Regarding Data Integrity and Submission Quality

The submissions were of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

2.3.2. Categorization of Adverse Events

The methods for summarizing clinical trial serious adverse events (SAE) were developed based on feedback from FDA provided during the November 2010 pre-submission meeting (PIND 107178) to discuss the proposed Rx-to-OTC switch of Patanol.

Clinical trial SAEs in Novartis' pharmacovigilance database were summarized by clinical trial product and further stratified by subject age. SAEs were accumulated across the 98 clinical trials. The data cut-off for clinical trial SAE review was December 31, 2018. At data cut-off there were no known Novartis-sponsored trials of olopatadine ongoing in any jurisdiction, globally. Thus, Novartis' pharmacovigilance database reflects all known clinical trial SAEs.

Clinical trial SAEs were grouped and analyzed according to product received in each trial.

2.4. Safety Results

2.4.1. Deaths

There were no safety issues identified that would preclude the safe administration of olopatadine ophthalmic solution 0.1%, 0.2% or 0.7% as an OTC product.

Summaries of Deaths from Post-Market Surveillance: A total of 6 deaths were reported in the post-marketing surveillance for olopatadine (including nasal preparations). Two of the deaths appear unrelated to olopatadine use (a homicide and a car accident). One of the deaths is associated with pre-existing complex medical conditions (microcephaly, seizures, breathing problems) and concomitant drug use (barbiturates). Two of the deaths were of unreported/unknown causes, do not contain enough information to assign causality, and are confounded by use of multiple concomitant medications. The remaining report of death (myocardial infarction) did not contain enough information to determine causality and is confounded by multiple concomitant medications.

- Case ALCN2015BR006903

This report refers to a female consumer of an unknown age. Medical history was not reported. Concomitant medication was not reported. The consumer received Pataday (olopatadine hydrochloride ophthalmic solution) 0.2% for the treatment of an unknown indication from an unknown start date at an unknown dose (ophthalmic). On an unknown date, the consumer developed eye redness (ocular hyperaemia). The therapy with Pataday was ongoing. The outcome of the event ocular hyperaemia was not reported. The reporter suspects her father may have altered the product with intent to do harm. He had attempted to kill his wife in the past by an unknown means and has a history of domestic violence (beatings).

New information received 02 Feb 2016: During affiliate follow up to try and obtain Pataday sample the reporter (daughter) stated that her mother (consumer) was killed (victim of homicide) by her father by unknown means on an unknown date. It is not known if an autopsy was performed.

- ALCN2015US003474

This report refers to a male consumer of unknown age. Medical history included nasal septum deviation and blood pressure increased. Concomitant medications included 26 vitamins such as Niacin, Krill Oil, Vitamin C, Garlic, Wine Vitamin, Flax Oil, Vitamin D, Baby Aspirin, Calcium, CoQ-10, Selenium, and Vitamin E. The consumer visited his physician on (b) (6) because he was due to have a deviated septum surgery on (b) (6). On (b) (6), the consumer had an elevated blood pressure (values not provided). The consumer's physician prescribed Patanase (olopatadine hydrochloride) nasal spray 0.6 % for the treatment of sinus drip and

headache on (b) (6). On (b) (6), the consumer developed vomiting (vomiting) and passed away due to a heart attack (myocardial infarction). An autopsy was not performed.

- ALCN2017US001520

This report refers to a 73-year-old female patient. Medical history was not reported. Concomitant medication was not reported. The patient received Pazeo (olopatadine hydrochloride ophthalmic solution) 0.7% for the treatment of an unknown indication from an unknown start date at an unknown dose (ophthalmic). On (b) (6), the patient was struck by a car and died (road traffic accident). The death was due to road traffic accident. It was unknown if an autopsy was performed. The causality of the event road traffic accident was not reported.

- PHEH2017US021651

This report refers to an elderly male patient. Medical history was not reported. Concomitant medication was not reported. The patient received Azopt (brinzolamide ophthalmic solution) for the treatment of an unknown indication from an unknown start date at an unknown dose (route: unknown). The patient received Pataday (olopatadine hydrochloride ophthalmic solution) 0.2% for the treatment of an unknown indication from an unknown start date at an unknown dose (route: unknown). The patient received Travatan Z (travoprost ophthalmic solution) for the treatment of an unknown indication from an unknown start date at an unknown dose (route: unknown). On an unknown date, the patient "deceased" (death) due to unknown cause. It was unknown if an autopsy was performed. The therapy status of Azopt, Pataday and Travatan Z was unknown at the time of death.

- PHEH2018US006977

This report refers to a 49- year-old female patient. Medical history was not reported. The patient was being treated with multiple concomitant medications. The patient received Ritalin (methylphenidate hydrochloride) for the treatment of narcolepsy from an unknown start date (years ago) at an unknown dose, QD (route: unknown). The patient also received Patanol (olopatadine hydrochloride ophthalmic solution) 0.1%, Singulair (montelukast sodium) and Grastek for the treatment of several allergies from an unknown start date (years ago) at an unknown dose (route: unknown). The patient also received Lyrica (pregabalin) and Dilaudid (hydromorphone hydrochloride) for the treatment of pain from an unknown start date (years ago) at an unknown dose, QD (route: unknown). The patient also received Xyrem (oxybate sodium) for the treatment of narcolepsy from an unknown start date (years ago) at an unknown dose (nightly) (route: unknown). The patient received Imitrex (sumatriptan) for the treatment of migraine from an unknown start date (years ago) at an unknown dose, as needed (route: unknown). The patient received Lidoderm (lidocaine) patch for the treatment of pain from an unknown start date (years ago) at an unknown dose, as needed (route: unknown). The patient also received Klor-Con (potassium chloride) tablet for the treatment of potassium low from an

unknown start date at a dose of 1 DF, BID (route: unknown).

On (b) (6), the patient died. The cause of death was not reported. It was unknown if an autopsy was performed. Per Novartis, the event death cannot be assessed properly due to lack of information regarding start date of suspect drugs, date of death, cause of death, autopsy report details, concomitant medication and any comorbid conditions which can contribute to the event.

- PHHY2015US080028

Case number PHHY2015US080028, is an initial combined spontaneous report received from physician (physician office) via a company representative on 25 Jun 2015, 30 Jun 2015, and form consumer (medical examiner) on 01 Jul 2015 and forwarded by (b) (4). (ADR 2015 01263) on 02 Jul 2015, with a follow up report received from physician (physician office) via a company representative on 27 Jul 2015 and forwarded by (b) (4) (ADR 2015 01263) on 04 Aug 2015. This case refers to 13 years old male patient. Historical conditions included microcephaly and a brain with microgyri and gliosis, complex patient, breathing problems, status post spinal fusion and supraglottoplasty, G tube, ventriculoperitoneal (VP) shunt, status post baclofen pump, pump implant on (b) (6) and catheter implant on 20 (b) (6). Current conditions included cerebral palsy and seizures. No concomitant medication was reported. The patient received Lioresal intrathecal (baclofen) 2000 mcg/mL (lot number was not known) for the treatment of intractable spasticity from an unknown date at a dose of 1472 mcg/day via an intrathecal pump. The patient also received baclofen (manufacture unknown) as per needed via G tube, Ibuprofen (manufacture unknown), Albuterol (salbutamol), diazepam (manufacture unknown), triamcinolone (manufacture unknown), azithromycin (manufacture unknown) for GI motility, Tylenol (paracetamol), Zyrtec (cetirizine hydrochloride), vitamin D (ergocalciferol), erythromycin (manufacture unknown), milk of magnesia (magnesium hydroxide), Patanase (olopatadine hydrochloride) nasal spray 0.6 %, phenobarbital (manufacture unknown) for seizures, Miralax (macrogol), Sudafed (pseudoephedrine hydrochloride), and Benadryl (camphor, diphenhydramine hydrochloride and zinc oxide), all for unknown indications, from an unknown date and dose.
The patient had a history of breathing problems and died because he stopped breathing in his sleep. The breathing problems were pre-existing to the use of the infusion system. It was reported that, the patient's co morbidities, including the seizures, were pre-existing to the infusion therapy.

Per Novartis, the patient's underlying condition of microcephaly and a brain with microgyri and gliosis, complex patient, breathing problems and their progression and use with the suspect drug phenobarbitone can explain the causality of the reported events versus the rest of the suspect drugs.

WHO Reports for Olopatadine (Including Deaths): A search of the WHO database from 1997 to March 2019 returned 3,427 cases in which olopatadine was reported. Of these cases, 1,255 (36.6%) originated from the Americas, and 2,172 (63.4%) originated from non-Americas locations. The following Table 20 provides a summary of the 1,643 cases where olopatadine was reported as the primary suspect. Among these cases, 171 were serious and 1,472 non-serious, and there were 9 deaths, one of which was reported as a road traffic accident.

Table 20: Summary of Cases with Olopatadine Reported as the Primary Suspect

Drug	Overall Total	Death	Serious (Incl death)	Non-serious
	N	N (%)	N (%)	N (%)
Olopatadine	173	2 (1.16)	29 (16.76)	144 (83.24)
Olopat	7	0 (0)	0 (0)	7 (100)
Patanol/Patanol S	336	0 (0)	18 (5.36)	318 (94.64)
Opatanol	54	0 (0)	8 (14.81)	46 (85.19)
Patanase	35	0 (0)	14 (40)	21 (60)
Pazeo	272	1 (.37)	10 (3.68)	262 (96.32)
Pataday	396	2 (.51)	22 (5.56)	374 (94.44)
Allelock	370	4 (1.08)	70 (18.92)	300 (81.08)

Source: NDA 20688/S-032 Module 5.3.5.3

FDA Adverse Events Reporting System (FAERS) (Including Deaths): A search of the FAERS database from the fourth quarter of 1997 to the fourth quarter of 2018 (the most recent release of quarterly data at the time of this report) was searched for cases in which olopatadine was reported. The database was searched in a non-case sensitive manner for the following terms: Olopatadine; Pataday; Patanol; Patanase; Pazeo; Opatanol; Olopat; Allelock.

The search returned 7,390 cases in which olopatadine was reported. Of these cases, 3,787 (51.2%) originated from the U.S., and 3,603 (48.8%) originated from non-Americas locations. Table 14 provides a summary of the 1,217 cases where olopatadine was reported as the primary suspect. Among these cases, 137 were serious and 1,080 non-serious, and there were 5 deaths, one of which was reported as a road traffic accident and another as a homicide.

Table 14: FAERS AE Report Summary with Olopatadine Reported as the Primary Suspect

Drug	Overall Total	Death	Serious (Incl death)	Non-serious
	N	N (%)	N (%)	N (%)
Olopatadine	87	0 (0)	18 (20.69)	69 (79.31)
Patanol/Patanol S	316	0 (0)	37 (11.71)	279 (88.29)
Opatanol	10	0 (10)	10 (100)	0 (0)
Patanase	51	2 (3.92)	26 (50.98)	25 (49.02)
Pazeo	348	1 (.29)	17 (4.89)	331 (95.11)
Pataday	405	2 (.49)	29 (7.16)	376 (92.84)
Allelock	0	0 (0)	0 (0)	0 (0)
Olopat	0	0 (0)	0 (0)	0 (0)

Source: NDA 20688/S-032 Module 5.3.5.3

Clinical Information Amendment dated 10/17/19: The applicant submitted a clinical information amendment to address Agency concerns that data submitted from the WHO database (of the 9/16/2019 submission, 175-page Data Tables Q4) for "Patanol" was not consistent with information the Sponsor provided in the accompanying 10-page narrative.

Table 1 below represents the most up to date information regarding the number of deaths for Olopatadine, Pazeo, Pataday, Patanol and Patanase, as a result of analysis of MedDRA preferred terms.

Table 1: Summary of Deaths from WHO and FAERS Databases

DEATHS		
Drug	**WHO**	**FAERS**
Olopatadine	2	0
Pazeo	1	1
Pataday	2	2
Patanol	6	0
Patanase	0	2

Source: NDA 20688/S-032 Amendment 10/17/19 Module 1.11.3

2.4.2. Serious Adverse Events

Serious Adverse Events in Clinical Trials: Clinical trial SAEs in Novartis' pharmacovigilance database were summarized by clinical trial product and further stratified by subject age. SAEs were accumulated across the 98 clinical trials. The data cut-off for clinical trial SAE review was December 31, 2018. At data cut-off there were no known Novartis-sponsored trials of olopatadine ongoing in any jurisdiction, globally. Thus, Novartis' pharmacovigilance database reflects all known clinical trial SAEs.

Table 7: Frequency and Incidence of Clinical Trial Serious Adverse Events

	Patanol	Pataday	Pazeo	Patanase	Other Olopatadine*	Active Control	Topical Ocular Placebo	Nasal Placebo	Oral Placebo
	n %	n %	n %	n %	n %	n %	n %	n %	n %
All SAEs	2844 11 0.39	2700 14 0.52	827 0 0.00	4312 44 1.02	612 0 0.00	1722 3 0.17	2702 8 0.30	3988 52 1.30	140 0 0.00
Subjects 3 years to <12 years	161 0 0.00	84 0 0.00	47 0 0.00	1163 1 0.09	0 0 0.00	114 1 0.88	75 0 0.00	937 1 0.11	0 0 0.00
Subjects 12 years to 65 years	2115 10 0.47	2330 12 0.52	756 0 0.00	3062 41 1.34	493 0 0.00	1418 2 0.14	2378 8 0.34	2977 44 1.48	33 0 0.00
Subjects >65 years	91 1 1.10	223 2 0.90	24 0 0.00	80 2 2.50	5 0 0.00	45 0 0.00	110 0 0.00	74 7 9.46	1 0 0.00

Patanol (Olopatadine 0.1%) includes generic olopatadine 0.1%
Pataday (Olopatadine 0.2%)
Pazeo (Olopatadine 0.7%)
Patanase (Olopatadine 0.6%)

Source: NDA 20688/S-032 Module 5.3.5.3

A total of 132 serious adverse events (SAEs) were reported in the combined olopatadine development programs. Of these, a total of 11 SAEs were reported for patients exposed to Patanol, 14 SAEs for patients exposed to Pataday, no SAEs reported among patients exposed to Pazeo, and 44 SAEs reported among patients exposed to Patanase. The remaining SAEs were reported in either the active comparator groups or placebo. All SAEs in the topical ocular administered olopatadine groups were single occurrences (except for 2 patients that reported nephrolithiasis in the Pataday group), with no particular clustering of any adverse event term. Among the Patanol and Pataday treatment groups, no SAE was reported at an incidence greater than 0.08%. No meaningful imbalances of reported SAEs were noted compared to either active

comparators or placebo.

Among all olopatadine studies, the majority of SAEs were reported in the 12-65-year age group. No SAEs were reported for either Patanol or Pataday among patients in the 3-12-year age group. In the >65-year age group, a total of 3 SAEs were reported for Patanol and Pataday. No patient exposed to olopatadine in any clinical study experienced an SAE assessed as related to study treatment.

No patient exposed to olopatadine in any clinical study experienced a fatal SAE. One fatal SAE was reported in a patient who received placebo treatment in clinical study C-05-69. The fatality resulted from an automobile accident, assessed as unrelated to study treatment.

Complete tabular listings for the frequency and incidence of serious adverse events by system organ class and preferred term for all subjects can be found in Appendix 1 of this review.

There were no safety issues identified that would preclude the safe administration of olopatadine ophthalmic solution 0.1%, 0.2% or 0.7% as an OTC product.

WHO Reports for Olopatadine: See Section 2.4.1 of this review.

There were no safety issues identified that would preclude the safe administration of Patanol, Pataday, or Pazeo as an OTC product.

FDA Adverse Events Reporting System (FAERS): See Section 2.4.1 of this review.

There were no safety issues identified that would preclude the safe administration of olopatadine ophthalmic solution 0.1%, 0.2% or 0.7% as an OTC product.

Significant Adverse Events: See Section 2.4.4 of this review.

2.4.3. Dropouts and/or Discontinuations in Clinical Trials Due to Adverse Effects

There were no safety issues identified that would preclude the safe administration of olopatadine ophthalmic solution 0.1%, 0.2% or 0.7% as an OTC product.

The methods for summarizing discontinuations from clinical trials were developed based on feedback from FDA provided during the November 2010 pre-submission meeting (PIND 107178) to discuss the proposed Rx-to-OTC switch of Patanol.

Subjects who discontinued from a clinical trial due to any AE (serious or non-serious) were included. Clinical trial discontinuations due to an AE were grouped and analyzed by product received in each trial. Table 8 below, summarizes the frequency and incidence of adverse events during olopatadine clinical trials that led to discontinuation, with respect to age group and product. Complete tabular listings for the frequency and incidence of adverse events in that resulted in discontinuation by system organ class and preferred term by age can be found in Appendix 2 of this review.

Table 8: Frequency and Incidence of Adverse Events that Resulted in Clinical Trial Discontinuation

	Patanol	Pataday	Pazeo	Patanase	Other Olopatadine*	Active Control	Topical Ocular Placebo	Nasal Placebo	Oral Placebo
	n %	n %	n %	n %	n %	n %	n %	n %	n %
All AE-related discontinuations	2844 59 2.07	2700 42 1.56	827 4 0.48	4312 142 3.29	612 28 4.58	1722 34 1.97	2702 25 0.93	3988 246 6.17	140 3 2.14
Subjects 3 years to <12 years	161 7 4.35	84 0 0.00	47 0 0.00	1163 21 1.81	0 0 0.00	114 3 2.63	75 0 0.00	937 105 11.21	0 0 0.00
Subjects 12 years to 65 years	2115 50 2.36	2330 40 1.72	756 4 0.53	3062 116 3.79	493 28 5.68	1418 26 1.83	2378 25 1.05	2977 138 4.64	33 3 9.09
Subjects >65 years	91 2 2.20	223 2 0.90	24 0 0.00	80 5 6.25	5 0 0.00	45 5 11.11	110 0 0.00	74 2 2.70	1 0 0.00

Patanol (Olopatadine 0.1%) includes generic olopatadine 0.1%
Pataday (Olopatadine 0.2%)
Pazeo (Olopatadine 0.7%)
Patanase (Olopatadine 0.6%)

Source: NDA 20688/S-032 Module 5.3.5.3

A total of 583 adverse events (AEs) that led to patient discontinuations were reported in the combined olopatadine development programs. Of these, a total of 59 AEs were reported for patients exposed to Patanol, 42 AEs for patients exposed to Pataday, 4 AEs reported among patients exposed to Pazeo, and 142 AEs reported among patients exposed to Patanase. A total of 28 AEs occurred in patients exposed to non-marketed concentrations of olopatadine. The remaining AEs that led to patient discontinuations were reported in either the active comparator groups or placebo.

The most common AEs that led to patient discontinuations in the Patanol and Pataday groups were:

- Conjunctivitis
  n=4 (0.14%); Patanol group

- Rhinitis
  - n=3 (0.1%); Patanol group
  - n=1 (0.04%); Pataday group
- Asthma
  - n=3 (0.1%); Patanol group
  - n=1 (0.04%); Pataday group

The most common AE that led to patient discontinuations in the Pazeo group was viral gastroenteritis (n=3; 0.36%).

2.4.4. Significant Adverse Events

"Blindness": Narratives for the three Serious Adverse Events cases with the Preferred Term "blindness" reported under Pataday, noted in the Argon database (as well as FAERS and WHO) were submitted in the Clinical Information Amendment of 9/16/2019.

The limited information available on the three cases with the preferred term "blindness" precludes a meaningful causality assessment. All three cases are in an elderly population which is susceptible to multiple reasons for decreased visual acuity risk including cataract, corneal disease, glaucoma, and macular degeneration. There were no safety issues identified that would preclude the safe administration of olopatadine ophthalmic solution 0.1%, 0.2% or 0.7% as an OTC product.

Narratives for the three SAEs for blindness reported for Pataday as they appear in the Safety database (Argus) are provided below:

- ALCN2016US008012

This report refers to an elderly female patient. Medical history was not reported. Concomitant medication was not reported. The patient received Pataday (olopatadine hydrochloride ophthalmic solution) 0.2% and Restasis (cyclosporine ophthalmic emulsion) for the treatment of an unknown indication from an unknown start date at an unknown dose and route. On an unknown date, the patient mentioned that, she was on chemo. She also said, her sight was impaired (visual impairment) and legally blind (blindness). Action taken with Pataday and Restasis was not reported. The outcome of the events blindness and visual impairment was unknown. The seriousness and causality of the events were not reported. Seriousness assessment of the events, blindness (medically significant) was upgraded based on the Novartis-Important Medical Event List. The patient reported that she was on chemotherapy and other limited information regarding therapy details and event details. Novartis concluded that the limited information available precludes meaningful causality assessment.

- PHEH2017US019370

This report refers to a male patient of an unknown age. Medical history was not reported. Concomitant medication was not reported. The patient received Pataday (olopatadine hydrochloride ophthalmic solution) 0.2% for the treatment of an unknown indication from an unknown start date at an unknown dose (ophthalmic). On an unknown date, the patient developed allergies (hypersensitivity) 12 months out of year and legally blind (blindness). Action taken with Pataday was unknown. The outcome of the events blindness and hypersensitivity was unknown. The seriousness and causality of the events were not reported. Seriousness assessment of the event blindness (medically significant) was upgraded based on the Novartis Important Medical Event List.

Per Novartis, the event blindness is not assessable with the suspect drug due to absence of information regarding age of the patient, underlying indication, the suspect drug start date, event onset date, clinical context, diagnostic tests, concurrent conditions, action taken, outcome and medical history of any visual impairment or eye disease.

- PHEH2017US025797

This report refers to a 90-year-old male patient. The patient's medical history was not reported. Concomitant medication was not reported. The patient received Pataday (olopatadine hydrochloride ophthalmic solution) 0.2% and Systane (polyethylene glycol 400, propylene glycol) for an unknown indication from an unknown start date at an unknown dose and frequency (route: unknown). The patient's wife stated that the patient was having problems with his eyes (eye disorder). On an unknown date, the reporter stated that he was legally blind (blindness). Therapy status with Pataday and Systane was unknown at the time of this report. The outcome of the events eye disorder and blindness was unknown. The seriousness of the events was not reported. Seriousness assessment of the event blindness (medically significant) was upgraded based on the Novartis-Important Medical Event List. The causality of the events was not reported.

In the absence of information regarding patient's medical history, concomitant medication, therapy details including indication for both suspect drugs, event onset date and laboratory data, Novartis concluded that the causality for the event blindness is not assessable. The case will be reassessed upon receipt of follow up information.

"Cerebrovascular Accident": Regarding the 3 cases of cerebrovascular accident reported for Patanol in the WHO database, case narratives were not available. Per the WHO database administrator, narrative information cannot be provided due to legal requirements on data protection (Regulation (EU) 2016/679, GDPR). Narratives for two Pataday cases of cerebrovascular accident (Internal Alcon Database and FAERs) were submitted in the Clinical Information Amendment of 9/16/2019.

The limited information available on the two cases with the preferred term “cerebrovascular accident” precludes a meaningful causality assessment with the suspect drug due to absence of information regarding age of the patient, underlying indication, the suspect drug start date, event onset date, clinical context, diagnostic tests, concurrent conditions, action taken, outcome and medical history. There are no safety issues identified that would preclude the safe administration of Patanol, Pataday, or Pazeo as an OTC product.

- PHEH2017US038115

This report refers to an elderly male patient. Medical history was not reported. Concomitant medication was not reported. The patient received Pataday (olopatadine hydrochloride ophthalmic solution) 0.2% for the treatment of an unknown indication from an unknown start date at an unknown dose and frequency (route: unknown). The patient received Simbrinza (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2% for the treatment of an unknown indication from an unknown start date at an unknown dose and frequency (route: unknown). On an unknown date, the patient's wife mentioned the patient had "stroke" (cerebrovascular accident). The therapy with Simbrinza and Pataday were unknown. The outcome of the event cerebrovascular accident was unknown. Seriousness of the event was not reported by the reporter. Seriousness assessment of the event cerebrovascular accident (medically significant) was upgraded based on Novartis Important Medical Events list. Causality of the event was reported as unknown by the reporter. The reporter asked that the health care professional not be contacted.

- (b) (6) (ALCN2012US003041)

This is a spontaneous case report involving PATADAY submitted by a pharmacy regarding a female patient (demographics unknown). This adverse event has been assessed as SERIOUS (MEDICALLY SIGNIFICANT/HOSPITALIZATION). Coded Preferred Terms: CEREBROVASCULAR ACCIDENT, HEADACHE, DIZZINESS, LETHARGY. No medical or drug history provided. Pharmacy reports that a female patient administered Pataday (olopatadine hydrochloride ophthalmic solution) 0.2% (dose, duration, indication not provided) to the right eye and a severe headache occurred. Pharmacy states the patient suffered dizziness, became lethargic, and displayed symptoms of a stroke. Pharmacy reported that emergency help arrived and verified a stroke had occurred, transported the patient to the hospital.

2.4.5. Common Adverse Events

There were no safety issues identified that would preclude the safe administration of olopatadine ophthalmic solution 0.1%, 0.2% or 0.7% as an OTC product. See Section 2.6 of this review regarding 120 day safety update.

Olopatadine 0.1%: The most common adverse clinical trial reaction noted in the approved labeling (revised April 2018) for NDA 20688 olopatadine hydrochloride ophthalmic solution, 0.1% is headache which was reported at an incidence of 7%. Additional adverse experiences reported in less than 5% of patients: asthenia, blurred vision, burning or stinging, cold syndrome, dry eye, foreign body sensation, hyperemia, hypersensitivity, keratitis, lid edema, nausea, pharyngitis, pruritus, rhinitis, sinusitis, and taste perversion. Some of these events were similar to the underlying disease being studied.

Olopatadine 0.2%: The most common adverse clinical trial reactions noted in the approved labeling (revised December 2010) for NDA 21545 olopatadine hydrochloride ophthalmic solution, 0.2% are symptoms similar to cold syndrome and pharyngitis that were reported at an incidence of approximately 10%. Additional adverse experiences reported in 5% or less of patients: *Ocular:* blurred vision, burning or stinging, conjunctivitis, dry eye, foreign body sensation, hyperemia, hypersensitivity, keratitis, lid edema, pain and ocular pruritus. *Non-ocular:* asthenia, back pain, flu syndrome, headache, increased cough, infection, nausea, rhinitis, sinusitis and taste perversion. Some of these events were similar to the underlying disease being studied.

Olopatadine 0.7%: The most common adverse clinical trial reactions noted in the approved labeling (revised January 2015) for NDA 206276 olopatadine hydrochloride ophthalmic solution, 0.7% were blurred vision, superficial punctate keratitis, dry eye, abnormal sensation in eye, and dysgeusia at 2-5%.

2.5. Safety Analyses by Demographic Subgroups

There were no safety issues identified that would preclude the safe administration of olopatadine ophthalmic solution 0.1%, 0.2% or 0.7% as an OTC product.

There were no demographic characteristics noted in the original NDAs for these olopatadine products that affected safety or efficacy. Labeling of the olopatadine products in the pediatric population was set at 3 years of age because the Pulmonary group in the Center for Drug Evaluation and Research determined that seasonal allergic conditions could not be reliably diagnosed prior to age 3. In between the approval of the 0.1% concentration and the 0.2% concentration, the Pulmonary group changed their determination and concluded that accurate diagnoses could be made down to 2 years of age. The labeling of the minimum age for use of these products reflects the Pulmonary group's determination at the time of approval of each product. There are no known safety issues of using olopatadine ophthalmologic solution at any age.

NDA 20688 olopatadine hydrochloride ophthalmic solution, 0.1% is currently labeled:

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

NDA 21545 olopatadine hydrochloride ophthalmic solution, 0.2% is currently labeled:

> 8.4 Pediatric Use
> Safety and effectiveness in pediatric patients below the age of 2 years have not been established.

NDA 206276 olopatadine hydrochloride ophthalmic solution, 0.7% is currently labeled:

> 8.4 Pediatric Use
> The safety and effectiveness of PAZEO have been established in pediatric patients two years of age and older. Use of PAZEO in these pediatric patients is supported by evidence from adequate and well-controlled studies of PAZEO in adults and an adequate and well controlled study evaluating the safety of PAZEO in pediatric and adult patients.

Adverse events (serious and non-serious) were reported to have occurred more frequently in individuals aged 12-65 years, commensurate with that being the largest category of consumers. However, age was not provided in approximately 42% of all reports, making it difficult to identify trends or draw definitive conclusions.

Table 13 summarizes the total number of serious adverse events, non-serious adverse events, and all adverse events (serious and non-serious combined), with respect to the age of the subject for olopatadine-containing products.

Table 13: Frequency of Post-Market Adverse Events for Olopatadine-Containing Products, Stratified by Subject Age

		Subject Age			
Dosage Strength	Total n	3y to <12y n	12y to 65y n	>65y n	Other* n
Patanol					
Serious adverse events	160	14	95	20	31
Non-serious adverse events	3912	265	1471	664	1512
Total adverse events (serious + non-serious)	4072	279	1566	684	1543
Pataday					
Serious adverse events	55	0	22	6	27
Non-serious adverse events	1995	89	513	396	997
Total adverse events (serious + non-serious)	2050	89	535	402	1024
Pazeo					
Serious adverse events	21	0	7	3	11
Non-serious adverse events	742	6	191	162	383
Total adverse events (serious + non-serious)	763	6	198	165	394
Patanase					
Serious adverse events	30	1	10	16	3
Non-serious adverse events	672	35	197	195	245
Total adverse events (serious + non-serious)	702	36	207	211	248

*Value missing or not determinable
Patanol (Olopatadine 0.1%) includes generic olopatadine 0.1%
Pataday (Olopatadine 0.2%)
Pazeo (Olopatadine 0.7%)
Patanase (Olopatadine 0.6%)
MedDRA Version 21.1

Source: NDA 20688/S-032 Module 5.3.5.3

2.6. Safety in the Post-market Setting

2.6.1. Safety Concerns Identified Through Post-market Experience

The data reveal no evidence indicative of a change in the number, or characteristics, of the AEs in association with the use of these products compared to the previously submitted data and does not differ from those presented in the NDA approval packages. There are no safety issues identified that would preclude the safe administration of olopatadine ophthalmic solution, 0.1%, 0.2% or 0.7% as an OTC product.

Post-market adverse event data has been submitted to fulfill the FDA request for a 120-day safety update. The products involved are well established in the market. In addition, there are no new data from either clinical or pre-clinical studies. The data lock point for the sNDA was 31Dec2018; therefore, the applicant is providing post-market adverse event data for the period 01Jan2019 to 31Oct2019. Alcon's internal database (ARGUS) as well as two external safety databases (FAERS and WHO) were queried for post-market (PM) adverse events related to three brands of olopatadine eye drop solutions—Patanol, Pataday, Pazeo—where these products were primary suspect, broken down by age and duration of use. A review of the literature for the period was also conducted.

Internal Argus Safety Database: A review of the Alcon's internal data for the olopatadine eye drop solutions olopatadine 0.1%, olopatadine 0.2%, and olopatadine 0.7% for the period of 01Jan2019 to 31Oct2019, partitioned by subject age and product duration of use, reveals no evidence indicative of a change in the number, or characteristics, of the adverse events in association with the use of these products compared to the previously submitted sNDA data and do not differ meaningfully from those events presented in the NDA approval packages. The total number of events reported are: 302 (olopatadine 0.1%; 36 serious), 139 (olopatadine 0.2; 7 serious), and 173 (olopatadine 0.7%; 5 serious). The AEs do not appear to be dose-related (i.e., no consistent trends across increasing dose) and are typically mild in nature (e.g., eye pruritus, eye irritation, ocular hyperemia, vision blurred, hypersensitivity) and likely due to the underlying condition being treated.

The 5 most frequently reported SAE SOCs for all three products are:

Order	Patanol (N=36)	Pataday (N=7)	Pazeo (N=5)
1	Eye disorders (N=16)	Eye disorders (N=2)	Eye disorders (N=2)
2	Respiratory, thoracic and mediastinal disorders (N=6)	Nervous system disorders (N=2)	Nervous system disorders (N=2)
3	Skin and subcutaneous tissue disorders (N=5)	General disorders and administration site conditions (N=1)	Immune system disorders (N=1)
4	General disorders and administration site conditions (N=2)	Renal and urinary disorders (N=1)	NA
5	Immune system disorders (N=2)	Skin and subcutaneous tissue disorders (N=1)	NA

Source data: Appendix 1, Tables 1-5, 21-23

Source: NDA 20688/S-032 Module 2.7.4

FAERS Analysis: FAERS Data are published on a quarterly basis; therefore, the time period covers 01Jan2019 –30Sep2019. The FAERS database was queried for AEs related to three brands of olopatadine eye drop solutions— Patanol [olopatadine 0.1%], Pataday [olopatadine 0.2%], and Pazeo [olopatadine 0.7%]—where these products were primary suspect.

The total number of cases reported are: 35 (olopatadine 0.1%), 65 (olopatadine 0.2%), and 73 (olopatadine 0.7%). The AEs do not appear to be dose-related (i.e., no consistent meaningful trends across increasing dose). The top SAE SOCs across the three brands are Eye Disorders/Immune System Disorders (tie), General Disorders and Administration Site Conditions, and Eye Disorders, for Patanol, Pataday, and Pazeo, respectively. The top non-

serious AE SOC is General Disorders and Administration Site Conditions for Patanol and Pataday, and Eye Disorders for Pazeo.

Two (2) deaths were reported for olopatadine 0.2% (as primary suspect) in the FAERS database. Both reports indicate that the Reporter Type was a Consumer and from the U.S.

1) Case ID 16107383 was initially reported on March 22, 2019 for a male of unknown age. Pataday is listed as the primary suspect medication, and Systane is listed as a secondary suspect medication. The Manufacturer Control Number PHHY2019US065258 matches the case that was also identified in Alcon's Internal Safety database Argus (see Section 2.4.1 of this review).

2) Case ID 16206785 was initially reported on April 17, 2019 for a female of 82 years of age. The Manufacturer Control Number PHEH2019US016520 matches the case that was also identified in Alcon's Internal Safety database (see Section 2.4.1 of this review).

WHO Analysis: The WHO database was queried for AEs related to three brands of olopatadine eye drop solutions— Patanol [olopatadine 0.1%], Pataday [olopatadine 0.2%], and Pazeo [olopatadine 0.7%]—where these products were primary suspect.

The total number of events reported are: 57 (olopatadine 0.1%), 123 (olopatadine 0.2%), and 152 (olopatadine 0.7%). The AEs do not appear to be dose-related (i.e., no consistent meaningful trends across increasing dose). The top SAE SOCs across the three brands are Eye Disorders/Immune System Disorders/General Disorders and Administration Site Conditions/Infections and Infestations/Skin and Subcutaneous Tissue Disorders (tie), General Disorders and Administration Site Conditions, and Eye Disorders, for Patanol, Pataday, and Pazeo, respectively. The top non-serious AE SOC is General Disorders and Administration Site Conditions for Patanol and Pataday, and Eye Disorders for Pazeo.

Literature Analysis: A literature search was conducted to update the search period to include relevant publications containing important, new safety information published from 15Mar2019 – 31Oct2019 for treatment-emergent adverse events (TEAEs) related to the olopatadine eye drop solutions Patanol [0.1%], Pataday [0.2%], and Pazeo [0.7%].

The literature articles provided were reviewed. There are no safety issues identified that would preclude the safe administration of olopatadine ophthalmic solution 0.1%, 0.2%, or 0.7% as an OTC product.

2.7. Integrated Assessment of Safety

There are no safety issues identified that would preclude the safe administration of olopatadine 0.1%, 0.2% or 0.7% as an OTC product.

From 01 Jan 2000 onwards, the patient exposure is estimated to be approximately (b) (4) patient-months. The analysis population comprises subjects from clinical trials as well as post-marketing reports of patients experiencing AEs. The clinical trial portion of the analysis population includes healthy normal subjects and subjects with allergic conjunctivitis or rhinitis, ranging in age from 3 years to >65 years of age. The post-marketing portion of the analysis population comprises real-world patients from the 129 countries where olopatadine is marketed.

In controlled clinical trials, the most common AEs that led to patient discontinuations in the olopatadine 0.1%, 0.2% and 0.7% groups were:

- Conjunctivitis
  - n=4 (0.14%); olopatadine 0.1% group
- Rhinitis
  - n=3 (0.1%); olopatadine 0.1% group
  - n=1 (0.04%); olopatadine 0.2% group
- Asthma
  - n=3 (0.1%); olopatadine 0.1% group
  - n=1 (0.04%); olopatadine 0.2% group
- Viral gastroenteritis
  - n=3 (0.36%); olopatadine 0.7% group

The safety and effectiveness of the highest concentration olopatadine ophthalmic solution (Pazeo) have been established in pediatric patients two years of age and older with evidence from adequate and well-controlled studies in adults and an adequate and well controlled study evaluating the safety of olopatadine ophthalmic solution, 0.1%, 0.2% and 0.7% in pediatric and adult patients.

3. Labeling Recommendations

3.1. Nonprescription Drug Labeling

The Division of Ophthalmology will continue to work with the Division of Nonprescription Drug Products on the nonprescription drug labeling for these three products.

Draft Artwork submitted 1/3/2020 for NDA 20688/S-032

Draft Artwork submitted 1/3/2020 for NDA 21545/S-022

(b) (4)

Draft Artwork submitted 11/25/2019 for NDA 206276/S-005

4. Appendices

4.1. Clinical Trial Serious Adverse Events

There were no safety issues identified that would preclude the safe administration of olopatadine ophthalmic solution 0.1%, 0.2% or 0.7% as an OTC product.

Frequency and Incidence of Clinical Trial Serious Adverse Events by System Organ Class and Preferred Term for All Subjects

	Patanol (N = 2844)	Pataday (N = 2700)	Pazeo (N = 827)	Patanase (N = 4312)	Other Olopatadine* (N = 612)	Active Control (N = 1722)	Topical Ocular Placebo (N = 2702)	Nasal Placebo (N = 3988)	Oral Placebo (N = 140)
	n %	n %	n %	n %	n %	n %	n %	n %	n %
All events	**11 0.39**	**14 0.52**	**0 0.00**	**44 1.02**	**0 0.00**	**3 0.17**	**8 0.30**	**52 1.30**	**0 0.00**
Cardiac disorders	**0 0.00**	**0 0.00**	**0 0.00**	**2 0.05**	**0 0.00**	**1 0.06**	**1 0.04**	**5 0.13**	**0 0.00**
Angina pectoris	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.06	1 0.04	0 0.00	0 0.00
Atrial flutter	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Atrioventricular block complete	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	2 0.05	0 0.00
Cardiac failure congestive	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Myocardial infarction	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Supraventricular tachycardia	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Tachycardia	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Congenital, familial and genetic disorders	**0 0.00**	**0 0.00**	**0 0.00**	**1 0.02**	**0 0.00**	**0 0.00**	**0 0.00**	**1 0.03**	**0 0.00**
Atrial septal defect	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Developmental hip dysplasia	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Endocrine disorders	**0 0.00**	**0 0.00**	**0 0.00**	**1 0.02**	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**
Thyroid mass	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Eye disorders	**0 0.00**	**2 0.07**	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**

	Patanol (N = 2844)	Pataday (N = 2700)	Pazeo (N = 827)	Patanase (N = 4312)	Other Olopatadine* (N = 612)	Active Control (N = 1722)	Topical Ocular Placebo (N = 2702)	Nasal Placebo (N = 3988)	Oral Placebo (N = 140)
	n %	n %	n %	n %	n %	n %	n %	n %	n %
Retinal tear	0 0.00	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Vitreous floaters	0 0.00	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Gastrointestinal disorders	**1 0.04**	**1 0.04**	**0 0.00**	**6 0.14**	**0 0.00**	**0 0.00**	**0 0.00**	**3 0.08**	**0 0.00**
Abdominal pain	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Abdominal strangulated hernia	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Faecaloma	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Food poisoning	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Gastritis	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Gastrointestinal disorder	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Gastrooesophageal reflux disease	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Hiatus hernia	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Impaired gastric emptying	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Rectal haemorrhage	0 0.00	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Small intestinal obstruction	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
General disorders and administration site conditions	**0 0.00**	**1 0.04**	**0 0.00**	**1 0.02**	**0 0.00**	**0 0.00**	**0 0.00**	**1 0.03**	**0 0.00**
Chest pain	0 0.00	1 0.04	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Hepatobiliary disorders	**0 0.00**	**0 0.00**	**0 0.00**	**2 0.05**	**0 0.00**	**0 0.00**	**0 0.00**	**1 0.03**	**0 0.00**
Biliary colic	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Cholecystitis	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00

	Patanol (N = 2844)	Pataday (N = 2700)	Pazeo (N = 827)	Patanase (N = 4312)	Other Olopatadine* (N = 612)	Active Control (N = 1722)	Topical Ocular Placebo (N = 2702)	Nasal Placebo (N = 3988)	Oral Placebo (N = 140)
	n %	n %	n %	n %	n %	n %	n %	n %	n %
Immune system disorders	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**	**1 0.04**	**0 0.00**	**0 0.00**
Allergy to animal	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.04	0 0.00	0 0.00
Infections and infestations	**3 0.11**	**1 0.04**	**0 0.00**	**6 0.14**	**0 0.00**	**2 0.12**	**3 0.11**	**7 0.18**	**0 0.00**
Appendicitis	1 0.04	1 0.04	0 0.00	2 0.05	0 0.00	1 0.06	1 0.04	4 0.10	0 0.00
Bronchitis	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Cellulitis	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Gastroenteritis	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Herpes zoster oticus	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Lymphangitis	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.04	0 0.00	0 0.00
Periorbital cellulitis	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Pneumonia	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	1 0.06	1 0.04	0 0.00	0 0.00
Sepsis	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Sialoadenitis	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Urinary tract infection	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Injury, poisoning and procedural complications	**0 0.00**	**2 0.07**	**0 0.00**	**4 0.09**	**0 0.00**	**0 0.00**	**0 0.00**	**11 0.28**	**0 0.00**
Accidental overdose	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Bladder injury	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Corneal abrasion	0 0.00	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Hip fracture	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00

	Patanol (N = 2844)	Pataday (N = 2700)	Pazeo (N = 827)	Patanase (N = 4312)	Other Olopatadine* (N = 612)	Active Control (N = 1722)	Topical Ocular Placebo (N = 2702)	Nasal Placebo (N = 3988)	Oral Placebo (N = 140)
	n %	n %	n %	n %	n %	n %	n %	n %	n %
Incisional hernia	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Injury	0 0.00	0 0.00	0 0.00	2 0.05	0 0.00	0 0.00	0 0.00	3 0.08	0 0.00
Jaw fracture	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Overdose	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Road traffic accident	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Upper limb fracture	0 0.00	1 0.04	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Wrist fracture	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Metabolism and nutrition disorders	**0 0.00**	**1 0.04**	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**
Diabetes mellitus	0 0.00	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Musculoskeletal and connective tissue disorders	**0 0.00**	**0 0.00**	**0 0.00**	**1 0.02**	**0 0.00**	**0 0.00**	**0 0.00**	**3 0.08**	**0 0.00**
Intervertebral disc protrusion	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Jaw disorder	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Osteoarthritis	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	2 0.05	0 0.00
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0 0.00**	**1 0.04**	**0 0.00**	**2 0.05**	**0 0.00**	**0 0.00**	**0 0.00**	**2 0.05**	**0 0.00**
Adenocarcinoma of the cervix	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Lung neoplasm malignant	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Pancreatic carcinoma	0 0.00	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00

	Patanol (N = 2844)	Pataday (N = 2700)	Pazeo (N = 827)	Patanase (N = 4312)	Other Olopatadine* (N = 612)	Active Control (N = 1722)	Topical Ocular Placebo (N = 2702)	Nasal Placebo (N = 3988)	Oral Placebo (N = 140)
	n %	n %	n %	n %	n %	n %	n %	n %	n %
Uterine leiomyoma	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Nervous system disorders	**2 0.07**	**0 0.00**	**0 0.00**	**1 0.02**	**0 0.00**	**0 0.00**	**0 0.00**	**5 0.13**	**0 0.00**
Cerebral haemorrhage	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Cervicobrachial syndrome	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Headache	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Loss of consciousness	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Nerve compression	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Seizure	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Syncope	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	2 0.05	0 0.00
Pregnancy, puerperium and perinatal conditions	**0 0.00**	**0 0.00**	**0 0.00**	**1 0.02**	**0 0.00**	**0 0.00**	**1 0.04**	**0 0.00**	**0 0.00**
Abortion spontaneous	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.04	0 0.00	0 0.00
Hyperemesis gravidarum	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Psychiatric disorders	**0 0.00**	**1 0.04**	**0 0.00**	**3 0.07**	**0 0.00**	**0 0.00**	**0 0.00**	**1 0.03**	**0 0.00**
Anxiety	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Depression	0 0.00	1 0.04	0 0.00	3 0.07	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Renal and urinary disorders	**0 0.00**	**2 0.07**	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**	**1 0.04**	**0 0.00**	**0 0.00**
Calculus urinary	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.04	0 0.00	0 0.00
Nephrolithiasis	0 0.00	2 0.07	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00

	Patanol (N = 2844)	Pataday (N = 2700)	Pazeo (N = 827)	Patanase (N = 4312)	Other Olopatadine* (N = 612)	Active Control (N = 1722)	Topical Ocular Placebo (N = 2702)	Nasal Placebo (N = 3988)	Oral Placebo (N = 140)
	n %	n %	n %	n %	n %	n %	n %	n %	n %
Reproductive system and breast disorders	**0 0.00**	**0 0.00**	**0 0.00**	**2 0.05**	**0 0.00**	**0 0.00**	**0 0.00**	**4 0.10**	**0 0.00**
Dysmenorrhoea	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Endometriosis	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Genital prolapse	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Menometrorrhagia	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Menstruation irregular	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Respiratory, thoracic and mediastinal disorders	**2 0.07**	**0 0.00**	**0 0.00**	**1 0.02**	**0 0.00**	**0 0.00**	**0 0.00**	**2 0.05**	**0 0.00**
Pleurisy	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Pneumothorax spontaneous	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	2 0.05	0 0.00
Pulmonary embolism	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Surgical and medical procedures	**3 0.11**	**2 0.07**	**0 0.00**	**7 0.16**	**0 0.00**	**0 0.00**	**1 0.04**	**6 0.15**	**0 0.00**
Alcohol detoxification	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Appendicectomy	0 0.00	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Arthrodesis	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Bladder repair	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Cardiac pacemaker insertion	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Chest tube insertion	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Cholecystectomy	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Cystostomy closure	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00

	Patanol (N = 2844)	Pataday (N = 2700)	Pazeo (N = 827)	Patanase (N = 4312)	Other Olopatadine* (N = 612)	Active Control (N = 1722)	Topical Ocular Placebo (N = 2702)	Nasal Placebo (N = 3988)	Oral Placebo (N = 140)
	n %	n %	n %	n %	n %	n %	n %	n %	n %
Drug detoxification	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Gastric bypass	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Hysterectomy	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Internal fixation of fracture	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Intervertebral disc operation	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.04	1 0.03	0 0.00
Knee arthroplasty	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Renal stone removal	0 0.00	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Spinal fusion surgery	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Thyroidectomy	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Vascular disorders	**0 0.00**	**0 0.00**	**0 0.00**	**3 0.07**	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**
Haemorrhage	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Peripheral embolism	0 0.00	0 0.00	0 0.00	2 0.05	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00

Patanol (Olopatadine 0.1%) includes generic Olopatadine 0.1%
Pataday (Olopatadine 0.2%)
Pazeo (Olopatadine 0.7%)
Patanase (Olopatadine 0.66%)

4.2. Clinical Trial Adverse Events that Resulted in Clinical Trial Discontinuation

There were no safety issues identified that would preclude the safe administration of olopatadine ophthalmic solution 0.1%, 0.2% or 0.7% as an OTC product.

Frequency and Incidence of Adverse Events that Resulted in Clinical Trial Discontinuation by System Organ Class and Preferred Term All Subjects

	Patanol (N = 2844)	Pataday (N = 2700)	Pazeo (N = 827)	Patanase (N = 4312)	Other Olopatadine* (N = 612)	Active Control (N = 1722)	Topical Ocular Placebo (N = 2702)	Nasal Placebo (N = 3988)	Oral Placebo (N = 140)
	n %	n %	n %	n %	n %	n %	n %	n %	n %
All events	**59 2.07**	**42 1.56**	**4 0.48**	**142 3.29**	**28 4.58**	**34 1.97**	**25 0.93**	**246 6.17**	**3 2.14**
Blood and lymphatic system disorders	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**	**1 0.04**	**1 0.03**	**0 0.00**
Anaemia	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.04	0 0.00	0 0.00
Lymphadenopathy	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Cardiac disorders	**0 0.00**	**2 0.07**	**0 0.00**	**2 0.05**	**3 0.49**	**0 0.00**	**0 0.00**	**2 0.05**	**1 0.71**
Atrioventricular block	0 0.00	0 0.00	0 0.00	0 0.00	1 0.16	0 0.00	0 0.00	0 0.00	0 0.00
Cardiac failure	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Myocardial infarction	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Palpitations	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Supraventricular tachycardia	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Tachycardia	0 0.00	2 0.07	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Ventricular tachycardia	0 0.00	0 0.00	0 0.00	0 0.00	2 0.33	0 0.00	0 0.00	0 0.00	1 0.71
Ear and labyrinth disorders	**0 0.00**	**1 0.04**	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**	**1 0.03**	**0 0.00**
Ear pain	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Middle ear effusion	0 0.00	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00

	Patanol (N = 2844)	Pataday (N = 2700)	Pazeo (N = 827)	Patanase (N = 4312)	Other Olopatadine* (N = 612)	Active Control (N = 1722)	Topical Ocular Placebo (N = 2702)	Nasal Placebo (N = 3988)	Oral Placebo (N = 140)
	n %	n %	n %	n %	n %	n %	n %	n %	n %
Eye disorders	**27 0.95**	**15 0.56**	**0 0.00**	**0 0.00**	**0 0.00**	**13 0.75**	**7 0.26**	**0 0.00**	**0 0.00**
Blepharitis	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Chalazion	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	1 0.06	0 0.00	0 0.00	0 0.00
Conjunctival follicles	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Conjunctival haemorrhage	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	2 0.07	0 0.00	0 0.00
Conjunctival hyperaemia	0 0.00	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Conjunctival oedema	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.06	0 0.00	0 0.00	0 0.00
Conjunctivitis allergic	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.04	0 0.00	0 0.00
Corneal epithelium defect	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Corneal erosion	2 0.07	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Dry eye	0 0.00	1 0.04	0 0.00	0 0.00	0 0.00	1 0.06	1 0.04	0 0.00	0 0.00
Erythema of eyelid	0 0.00	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Eye discharge	2 0.07	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Eye haemorrhage	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Eye irritation	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.06	0 0.00	0 0.00	0 0.00
Eye oedema	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Eye pain	3 0.11	1 0.04	0 0.00	0 0.00	0 0.00	1 0.06	0 0.00	0 0.00	0 0.00
Eye pruritus	2 0.07	2 0.07	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Eyelid oedema	0 0.00	2 0.07	0 0.00	0 0.00	0 0.00	0 0.00	1 0.04	0 0.00	0 0.00
Eyelids pruritus	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Foreign body sensation in eyes	2 0.07	0 0.00	0 0.00	0 0.00	0 0.00	1 0.06	1 0.04	0 0.00	0 0.00
Keratitis	2 0.07	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Lacrimation increased	0 0.00	1 0.04	0 0.00	0 0.00	0 0.00	2 0.12	0 0.00	0 0.00	0 0.00

	Patanol (N = 2844)	Pataday (N = 2700)	Pazeo (N = 827)	Patanase (N = 4312)	Other Olopatadine* (N = 612)	Active Control (N = 1722)	Topical Ocular Placebo (N = 2702)	Nasal Placebo (N = 3988)	Oral Placebo (N = 140)
	n %	n %	n %	n %	n %	n %	n %	n %	n %
Ocular discomfort	1 0.04	1 0.04	0 0.00	0 0.00	0 0.00	2 0.12	0 0.00	0 0.00	0 0.00
Ocular hyperaemia	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	2 0.12	0 0.00	0 0.00	0 0.00
Panophthalmitis	0 0.00	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Periorbital oedema	0 0.00	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Pigment dispersion syndrome	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Punctate keratitis	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Retinal tear	1 0.04	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Ulcerative keratitis	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.04	0 0.00	0 0.00
Vision blurred	0 0.00	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Visual impairment	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	1 0.06	0 0.00	0 0.00	0 0.00
Vitreous floaters	0 0.00	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Gastrointestinal disorders	**1 0.04**	**2 0.07**	**0 0.00**	**9 0.21**	**1 0.16**	**1 0.06**	**0 0.00**	**11 0.28**	**0 0.00**
Abdominal discomfort	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Abdominal pain	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Colitis ulcerative	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Constipation	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Diarrhoea	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Dry mouth	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	1 0.06	0 0.00	0 0.00	0 0.00
Dyspepsia	0 0.00	0 0.00	0 0.00	3 0.07	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Mouth ulceration	0 0.00	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Nausea	0 0.00	1 0.04	0 0.00	2 0.05	1 0.16	0 0.00	0 0.00	4 0.10	0 0.00
Oral pruritus	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00

	Patanol (N = 2844)	Pataday (N = 2700)	Pazeo (N = 827)	Patanase (N = 4312)	Other Olopatadine* (N = 612)	Active Control (N = 1722)	Topical Ocular Placebo (N = 2702)	Nasal Placebo (N = 3988)	Oral Placebo (N = 140)
	n %	n %	n %	n %	n %	n %	n %	n %	n %
Retching	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Vomiting	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	2 0.05	0 0.00
General disorders and administration site conditions	**1 0.04**	**0 0.00**	**0 0.00**	**3 0.07**	**2 0.33**	**1 0.06**	**2 0.07**	**8 0.20**	**0 0.00**
Asthenia	0 0.00	0 0.00	0 0.00	0 0.00	1 0.16	0 0.00	1 0.04	2 0.05	0 0.00
Chest pain	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Chills	0 0.00	0 0.00	0 0.00	0 0.00	1 0.16	0 0.00	0 0.00	0 0.00	0 0.00
Fatigue	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.06	1 0.04	0 0.00	0 0.00
Malaise	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Pain	0 0.00	0 0.00	0 0.00	2 0.05	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Pyrexia	1 0.04	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	3 0.08	0 0.00
Hepatobiliary disorders	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**	**1 0.71**
Hepatitis	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.71
Immune system disorders	**0 0.00**	**2 0.07**	**0 0.00**	**4 0.09**	**0 0.00**	**0 0.00**	**0 0.00**	**8 0.20**	**0 0.00**
Allergy to arthropod sting	0 0.00	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Hypersensitivity	0 0.00	1 0.04	0 0.00	3 0.07	0 0.00	0 0.00	0 0.00	4 0.10	0 0.00
Milk allergy	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Seasonal allergy	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	3 0.08	0 0.00
Infections and infestations	**15 0.53**	**6 0.22**	**4 0.48**	**40 0.93**	**6 0.98**	**10 0.58**	**7 0.26**	**89 2.23**	**0 0.00**

	Patanol (N = 2844)	Pataday (N = 2700)	Pazeo (N = 827)	Patanase (N = 4312)	Other Olopatadine* (N = 612)	Active Control (N = 1722)	Topical Ocular Placebo (N = 2702)	Nasal Placebo (N = 3988)	Oral Placebo (N = 140)
	n %	n %	n %	n %	n %	n %	n %	n %	n %
Appendicitis	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.06	0 0.00	0 0.00	0 0.00
Bronchitis	1 0.04	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	4 0.10	0 0.00
Cellulitis	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Conjunctivitis	4 0.14	0 0.00	0 0.00	1 0.02	0 0.00	1 0.06	0 0.00	1 0.03	0 0.00
Conjunctivitis bacterial	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Conjunctivitis viral	0 0.00	1 0.04	0 0.00	0 0.00	0 0.00	1 0.06	1 0.04	0 0.00	0 0.00
Ear infection	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.04	0 0.00	0 0.00
Gastroenteritis	0 0.00	1 0.04	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Gastroenteritis viral	0 0.00	0 0.00	3 0.36	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Hordeolum	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Hypersensitivity	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	1 0.06	0 0.00	0 0.00	0 0.00
Infection	0 0.00	0 0.00	0 0.00	1 0.02	2 0.33	1 0.06	1 0.04	10 0.25	0 0.00
Influenza	2 0.07	0 0.00	1 0.12	2 0.05	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Nasopharyngitis	2 0.07	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Otitis externa	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.06	0 0.00	0 0.00	0 0.00
Otitis media	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.06	2 0.07	8 0.20	0 0.00
Periorbital cellulitis	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Pharyngitis	0 0.00	1 0.04	0 0.00	3 0.07	2 0.33	0 0.00	0 0.00	9 0.23	0 0.00
Pharyngitis streptococcal	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	6 0.15	0 0.00
Pneumonia	0 0.00	0 0.00	0 0.00	2 0.05	0 0.00	1 0.06	0 0.00	1 0.03	0 0.00
Respiratory tract infection viral	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Rhinitis	3 0.11	1 0.04	0 0.00	6 0.14	1 0.16	0 0.00	1 0.04	11 0.28	0 0.00
Sepsis	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00

	Patanol (N = 2844)	Pataday (N = 2700)	Pazeo (N = 827)	Patanase (N = 4312)	Other Olopatadine* (N = 612)	Active Control (N = 1722)	Topical Ocular Placebo (N = 2702)	Nasal Placebo (N = 3988)	Oral Placebo (N = 140)
	n %	n %	n %	n %	n %	n %	n %	n %	n %
Sinusitis	1 0.04	1 0.04	0 0.00	15 0.35	1 0.16	1 0.06	1 0.04	27 0.68	0 0.00
Staphylococcal infection	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Upper respiratory tract infection	0 0.00	0 0.00	0 0.00	4 0.09	0 0.00	0 0.00	0 0.00	5 0.13	0 0.00
Urinary tract infection	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	2 0.05	0 0.00
Viral upper respiratory tract infection	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.06	0 0.00	1 0.03	0 0.00
Injury, poisoning and procedural complications	**1 0.04**	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**	**3 0.11**	**6 0.15**	**1 0.71**
Arthropod bite	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	1 0.71
Bladder injury	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Corneal abrasion	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	2 0.07	0 0.00	0 0.00
Ligament sprain	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.04	0 0.00	0 0.00
Overdose	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Road traffic accident	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Tendon rupture	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Wound	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Investigations	**1 0.04**	**0 0.00**	**0 0.00**	**1 0.02**	**1 0.16**	**0 0.00**	**0 0.00**	**1 0.03**	**0 0.00**
Electrocardiogram QT prolonged	0 0.00	0 0.00	0 0.00	0 0.00	1 0.16	0 0.00	0 0.00	1 0.03	0 0.00
Intraocular pressure increased	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Weight increased	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00

	Patanol (N = 2844)	Pataday (N = 2700)	Pazeo (N = 827)	Patanase (N = 4312)	Other Olopatadine* (N = 612)	Active Control (N = 1722)	Topical Ocular Placebo (N = 2702)	Nasal Placebo (N = 3988)	Oral Placebo (N = 140)
	n %	n %	n %	n %	n %	n %	n %	n %	n %
Musculoskeletal and connective tissue disorders	**2 0.07**	**0 0.00**	**0 0.00**	**2 0.05**	**1 0.16**	**0 0.00**	**0 0.00**	**4 0.10**	**0 0.00**
Arthralgia	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Back pain	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Bursitis	0 0.00	0 0.00	0 0.00	0 0.00	1 0.16	0 0.00	0 0.00	0 0.00	0 0.00
Intervertebral disc protrusion	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Myalgia	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Pain in extremity	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Pathological fracture	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0 0.00**	**1 0.04**	**0 0.00**	**3 0.07**	**0 0.00**	**1 0.06**	**0 0.00**	**3 0.08**	**0 0.00**
Breast cancer	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	1 0.06	0 0.00	0 0.00	0 0.00
Gastrointestinal carcinoma	0 0.00	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Lung neoplasm malignant	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Neoplasm	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	2 0.05	0 0.00
Neoplasm malignant	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Nervous system disorders	**4 0.14**	**3 0.11**	**0 0.00**	**31 0.72**	**10 1.63**	**2 0.12**	**2 0.07**	**24 0.60**	**0 0.00**
Dizziness	2 0.07	0 0.00	0 0.00	2 0.05	2 0.33	0 0.00	0 0.00	5 0.13	0 0.00
Dysgeusia	0 0.00	0 0.00	0 0.00	15 0.35	1 0.16	0 0.00	0 0.00	0 0.00	0 0.00
Facial paralysis	0 0.00	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Headache	1 0.04	2 0.07	0 0.00	9 0.21	3 0.49	2 0.12	1 0.04	12 0.30	0 0.00

	Patanol (N = 2844)	Pataday (N = 2700)	Pazeo (N = 827)	Patanase (N = 4312)	Other Olopatadine* (N = 612)	Active Control (N = 1722)	Topical Ocular Placebo (N = 2702)	Nasal Placebo (N = 3988)	Oral Placebo (N = 140)
	n %	n %	n %	n %	n %	n %	n %	n %	n %
Hypoaesthesia	1 0.04	0 0.00	0 0.00	0 0.00	1 0.16	0 0.00	0 0.00	0 0.00	0 0.00
Migraine	0 0.00	0 0.00	0 0.00	2 0.05	0 0.00	0 0.00	0 0.00	3 0.08	0 0.00
Multiple sclerosis	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Paraesthesia	0 0.00	0 0.00	0 0.00	0 0.00	1 0.16	0 0.00	0 0.00	1 0.03	0 0.00
Sinus headache	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Somnolence	0 0.00	0 0.00	0 0.00	0 0.00	1 0.16	0 0.00	0 0.00	0 0.00	0 0.00
Syncope	0 0.00	0 0.00	0 0.00	1 0.02	1 0.16	0 0.00	1 0.04	1 0.03	0 0.00
Psychiatric disorders	**0 0.00**	**0 0.00**	**0 0.00**	**1 0.02**	**0 0.00**	**2 0.12**	**0 0.00**	**3 0.08**	**0 0.00**
Anxiety	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Insomnia	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	2 0.05	0 0.00
Irritability	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.06	0 0.00	0 0.00	0 0.00
Thinking abnormal	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.06	0 0.00	0 0.00	0 0.00
Respiratory, thoracic and mediastinal disorders	**3 0.11**	**5 0.19**	**0 0.00**	**35 0.81**	**2 0.33**	**3 0.17**	**0 0.00**	**70 1.76**	**0 0.00**
Asthma	3 0.11	1 0.04	0 0.00	1 0.02	0 0.00	2 0.12	0 0.00	9 0.23	0 0.00
Cough	0 0.00	1 0.04	0 0.00	2 0.05	0 0.00	1 0.06	0 0.00	3 0.08	0 0.00
Dry throat	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Dyspnoea	0 0.00	1 0.04	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Epistaxis	0 0.00	1 0.04	0 0.00	12 0.28	2 0.33	0 0.00	0 0.00	24 0.60	0 0.00
Laryngospasm	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Nasal discomfort	0 0.00	0 0.00	0 0.00	3 0.07	0 0.00	0 0.00	0 0.00	7 0.18	0 0.00

	Patanol (N = 2844)	Pataday (N = 2700)	Pazeo (N = 827)	Patanase (N = 4312)	Other Olopatadine* (N = 612)	Active Control (N = 1722)	Topical Ocular Placebo (N = 2702)	Nasal Placebo (N = 3988)	Oral Placebo (N = 140)
	n %	n %	n %	n %	n %	n %	n %	n %	n %
Nasal dryness	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Nasal polyps	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Nasal septum disorder	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	3 0.08	0 0.00
Nasal septum perforation	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Nasal ulcer	0 0.00	0 0.00	0 0.00	6 0.14	0 0.00	0 0.00	0 0.00	9 0.23	0 0.00
Oropharyngeal pain	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Respiratory tract congestion	0 0.00	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Rhinalgia	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	3 0.08	0 0.00
Rhinitis allergic	0 0.00	0 0.00	0 0.00	2 0.05	0 0.00	0 0.00	0 0.00	4 0.10	0 0.00
Rhinorrhoea	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Sinus perforation	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Sneezing	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	2 0.05	0 0.00
Throat irritation	0 0.00	0 0.00	0 0.00	2 0.05	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Wheezing	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Skin and subcutaneous tissue disorders	**2 0.07**	**3 0.11**	**0 0.00**	**8 0.19**	**1 0.16**	**0 0.00**	**2 0.07**	**13 0.33**	**0 0.00**
Dermatitis	1 0.04	1 0.04	0 0.00	4 0.09	0 0.00	0 0.00	1 0.04	1 0.03	0 0.00
Dermatitis contact	1 0.04	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	6 0.15	0 0.00
Erythema multiforme	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Lichenoid keratosis	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Pruritus	0 0.00	1 0.04	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Rash	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	2 0.05	0 0.00

	Patanol (N = 2844)	Pataday (N = 2700)	Pazeo (N = 827)	Patanase (N = 4312)	Other Olopatadine* (N = 612)	Active Control (N = 1722)	Topical Ocular Placebo (N = 2702)	Nasal Placebo (N = 3988)	Oral Placebo (N = 140)
	n %	n %	n %	n %	n %	n %	n %	n %	n %
Rash follicular	0 0.00	0 0.00	0 0.00	0 0.00	1 0.16	0 0.00	0 0.00	0 0.00	0 0.00
Urticaria	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	1 0.04	4 0.10	0 0.00
Social circumstances	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**	**0 0.00**	**1 0.04**	**0 0.00**	**0 0.00**
Menopause	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.04	0 0.00	0 0.00
Surgical and medical procedures	**2 0.07**	**1 0.04**	**0 0.00**	**1 0.02**	**0 0.00**	**1 0.06**	**0 0.00**	**1 0.03**	**0 0.00**
Ankle operation	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00
Dental implantation	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1 0.06	0 0.00	0 0.00	0 0.00
Keratomileusis	0 0.00	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Nasal septal operation	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Removal of foreign body from eye	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Wisdom teeth removal	1 0.04	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Vascular disorders	**0 0.00**	**1 0.04**	**0 0.00**	**2 0.05**	**1 0.16**	**0 0.00**	**0 0.00**	**1 0.03**	**0 0.00**
Embolism	0 0.00	0 0.00	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00
Hot flush	0 0.00	0 0.00	0 0.00	0 0.00	1 0.16	0 0.00	0 0.00	0 0.00	0 0.00
Hypertension	0 0.00	1 0.04	0 0.00	1 0.02	0 0.00	0 0.00	0 0.00	1 0.03	0 0.00

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM M BOYD
01/11/2020 10:40:45 AM

WILEY A CHAMBERS
01/11/2020 10:44:18 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

0206276Orig1s005

OTHER REVIEW(S)

Labeling Review for Pataday® Once Daily Relief (Olopatadine hydrochloride) Ophthalmic Solution 0.7%
Draft Labeling
Addendum 2

SUBMISSION DATE(S):	July 9, 2020
NDA/SUBMISSION TYPE:	206276/S-005
ACTIVE INGREDIENTS:	Olopatadine hydrochloride (0.7%)
DOSAGE FORM:	Ophthalmic solution
SPONSOR:	Alcon Research, LLC 6201 South Freeway Fort Worth, TX 76134-2009 NanevieVincent MS, MBA, RAC Director, Global Regulatory Affairs
REVIEWER:	Arlene Solbeck, MS
TEAM LEADER:	Sergio Coelho, PhD
PROJECT MANAGER	LCDR Jung E. Lee, MS, RPh

BACKGROUND:

This is an addendum to the labeling reviews of Pataday Extra Strength, NDA 206276/S005, olopatadine hydrochloride (0.7%) ophthalmic solution, entered Darrts on June 23, 2020 and June 26, 2020. This second addendum is a review of revised labeling submitted by the sponsor on July 9, 2020 in response to FDA's Information Request sent to the sponsor on July 8, 2020.

In the July 8, 2020 Information Request to the sponsor, FDA requested the following revisions to the carton and Drug Facts labeling:

For the Twin-Pack (Two 2.5 mL bottles) carton

Principal Display Panel

- Revise the banner containing "Twin Pack" [redacted]" and the [redacted]:

Remove "[redacted]"*EXTRA STRENGTH*" so that it is clear that [redacted]". As currently presented, it appears this packaging configuration is [redacted] on the PDP while not changing the relative sizes of the Statement of Identity (SOI) and modifier "ONCE DAILY RELIEF" in the proposed proprietary name.

For the 2.5 mL carton, 0.5 mL carton, Twin-Pack (Two 2.5 mL bottles) carton

Drug Facts under the "Directions" heading

To address potential overuse/misuse of this drug product:

- Revise the first sub-bulleted statement which currently reads "put 1 drop in the affected eye(s) once daily, [redacted]" to read "put **1 drop** in the affected eye(s) **once daily**" (Note how bold text emphasis should be displayed in this bulleted statement).
- Add a new statement in bold text as the second sub-bulleted statement to read "**do not use more than 1 drop in each eye per day**".

SUBMITTED REVISED LABELING on July 9, 2020:

Submitted Draft Labeling	Representative of Following SKUs
Pataday® Once Daily Relief Extra Strength 2.5 mL (0.085 Fl oz) carton	N/A
Pataday® Once Daily Relief Extra Strength Two x 2.5 mL (0.085 Fl oz each) Carton – Twin Pack	N/A
Pataday® Once Daily Relief Extra Strength Sample 0.5 mL (0.017 Fl oz) Carton	N/A

REVIEWER'S COMMENTS:

The sponsor has accepted FDA feedback and has updated labeling accordingly.

For the Twin-Pack (Two 2.5 mL bottles) carton

Principal Display Panel

- The "Twin Pack" and [redacted]. The "Twin Pack" and [redacted]. The "*EXTRA STRENGTH*" remains in the green banner close to the proprietary name "Pataday Once Daily Relief". The sizing of the SOI and modifier "ONCE DAILY RELIEF" remain the same, as requested. This labeling is acceptable.

For the 2.5 mL carton, 0.5 mL carton, Twin-Pack (Two 2.5 mL bottles) carton

Drug Facts under the "Directions" heading

The Drug Facts "**Directions**" have been updated as requested as follows:

- The first sub-bullet was updated to read "put **1 drop** in the affected eye(s) **once daily**" (some bolded text for emphasis)

- A new bolded sub-bullet was added to read "**do not use more than 1 drop in each eye per day**"

To ensure that the two sub-bullets remained together and did not carry over to the side panel, the sponsor also adjusted the "arrow graphic" (graphic leading to next page) from the bottom right corner of the "**Directions**" box to the top right corner of the "**Directions**" box.

These labeling revisions are acceptable.

REVIEWER'S RECOMMENDATIONS:

Issue an **APPROVAL** letter to the sponsor for the submitted carton and container labeling for Pataday Once Daily Relief "*EXTRA STRENGTH"* (Olopatadine hydrochloride (0.7%) ophthalmic solution), in three package configurations: single 2.5mL bottle, "Twin Pack" (two 2.5mL bottles) and 0.5mL sample bottle.

Submit final printed labeling (FPL) for the carton and inner container labeling as soon as they are available, but no more than 30 days after they are printed. The FPL for the carton labeling for the three package configurations must be identical to the labeling submitted on July 9, 2020 and the inner container labeling must be identical to the labeling submitted on June 25, 2020. (summarized in table below).

Pataday® Once Daily Relief Extra Strength 2.5 mL (0.085 Fl oz) carton	July 9, 2020
Pataday® Once Daily Relief Extra Strength 2.5 mL (0.085 Fl oz) bottle, container	June 25, 2020
Pataday® Once Daily Relief Extra Strength Two X 2.5 mL (0.085 Fl oz) carton -Twin Pack	July 9, 2020
Pataday® Once Daily Relief Extra Strength Sample 0.5 mL (0.017 Fl oz) Carton	July 9, 2020
Pataday® Once Daily Relief Extra Strength Sample 0.5 mL (0.017 Fl oz) bottle, container	June 25, 2020
Pataday® Once Daily Relief Extra Strength Sample 0.5 mL (0.017 Fl oz) bottle, pouch	June 25, 2020

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ARLENE H SOLBECK
07/10/2020 04:37:28 PM

SERGIO N COELHO
07/10/2020 04:44:06 PM

Labeling Review for Pataday® Once Daily Relief (Olopatadine hydrochloride) Ophthalmic Solution 0.7%
Draft Labeling Addendum

SUBMISSION DATE(S):	June 25, 2020
NDA/SUBMISSION TYPE:	206276/S-005
ACTIVE INGREDIENTS:	Olopatadine hydrochloride (0.7%)
DOSAGE FORM:	Ophthalmic solution
SPONSOR:	Alcon Research, LLC 6201 South Freeway Fort Worth, TX 76134-2009 NanevieVincent MS, MBA, RAC Director, Global Regulatory Affairs
REVIEWER:	Arlene Solbeck, MS
TEAM LEADER:	Sergio Coelho, PhD
PROJECT MANAGER	LCDR Jung E. Lee, MS, RPh

BACKGROUND:

This is an addendum to the Labeling Review of Pataday Extra Strength, NDA 206276/S005, olopatadine hydrochloride (0.7%) ophthalmic solution, entered Darrts on June 23, 2020. This addendum is a review of revised labeling submitted by the sponsor on June 25, 2020 in response to FDA's Information Request sent to the sponsor on June 19, 2020.

SUBMITTED REVISED LABELING on June 25, 2020:

Submitted Draft Labeling	Representative of Following SKUs
Pataday® Once Daily Relief 2.5 mL (0.085 Fl oz) carton – Extra Strength	N/A

Pataday® Once Daily Relief 2.5 mL (0.085 Fl oz) container – Extra Strength	N/A
Pataday® Once Daily Relief Twin Pack Two 2.5 mL bottles (0.085 Fl oz each) Carton – Extra Strength	N/A
Pataday® Once Daily Relief Sample 0.5 mL (0.017 Fl oz) Carton – Extra Strength	N/A
Pataday® Once Daily Relief Sample 0.5 mL (0.017 Fl Oz) Container – Extra Strength	N/A
Pataday® Once Daily Relief Sample 0.5 mL (0.017 Fl oz) pouch – Extra Strength	N/A

REVIEWER'S COMMENTS:

A. 2.5 mL (0.017 Fl oz) - TRADE

i. Outer Carton Label Outside Drug Facts

Principal Display Panel:

a. Remove the word "(b) (4)" and the asterisk following it from "(b) (4) (b) (4)….." and replace with "Relief from allergens…." in accordance with prior approved OTC Pataday products.

Reviewer's Response: The word (b) (4) and the asterisk following it were removed and replaced with "Relief from allergens:….." in accordance with prior approved OTC Pataday products. This labeling is acceptable.

b. Increase the prominence of the "Once Daily Relief" in accordance with other approved OTC Pataday products.

Reviewer's Response: The sponsor increased the prominence of "Once Daily Relief" in accordance with other approved OTC Pataday products. This labeling is acceptable.

c. Revise the Statement of Identity (SOI) as follows:

1. Revise the proposed SOI from "Olopatadine hydrochloride ophthalmic solution 0.7% (b) (4) Antihistamine" by removing the word "(b) (4)" from the pharmacological category.

Reviewer's Response: The word "(b) (4)" was removed from the SOI. This labeling is acceptable.

2. Enlarge the font of the SOI and present in bold face type. The regulations (21 CFR 201.61(c)) state the SOI shall be "a size reasonably related to the most prominent printed matter…". We recommend that the font size be at least 25% of the most prominent printed matter (i.e. the proprietary name as currently proposed).

Reviewer's Response: The sponsor revised the SOI by bolding and increasing size. The SOI appears to be greater than 25% of the most prominent printed matter (i.e. Pataday) based on measuring the size of the "P" in Pataday and the "O" on Olopatadine (Table 1 of Quality Information Amendment – Measurements of SOI Locations). This labeling is acceptable.

3. Revise the SOI such that "ophthalmic" and "solution" are on the same line and there is no break between them. This would be consistent with other approved OTC Pataday products.

Reviewer's Response: The SOI was revised such that "ophthalmic" and "solution" are on the same line and there is no break between them. This labeling is acceptable.

d. Revise the claim "(b) (4)" to read "Eye Allergy Itch Relief" to be consistent with products in this category.

Reviewer's Response: The sponsor updated the claim to read "Eye Allergy Itch Relief". This labeling is acceptable.

Side Panel:

1. Revise claim "(b) (4)" to read "Eye Allergy Itch Relief.

Reviewer's Response: The claim "(b) (4)" was revised to read "Eye Allergy Itch Relief". This labeling is acceptable.

2. Increase the prominence of the tamper evident feature statements. The regulations at CFR 211.132(c)(ii) state that labeling be "prominently placed….". You may consider changing the font color to a darker color and bolding the font size.

Reviewer's Response: Tamper Evident statement was increased in size, moved out of the bottle silhouette, bolded and changed from white to black font to increase the prominence. Although the sponsor changed the color of the font to black, taking the tamper evident feature statement out of the bottle silhouette was not required; however, it appears to be the similar as to the labeling FDA approved for the Pataday Once Daily Relief 0.2% product. This is acceptable.

3. Delete or revise "[redacted]" if no longer appropriate.

Reviewer's Response: "[redacted]" was deleted. This labeling is acceptable.

Top Panel:

1. Enlarge the font of the SOI and present in bold face type (Refer to A.i.c.2. above).

Reviewer's Response: The SOI appears to be greater than 25% of the most prominent printed matter (i.e. Pataday) based on measuring the size of the "P" in Pataday and the "O" on Olopatadine (Table 1 of Quality Information Amendment – Measurements of SOI Locations). This labeling is acceptable.

2. Revise the claim "[redacted]" to "Eye Allergy Itch Relief to be consistent with products in this category.

Reviewer's Response: The claim "[redacted]" was updated to read "Eye Allergy Itch Relief" in accordance with products in this category. This labeling is acceptable.

3. Revise the SOI such that "ophthalmic" and "solution" are on the same line and there is no difference between them.

Reviewer's Response: The SOI was revised such that "ophthalmic" and "solution" are on the same line with no break between them. This labeling is acceptable.

Back panel (Outside Drug Facts):

1. Under Drug Facts box, remove the claim [redacted]

Reviewer's Response: The claim [redacted] was removed. This labeling is acceptable.

ii. Outer Carton Drug Facts Label

Drug Facts must be in accordance with content and format modifications set forth under 21 CFR 201.66. Confirm the font and format specifications using annotated labeling.

Reviewer's Response: The sponsor submitted the font and format specifications of the Drug Facts Label in annotated labeling in Appendix 1 of the Quality Information Amendment. The font and format specifications are acceptable with one exception – the bullet font and format specifications are not in the table. Sponsor should conform the bullet font and format specifications.

1. Revise horizontal hairlines to not extend on either side to each end of the Drug Facts box. "A horizontal hairline extending within two spaces on either side of the "Drug Facts" box or similar enclosure shall immediately follow the title and shall immediately precede each of the subheadings set forth in paragraph (c)(5)(ii)(A) through (c)(5)(ii)(G) of this section." (21 CFR 201.66(d)(8))

Reviewer's Response: Sponsor revised the DFL hairlines. This labeling is acceptable.

2. Under the (b) (4) heading, begin the (b) (4) statement with lower case "t" because only headings and subheadings use an upper-case letter for the first word (i.e., (b) (4)"). Lowercase letters are used for all other words (i.e., temporarily…").

Reviewer's Response: The sponsor made this change in the (b) (4) section. This labeling is acceptable. In addition, the sponsor revised "(b) (4)" to "***Use***". (b) (4) (b) (4) this labeling is acceptable.

3. Under the **When using this product** subheading:

   - Delete the bulleted statement (b) (4) (b) (4)
   - Add the new bulleted statement "do not wear a contact lens if your eye is red" as the last bulleted statement.

Reviewer's Response: The sponsor made these two changes to **When using this product**. This labeling is acceptable.

4. Under the ***Directions*** heading make the following revisions:

   - Under the bulleted subheading "**Adults and children 2 years of age and older:**" we recommend starting a new line, to create indented bulleted substatements starting with "put 1 drop…". Note that the "p" in "put" is lowercase, as the first bulleted substatement. Note also that the "a" in "Adults" should be lower-case.

Reviewer's Response: "adults and children 2 years of age and older:" was moved down to start a new line to create indented bulleted substatements. This labeling is acceptable. "the "a" in adults was changed to lower case. This labeling is acceptable. The "p" in "put" was changed to lowercase, as the first bulleted substatement. This labeling is acceptable.

   a. Add as the second bulleted substatement "if using other ophthalmic products while using this product, wait at least 5 minutes between each product".

Reviewer's Response: The substatement "if using other ophthalmic products while using this product, wait until at least 5 minutes between each product" was added to the ***Directions*** section as the second bulleted substatement. This labeling is acceptable.

b. Make the third bulleted substatement "replace cap after each use".

Reviewer's Response: "replace cap after each use" substatement has been added to the ***Directions*** section as a third bulleted substatement. This labeling is acceptable.

c. For the second bulleted subheading "Children under 2 years of age:" left-justify and align with the first bulleted subheading. Note that the "c" in "Children" and "Consult" should be lower-case.

Reviewer's Response: A second subheading "children under 2 years of age:" was added to align with the first bulleted subheading. The "C" in consult was changed to lowercase "c". This labeling is acceptable.

5. Under the ***Inactive ingredients*** heading, list the inactive ingredients in alphabetical order for drug products. (21 CFR 201.66(c)(8))

Reviewer's Response: The inactive ingredients were revised to be listed in alphabetical order. This labeling is acceptable.

iii. Immediate Container Label

1. Revise the SOI such that "ophthalmic solution" is on the same line.

Reviewer's Response: The SOI has been revised such that "ophthalmic" and "solution" is on the same line. This labeling is acceptable.

2. Delete the word (b) (4) from the SOI (Refer to A.i.c.1 above).

Reviewer's Response: "(b) (4)" has been removed from the pharmacologic category. This labeling is acceptable.

3. Increase the font size of the SOI and present in bold face type as requested above for the PDP (Refer to A.i.c.2 above).

Reviewer's Response: The SOI has been bolded, increased in size and appears to be greater than 25% of the most prominent printed matter i.e. Pataday, as stated in Sponsor's Table 1-Quality Information Amendment - Measurements of SOI Locations. This labeling is acceptable.

B. Two x 2.5 mL bottles (0.085 FL OZ EACH)

i. Outer Carton Label Outside Drug Facts

Refer to the changes requested above for the 2.5 mL carton PDP.

Reviewer's Response: The sponsor made the same changes requested for the single 2.5 mL bottle carton SKU. This labeling is acceptable.

ii. Outer Carton Drug Facts Label

Refer to the changes requested above for the 2.5 mL carton DFL.

Reviewer's Response: The sponsor made the same changes requested for the 2.5 mL single bottle carton SKU DFL. This labeling is acceptable.

iii. Immediate Container Label

Refer to the changes requested above for the 2.5 mL bottle container label.

Reviewer's Response: The 2.5 mL bottle container label is the same for the single bottle SKU and the twin pack. The changes are described above in section A.iii. This labeling is acceptable.

C. 0.5 mL (0.017 Fl oz) – SAMPLE

i. Outer Carton Label Outside Drug Facts

Principal Display Panel:

a. Remove the word (b) (4)" and the asterisk following it from (b) (4) (b) (4)….." and replace with "Relief from allergens…." in accordance with prior approved OTC Pataday products.

Reviewer's Response: The word (b) (4) and the asterisk following it were removed and replaced with "Relief from allergens:….." in accordance with prior approved OTC Pataday products. This labeling is acceptable.

b. Increase the prominence of the "Once Daily Relief" in accordance with other approved OTC Pataday products.

Reviewer's Response: The sponsor increased the prominence of "Once Daily Relief" in accordance with other approved OTC Pataday products. This labeling is acceptable.

c. Revise the Statement of Identity (SOI) as follows:

1. Revise the proposed SOI from "Olopatadine hydrochloride ophthalmic solution 0.7% (b) (4) Antihistamine" by removing the word (b) (4)" from the (b) (4).

Reviewer's Response: The word (b) (4)" was removed from the SOI. This labeling is acceptable.

2. Enlarge the font of the SOI and present in bold face type. The regulations (21 CFR 201.61(c)) state the SOI shall be "a size reasonably related to the most prominent printed matter…". We recommend that the font size be at least 25% of the most prominent printed matter (i.e. the proprietary name as currently proposed).

Reviewer's Response: The sponsor revised the SOI by bolding and increasing size. The SOI appears to be greater than 25% of the most prominent printed matter (i.e. Pataday) based on measuring the size of the "P" in Pataday and the "O" on Olopatadine (Table 1 of Quality Information Amendment – Measurements of SOI Locations). This labeling is acceptable.

3. Revise the SOI such that "ophthalmic" and "solution" are on the same line and there is no break between them. This would be consistent with other approved OTC Pataday products.

Reviewer's Response: The SOI was revised such that "ophthalmic" and "solution" are on the same line and there is no break between them. This labeling is acceptable.

d. Revise the claim (b) (4) to read "Eye Allergy Itch Relief" to be consistent with products in this category.

Reviewer's Response: The sponsor updated the claim to read "Eye Allergy Itch Relief". This labeling is acceptable.

Side Panel:

1. Revise claim (b) (4)" to read "Eye Allergy Itch Relief.

Reviewer's Response: The claim (b) (4) was revised to read "Eye Allergy Itch Relief". This labeling is acceptable.

2. Increase the prominence of the tamper evident feature statements. The regulations at 21 CFR 211.132(c)(ii) state that labeling be "prominently placed….". You may consider changing or bolding the font size.

Reviewer's Response: Tamper Evident statement was increased in size and bolded to increase the prominence. This labeling is acceptable.

- Delete or revise [redacted] (b) (4) " if no longer appropriate.

Reviewer's Response: The statement " [redacted] (b) (4) " was deleted. This labeling is acceptable.

Top Panel:

1. Enlarge the font of the SOI and present in bold face type.

Reviewer's Response: The SOI was enlarged, presented in bold face type and appears to be greater than 25% of the most prominent printed matter (i.e. Pataday) based on measuring the size of the "P" in Pataday and the "O" on Olopatadine (Table 1 of Quality Information Amendment – Measurements of SOI Locations). This labeling is acceptable.

2. Revise the claim [redacted] (b) (4) " to "Eye Allergy Itch Relief" to be consistent with products in this category.

Reviewer's Response: The claim was revised to "Eye Allergy Itch Relief" to be consistent with product in this category.

3. Revise the SOI such that "ophthalmic" and "solution" are on the same line and there is no difference between them.

Reviewer's Response: The SOI was revised such that "ophthalmic" and "solution" are on the same line with no break between them. This labeling is acceptable.

Back panel (Outside Drug Facts):

1. Under Drug Facts box, remove the claim [redacted] (b) (4)

Reviewer's Response: The sponsor removed the claim [redacted] (b) (4)

ii. Outer Carton Drug Facts Label

Drug Facts must be in accordance with content and format modifications set forth under 21 CFR 201.66. Confirm the font and format specifications using annotated labeling.

1. Revise horizontal hairlines to not extend on either side to each end of the Drug Facts box. "A horizontal hairline extending within two spaces on either side of the "Drug Facts" box or similar enclosure shall immediately follow the title and shall immediately precede each of the subheadings set forth in paragraph (c)(5)(ii)(A) through (c)(5)(ii)(G) of this section." (21 CFR 201.66(d)(8))

Reviewer's Response: Sponsor revised the hairlines. This labeling is acceptable.

2. Under the (b) (4) heading, begin the (b) (4) statement with lower case "t" because only headings and subheadings use an upper-case letter for the first word (i.e., (b) (4)"). Lowercase letters are used for all other words (i.e., temporarily…").

Reviewer's Response: The sponsor made this change in the (b) (4) section. This labeling is acceptable. In addition, the sponsor revised "(b) (4)" to "***Use***". (b) (4) (b) (4), this labeling is acceptable.

3. Under the **When using this product** subheading:

   - Delete the bulleted statement (b) (4) (b) (4)
   - Add the new bulleted statement "do not wear a contact lens if your eye is red" as the last bulleted statement.

Reviewer's Response: The sponsor made these two changes in "When using this product." This labeling is acceptable.

4. Under the ***Directions*** heading make the following revisions:

   - Under the bulleted subheading "**Adults and children 2 years of age and older:**" we recommend starting a new line, to create indented bulleted substatements starting with "put 1 drop…". Note that the "p" in "put" is lowercase, as the first bulleted substatement. Note also that the "a" in "Adults" should be lower-case.

Reviewer's Response: "adults and children 2 years of age and older:" was moved down to start a new line to create indented bulleted substatements. This labeling is acceptable. "the "a" in adults was changed to lower case. This labeling is acceptable. The "p" in "put" was changed to lowercase, as the first bulleted substatement. This labeling is acceptable.

   a. Add as the second bulleted substatement "if using other ophthalmic products while using this product, wait at least 5 minutes between each product".

Reviewer's Response: The substatement "if using other ophthalmic products while using this product, wait until at least 5 minutes between each product" was added to the ***Directions*** section as the second bulleted substatement. This labeling is acceptable

b. Make the third bulleted substatement "replace cap after each use".

Reviewer's Response: The "replace cap after each use" substatement has been added to the ***Directions*** section as a third bulleted substatement. This labeling is acceptable.

c. For the second bulleted subheading "Children under 2 years of age:" left-justify and align with the first bulleted subheading. Note that the "c" in "Children" and "Consult" should be lower-case.

Reviewer's Response: A second subheading "children under 2 years of age:" was added to align with the first bulleted subheading. The "C" in consult was changed to lowercase "c". This labeling is acceptable.

5. Under the ***Inactive ingredients*** heading, list the inactive ingredients in alphabetical order for drug products (21 CFR 201.66(c)(8)).

Reviewer's Response: The inactive ingredients were revised to be listed in alphabetical order. This labeling is acceptable.

iii. Immediate Container Label

1. Revise the SOI such that "ophthalmic solution" is on the same line.

Reviewer's Response: The SOI was revised such that "ophthalmic" and "solution" are on the same line with no break between them. This labeling is acceptable

2. Delete the word (b) (4) from the SOI.

Reviewer's Response: The word (b) (4) was deleted from the SOI. This labeling is acceptable.

3. Increase the font size of the SOI and present in bold face type as requested above for the PDP.

Reviewer's Response: The SOI font type and size was increased as much as possible. The labeling is acceptable.

iv. Pouch

1. Revise the SOI such that "ophthalmic solution" is on the same line.

Reviewer's Response: The SOI was revised such that "ophthalmic solution" is on the same line. This labeling is acceptable.

2. Delete the word (b) (4) from the SOI.

Reviewer's Response: The word (b) (4) was deleted from the SOI. This labeling is acceptable.

In addition to making the changes requested above by June 25, 2020, FDA requested that the sponsor:

- should submit actual size (i.e., at 100%) immediate container labels and carton labeling and confirm by annotating the submitted labels and labeling with ("Actual Size, 100%"). The sponsor should submit annotated labeling for all revisions.

Reviewer's Response: The sponsor submitted actual size immediate container labels and carton labeling along with annotated labeling for the revisions requested, and for additional revisions which are described below under "Additional Changes Made by Sponsor".

Placement	Additional Changes Made by the Sponsor	Reviewer's Response
Font for Drug Facts title all cartons	Increased to 14 pt to be in compliance with 21 CFR 201.66	Acceptable
Drug Facts Label all cartons	Updated (b) (4) in DLF to "Use"	Acceptable
Drug Facts Label on all cartons	For external use only – bolded as per 21 CFR 201.66	Acceptable
Drug Facts Label all cartons	"**Stop use and ask a doctor if** you experience (b) (4)" updated to "**Stop use and ask a doctor if** you experience	Acceptable; aligns to the 0.1% and 0.2% Pataday Products' DFL
Drug Facts Label all cartons	"C" in Consult (Directions section) changed to a lower case "c"	Acceptable
Principal Display Panel (PDP) on all cartons	"a" in allergens capitalized to "A"; "D" in dander capitalized to a "D"	Acceptable; aligns to the 0.1% and 0.2% DFL
PDP all cartons	Extra Strength changed to italics to emphasize call-out	Acceptable
PDP all cartons	Extra Strength changed to White Font to align to the 0.1% and 0.2% cartons submitted on 6/19/2020	Reviewer understands changing to white font to align with other OTC Patadays. Acceptability pending. See below.
PDP on all cartons	Updated clock graphic	Acceptable
Carton Side Panel on Single and Twin Pack	Updated bottle silhouette to enhance consumer understanding of actual size of oval bottle	Acceptable
Carton Side Panel on Single and Twin Pack	Bottle Silhouette Fill Line included to comply with Slack Fill Laws	Acceptable
Carton Side Panel on Single and Twin Pack	Moved claims (For Ages 2 and Older (b) (4) (b) (4), Works in Minutes) into the bottle silhouette to allow for additional	Agency asked for the Tamper Evident Feature to be increased in size and

	room for the tamper evident statement (increase in size and bolded) above the bottle silhouette per the agency's request	bolded but not necessarily moved over the bottle silhouette. However, the Tamper Evident Feature statement appears to be similar in size to what was approved for other Once Daily Pataday products. Acceptable
Sample Carton	Tamper Evident statement updated to include "TAMPER EVIDENT" at the beginning of statement	Acceptable
Sample Pouch	(b) (4)	Acceptable
Sample Carton Side Panels	Removed Red and Blue graphics from Left& Right Side Panels because of size constraints	Acceptable
Side Panels on 2.5 mL Single Carton	Change Address Color from white to black to enhance legibility	Acceptable
Side Panel on 2.5 mL Single Carton	Rotated UPC code to provide enough room on the side panel for the DFL	Acceptable
Left Side Panel on Twin Pack	Address relocated to right side panel due to size constraints	Acceptable
Sample Pouch and Sample Carton	Updated "SAMPLE-NOT FOR SALE" to Yellow Text to make it more prominent	Acceptability pending; see below

The sponsor was also advised that they may use the alternate color scheme ("Green") proposed in their email to Senior Regulatory Project Manager, LCDR Jung Lee on June 17, 2020 if the changes to the carton and container labels as outlined above are made. The sponsor accordingly changed the banner color to green and, as stated above, used white font for the "EXTRA STRENGTH" in the banner (2.5mL carton). For the 0.5mL sample carton, the sponsor used the white font for "EXTRA STRENGTH" and yellow font for the words "SAMPLE-NOT FOR SALE".

Reviewer's Response: This labeling is pending acceptability depending on what is decided for the Twin Pack (described next).

For the 2x2.5 mL Twin Pack the sponsor used white font for "Extra Strength" and (b) (4) font for "Twin Pack". The sponsor also used white for the bottles in the banner that apply to twin pack.

(b) (4)

In the original submission, the banner was (b) (4) and "EXTRA STRENGTH" was in (b) (4) (b) (4).

(b) (4)

The Division of Medication Error Prevention and Analysis (DMEPA) had recommended in their review of January 7, 2020 that, for the (b) (4), (b) (4) and (b) (4) Twin Pack banner from the original submission, the sponsor revise the banner (b) (4) (b) (4) (b) (4). However, with the green color scheme the sponsor has made "EXTRA STRENGTH" white matching the two bottles and the "Twin Pack" is now smaller and in yellow. From an IDS perspective, this presents an issue in the color scheme that was not a problem before. We would ask the sponsor to make the "Twin Pack" white and the "Extra Strength" yellow. However, the color of "EXTRA STRENGTH" would not align with the other two "EXTRA STRENGTH" cartons. It should also be noted that the prominence of the SOI and "Once Daily Relief" were increased by the sponsor in response to our information request. To accommodate the increase in prominence of those two items the banner was made smaller. DMEPA's recommendation remains and is pending clinical input.

REVIEWER'S RECOMMENDATIONS:

After reviewing the submitted labeling from June 25, 2020 for Pataday® ONCE DAILY RELIEF "EXTRA STRENGTH", there are still some outstanding issues before approval can be recommended. These are as follows:

- The white color of the "EXTRA STRENGTH" descriptor in the banner on the carton labeling of the three SKUs, as it affects the (b) (4) in particular. Concern has been expressed that the banner (b) (4) (b) (4). The decision on whether to ask the sponsor to change the color scheme is pending clinical input.

- Stronger labeling in the DFL for safety has been discussed but the decision is pending further clinical input.

- The sponsor did not submit the font specifications for the DFL bullets but that can be done in an email to the RPM in a future sponsor communication once the other issues pending clinical input are addressed.

The sponsor will be asked to submit clean labels when the decisions on further labeling revisions have been reached.

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ARLENE H SOLBECK
06/26/2020 12:19:11 PM

SERGIO N COELHO
06/26/2020 12:36:19 PM

Labeling Review for Pataday® Once Daily Relief (Olopatadine hydrochloride) Ophthalmic Solution 0.7%
Draft Labeling

SUBMISSION DATE(S):	September 13, 2019, November 25, 2019
NDA/SUBMISSION TYPE:	206276/S-005
ACTIVE INGREDIENTS:	Olopatadine hydrochloride (0.7%)
DOSAGE FORM:	Ophthalmic solution
SPONSOR:	Alcon Research, LLC 6201 South Freeway Fort Worth, TX 76134-2009 NanevieVincent MS, MBA, RAC Director, Global Regulatory Affairs
REVIEWER:	Arlene Solbeck, MS
TEAM LEADER:	Sergio Coelho, PhD
PROJECT MANAGER	LCDR Jung E. Lee, MS, RPh

BACKGROUND:

On April 15, 2019 Alcon submitted two (2) sNDAs to seek approval of the following olopatadine hydrochloride ophthalmic solutions to switch from Rx to OTC status:

- 0.1% olopatadine hydrochloride (NDA 20688/S-032; Patanol (Rx))
- 0.2% olopatadine hydrochloride (NDA 21545/S022; Pataday (Rx))

The sponsor stated in the cover letter that Novartis had not granted the Rx 0.7% olopatadine hydrochloride (Pazeo) switch rights to Alcon at that time, so the sNDA was not submitted for 0.7% olopatadine hydrochloride then. However, the sponsor subsequently stated that they obtained authorization for Alcon to act as an agent on behalf of Novartis regarding a Pazeo Rx to OTC switch and submitted proposed labeling on September 13, 2019. The first proposed name for the OTC 0.7% olopatadine hydrochloride was [redacted] (b) (4)

The 0.1% olopatadine hydrochloride and the 0.2% olopatadine hydrochloride switch submissions were approved on February 14, 2020. The approved name for 0.1% olopatadine hydrochloride is "Pataday® Twice Daily Relief" and the 0.2% olopatadine hydrochloride is "Pataday® Once Daily Relief".

The sponsor states that to support approval for the switch of Pazeo Rx to OTC status, the sNDA relies on FDA's prior finding of safety and efficacy for Rx Pazeo (NDA 206276) and for olopatadine at multiple doses and routes of administration via cross reference to the approved NDAs for Patanol (NDA 020688), Pataday (NDA 21545) and Patanase (NDA 21861).

Olopatadine is a potent selective antiallergic/antihistamine agent for use to temporarily relieve itchy eyes due to pollen, ragweed, grass, animal hair and dander.

SUBMITTED DRAFT LABELING on September 13, 2019:

Submitted Draft Labeling	Representative of Following SKUs
(b) (4)	N/A
	N/A
	N/A
	N/A
	N/A
	N/A

During the review of the 0.1% and 0.2% olopatadine products, the proposed names for all three products (0.1%, 0.2%, and 0.7%) were discussed amongst the team and also reviewed by the Division of Medication Error Prevention and Analysis (DMEPA). On November 22, 2019, Alcon withdrew the name (b) (4) for the 0.7% strength and proposed to differentiate the 0.2% once daily product and the 0.7% once daily strength via the labeling descriptor "Extra Strength" for the 0.7% strength product. On November 25, 2019 the sponsor submitted revised labeling with the new proposed name "Pataday Once Daily Relief" with "Extra Strength" descriptor for the 0.7% olopatadine product. On January 29, 2020 DMEPA communicated this to the Division of Nonprescription Drug Products (DNDP) via e-mail and published a review in Darrts on February 6, 2020 stating that the proposed name of Pataday (0.7%) "Once Daily Relief", and descriptor "Extra Strength", is acceptable.

SUBMITTED REVISED LABELING on November 25, 2019:

Submitted Draft Labeling	Representative of Following SKUs
Pataday® Once Daily Relief 2.5 mL (0.085 Fl oz) carton – Extra Strength	N/A
Pataday® Once Daily Relief 2.5 mL (0.085 Fl oz) container – Extra Strength	N/A
Pataday® Once Daily Relief Twin Pack Two 2.5 mL bottles (0.085 Fl oz each) Carton – Extra Strength	N/A
Pataday® Once Daily Relief Sample 0.5 mL (0.017 Fl oz) Carton – Extra Strength	N/A
Pataday® Once Daily Relief Sample 0.5 mL (0.017 Fl Oz) Container – Extra Strength	N/A
Pataday® Once Daily Relief Sample 0.5 mL (0.017 Fl oz) pouch – Extra Strength	N/A

The sponsor submitted an email to RPM LCDR Jung E. Lee on June 17, 2020 proposing an alternate design and color scheme (green) for the labeling in order to further distinguish the three Pataday products from each other. On June 19, 2020 we sent the sponsor a labeling Information Request. The response from the sponsor is pending. The labeling revisions requested from the sponsor for each labeling component of NDA 206276 are as follows:

REVIEWER'S COMMENTS:

A. 2.5 mL (0.017 Fl oz) - TRADE

i. Outer Carton Label Outside Drug Facts

Principal Display Panel:

a. Remove the word [redacted (b) (4)]" and the asterisk following it from [redacted (b) (4)]." and replace with "Relief from allergens…." in accordance with prior approved OTC Pataday products.

b. Increase the prominence of the "Once Daily Relief" in accordance with other approved OTC Pataday products.

c. Revise the Statement of Identity (SOI) as follows:

1. Revise the proposed SOI from "Olopatadine hydrochloride ophthalmic solution 0.7% (b) (4) Antihistamine" by removing the word (b) (4) from the (b) (4).

2. Enlarge the font of the SOI and present in bold face type. The regulations (21 CFR 201.61I) state the SOI shall be "a size reasonably related to the most prominent printed matter…". We recommend that the font size be at least 25% of the most prominent printed matter (i.e. the proprietary name as currently proposed).

3. Revise the SOI such that "ophthalmic" and "solution" are on the same line and there is no break between them. This would be consistent with other approved OTC Pataday products.

d. Revise the claim (b) (4) to read "Eye Allergy Itch Relief" to be consistent with products in this category.

Side Panel:

1. Revise claim (b) (4)" to read "Eye Allergy Itch Relief.

2. Increase the prominence of the tamper evident feature statements. The regulations at CFR 211.132(c)(ii) state that labeling be "prominently placed….". You may consider changing the font color to a darker color and bolding the font size.

3. Delete or revise (b) (4) if no longer appropriate.

Top Panel:

1. Enlarge the font of the SOI and present in bold face type (Refer to A.i.c.2. above).

2. Revise the claim (b) (4)" to "Eye Allergy Itch Relief to be consistent with products in this category (Refer to A.i.c.1 above)

3. Revise the SOI such that "ophthalmic" and "solution" are on the same line and there is no difference between them (Refer to A.i.c.3 above).

Back panel (Outside Drug Facts):

1. Under Drug Facts box, remove the claim (b) (4) (b) (4)

ii. Outer Carton Drug Facts Label

Drug Facts must be in accordance with content and format modifications wet forth under CFR 201.66. Confirm the font and format specifications using annotated labeling.

1. Revise horizontal hairlines to not extend on either side to each end of the Drug Facts box. "A horizontal hairline extending within two spaces on either side of the "Drug Facts" box or similar enclosure shall immediately follow the title and shall immediately precede each of the subheadings set forth in paragraph (c)(5)(ii)(A) through (c)(5)(ii)(G) of this section." (21 CFR 201.66(d)(8))

2. Under the (b) (4) heading, begin the (b) (4) statement with lower case "t" because only headings and subheadings use an upper-case letter for the first word (i.e., (b) (4)). Lowercase letters are used for all other words (i.e., temporarily…").

3. Under the **When using this product** subheading:

   - Delete the bulleted statement (b) (4)
   - Add the new bulleted statement "do not wear a contact lens if your eye is red" as the last bulleted statement.

4. Under the ***Directions*** heading make the following revisions:

   - Under the bulleted subheading "**Adults and children 2 years of age and older:**" we recommend starting a new line, to create indented bulleted substatements starting with "put 1 drop…". Note that the "p" in "put" is lowercase, as the first bulleted substatement. Note also that the "a" in "Adults" should be lower-case.

     a. Add as the second bulleted substatement "if using other ophthalmic products while using this product, wait at least 5 minutes between each product".

     b. Make the third bulleted substatement "replace cap after each use".

     c. For the second bulleted subheading "Children under 2 years of age:" left-justify and align with the first bulleted subheading. Note that the "c" in "Children" and "Consult" should be lower-case.

5. Under the ***Inactive ingredients*** heading, list the inactive ingredients in alphabetical order for drug products. (21 CFR 201.66(c)(8))

iii. Immediate Container Label

1. Revise the SOI such that "ophthalmic solution" is on the same line (Refer to A.i.c.3 above).

2. Delete the word (b) (4) from the SOI (Refer to A.i.c.1 above).

3. Increase the font size of the SOI and present in bold face type as requested above for the PDP (Refer to A.i.c.2 above).

B. Two x 2.5 mL bottles (0.085 FL OZ EACH)

i. Outer Carton Label Outside Drug Facts

Refer to the changes requested above for the 2.5 mL carton PDP.

ii. Outer Carton Drug Facts Label

Refer to the changes requested above for the 2.5 mL carton DFL.

iii. Immediate Container Label

Refer to the changes requested above for the 2.5 mL bottle container label.

C. 0.5 mL (0.017 Fl oz) – SAMPLE

i. Outer Carton Label Outside Drug Facts

Principal Display Panel:

a. Remove the word (b) (4)" and the asterisk following it from " (b) (4) (b) (4) ….." and replace with "Relief from allergens…." in accordance with prior approved OTC Pataday products.

b. Increase the prominence of the "Once Daily Relief in accordance with other approved OTC Pataday products.

c. Revise the Statement of Identity (SOI) as follows:

1. Revise the proposed SOI from "Olopatadine hydrochloride ophthalmic solution 0.7% (b) (4) Antihistamine" by removing the word (b) (4)" from the (b) (4).

2. Enlarge the font of the SOI and present in bold face type. The regulations (21 CFR 201.61(c)) state the SOI shall be "a size reasonably related to the most prominent printed matter…". We recommend that the font size be at least 25% of the most prominent printed matter (i.e. the proprietary name as currently proposed).

3. Revise the SOI such that "ophthalmic" and "solution" are on the same line and there is no break between them. This would be consistent with other approved OTC Pataday products.

d. Revise the claim [redacted] (b) (4) to read "Eye Allergy Itch Relief" to be consistent with products in this category.

Side Panel:

1. Revise claim [redacted] (b) (4) " to read "Eye Allergy Itch Relief.

2. Increase the prominence of the tamper evident feature statements. The regulations at CFR 211.132(c)(ii) state that labeling be "prominently placed….". You may consider changing or bolding the font size.

3. Delete or revise "[redacted] (b) (4) " if no longer appropriate.

Top Panel:

1. Enlarge the font of the SOI and present in bold face type.

2. Revise the claim [redacted] (b) (4) " to "Eye Allergy Itch Relief to be consistent with products in this category.

3. Revise the SOI such that "ophthalmic" and "solution" are on the same line and there is no difference between them.

Back panel (Outside Drug Facts):

1. Under Drug Facts box, remove the claim [redacted] (b) (4) [redacted] (b) (4)

ii. Outer Carton Drug Facts Label

Drug Facts must be in accordance with content and format modifications set forth under CFR 201.66. Confirm the font and format specifications using annotated labeling.

1. Revise horizontal hairlines to not extend on either side to each end of the Drug Facts box. "A horizontal hairline extending within two spaces on either side

of the "Drug Facts" box or similar enclosure shall immediately follow the title and shall immediately precede each of the subheadings set forth in paragraph (c)(5)(ii)(A) through (c)(5)(ii)(G) of this section." (21 CFR 201.66(d)(8))

2. Under the (b) (4) heading, begin the (b) (4) statement with lower case "t" because only headings and subheadings use an upper-case letter for the first word (i.e., (b) (4)"). Lowercase letters are used for all other words (i.e., temporarily…").

3. Under the **When using this product** subheading:

   - Delete the bulleted statement (b) (4) (b) (4)

   - Add the new bulleted statement "do not wear a contact lens if your eye is red" as the last bulleted statement.

4. Under the ***Directions*** heading make the following revisions:

   - Under the bulleted subheading "**Adults and children 2 years of age and older:**" we recommend starting a new line, to create indented bulleted substatements starting with "put 1 drop…". Note that the "p" in "put" is lowercase, as the first bulleted substatement. Note also that the "a" in "Adults" should be lower-case.

     a. Add as the second bulleted substatement "if using other ophthalmic products while using this product, wait at least 5 minutes between each product".

     b. Make the third bulleted substatement "replace cap after each use".

     c. For the second bulleted subheading "Children under 2 years of age:" left-justify and align with the first bulleted subheading. Note that the "c" in "Children" and "Consult" should be lower-case.

5. Under the ***Inactive ingredients*** heading, list the inactive ingredients in alphabetical order for drug products (21 CFR 201.66(c)(8)).

iii. Immediate Container Label

1. Revise the SOI such that "ophthalmic solution" is on the same line.

2. Delete the word (b) (4) from the SOI.

3. Increase the font size of the SOI and present in bold face type as requested above for the PDP.

iv. Pouch

1. Revise the SOI such that "ophthalmic solution" is on the same line.
2. Delete the word (b) (4) from the SOI.

REVIEWER'S RECOMMENDATIONS

The labeling revisions required of the sponsor are stated above (as requested in the Information Request of June 19, 2020).

The sponsor should submit actual size (i.e., at 100%) immediate container labels and carton labeling and confirm by annotating the submitted labels and labeling with ("Actual Size, 100%"). The sponsor should submit annotated labeling for all revisions.

In addition, the sponsor may use the alternate color scheme ("Green") proposed in their email to Senior Regulatory Project Manager, LCDR Jung Lee on June 17, 2020 if the changes to the carton and container labels as outlined above are made.

The sponsor is requested to submit labeling revisions by June 25, 2020.

The sponsor should be advised that the revisions requested do not designate an approval decision. More labeling comments may be forthcoming.

The sponsor will be asked to provide clean labeling without annotation (i.e., free of annotated DFL specification and free of the annotated color specification) once all the revisions are satisfactorily made.

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ARLENE H SOLBECK
06/23/2020 07:39:10 AM

SERGIO N COELHO
06/23/2020 10:49:30 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Memo

Date:	February 18, 2020
Reviewer:	Regina Lee, PharmD Division of Pharmacovigilance II
Team Leader:	Lynda McCulley, PharmD, BCPS Division of Pharmacovigilance II
Division Director:	S. Christopher Jones PharmD, MPH, MS Division of Pharmacovigilance II
Product Name:	Pazeo (olopatadine hydrochloride ophthalmic solution 0.7%)
Subject:	Serious adverse events
Application Type/Number:	NDA 206276
Applicant/Sponsor:	Alcon Laboratories, Inc. (Novartis)
OSE RCM #:	2019-2461

Special acknowledgement to Manish Kalaria, MD (Neuro-ophthalmologist), Medical Officer, Regulatory Science Staff, for his contribution to this memorandum.

EXECUTIVE SUMMARY

On September 13, 2019, Alcon Laboratories (sponsor) submitted a supplemental New Drug Application (sNDA, 206276/S-005) to FDA for a complete prescription (Rx) to over-the-counter (OTC) switch of Pazeo (olopatadine hydrochloride ophthalmic solution 0.7%). The Division of Pharmacovigilance (DPV) was consulted by the Office of Nonprescription Drug Products (ONDP) to evaluate reports of serious adverse events (SAEs) associated with Pazeo. This DPV memorandum will be used to inform the ONDP review team at the sNDA mid-cycle meeting, scheduled in February 2020. To conduct this evaluation, we reviewed adverse events reported to the FDA Adverse Event Reporting System (FAERS) through December 22, 2019, the sponsor's Summary of Clinical Safety 120-Day Safety Update Report, and most recent Periodic Adverse Drug Experience Report (PADER).

Of note, the ONDP consult requested DPV review the following serious adverse events (SAEs) of interest: misuse, death, blindness, corneal abrasion, and hypersensitivity. For the purposes of this review and to capture all SAEs associated with Pazeo, we broadened and categorized these adverse events as misuse, death, and ocular and non-ocular events.

We identified 26 FAERS cases associated with Pazeo 0.7% ophthalmic solution use that reported misuse (n=2), death (n=1), ocular SAEs (n=19), and non-ocular SAEs (n=4). The top five reported PTs among all PTs were *Eye irritation*, *Hypersensitivity*, *Ocular hyperaemia*, *Glaucoma*, and *Vision blurred*.

- In the misuse cases (n=2), the contributory role of Pazeo **could not be excluded** in one case of corneal abrasion associated with the concomitant use of Pazeo and contact lens. The second case did not provide sufficient information for assessment.

- In the death case (n=1), the contributory role of Pazeo was indeterminate due to the lack of clinical information provided.

- In the ocular SAEs cases (n=19), the contributory role of Pazeo **could not be excluded** in eight cases; the PTs described in these cases include *Blindness* (n=1), *Corneal abrasion* (n=2), *Hypersensitivity* (n=2), *Eye irritation* (n=1), *IOP increased* (n=1), and *Periorbital swelling* (n=1). We note that exposure to benzalkonium chloride in Pazeo solution has been associated with allergic contact sensitivity and corneal neurotoxicity and inflammation; although the extent of its contribution to the aforementioned ocular events is unclear. The contributory role of Pazeo was indeterminate in 11 cases due to the lack of clinical information provided.

- In the non-ocular SAEs cases (n=4), which include *Tachycardia* (n=1), *Metal poisoning* (n=1), *Migraine* (n=1), *and Lung disorder* (n=1), the contributory role of Pazeo was indeterminate given the lack of clinical information, including temporal association, past medical history, concomitant medications, and clinical outcome.

Our review of the sponsor's data confirms that the SAEs reported in the PADER and Summary of Clinical Safety are consistent with those reported in FAERS.

In DPV's opinion, the limited FAERS cases we identified are not sufficient to predict the misuse potential of Pazeo. Therefore, if a concern for potential misuse remains, DPV recommends that ONDP consider requesting the sponsor provide in their annual periodic reports a summary of worldwide experience of all misuse cases.

1 INTRODUCTION

On September 13, 2019, Alcon Laboratories (sponsor) submitted a supplemental New Drug Application (sNDA, 206276/S-005) to FDA for a complete prescription (Rx) to over-the-counter (OTC) switch of Pazeo (olopatadine hydrochloride ophthalmic solution 0.7%). The Division of Pharmacovigilance (DPV) was consulted by the Office of Nonprescription Drug Products (ONDP) to evaluate reports of serious adverse events (SAEs) associated with Pazeo. This DPV memorandum will be used to inform the ONDP review team at the sNDA mid-cycle meeting, scheduled in February 2020. The Prescription Drug User Fee Goal Date is July 13, 2020. To conduct this evaluation, we reviewed adverse events reported to the FDA Adverse Event Reporting System (FAERS) through December 22, 2019, the sponsor's Summary of Clinical Safety 120-Day Safety Update Report, and most recent Periodic Adverse Drug Experience Report (PADER).

Of note, the ONDP consult requested DPV review the following serious adverse events (SAEs) of interest: misuse, death, blindness, corneal abrasion, and hypersensitivity. For the purposes of this review and to capture all SAEs associated with Pazeo, we broadened and categorized these adverse events as misuse, death, and ocular and non-ocular events.

1.1 REGULATORY HISTORY

Pazeo, a mast cell stabilizer and a histamine H1 antagonist, was FDA-approved on January 30, 2015 for the treatment of ocular itching associated with allergic conjunctivitis.[1] The recommended dosage is one drop in each affected eye once daily.[1] Pazeo's formulation contains the active ingredient olopatadine hydrochloride, the inactive ingredients benzalkonium chloride 0.015% (preservative), boric acid, hydrochloric acid/sodium hydroxide, hydroxypropyl-gamma-cyclodextrin, hydroxypropyl methylcellulose, mannitol, polyethylene glycol 400, and povidone, and purified water.[1] Of note, exposure to benzalkonium chloride, the preservative in Pazeo solution, has been associated with allergic contact sensitivity.[2]

DPV completed a Pediatric Postmarketing Pharmacovigilance Review for Pazeo dated November 21, 2017, which did not identify any pediatric SAEs or new pediatric safety concerns.

Two other FDA-approved ophthalmic products containing the active ingredient olopatadine hydrochloride are olopatadine 0.1% (Patanol) and 0.2% (Pataday), which were FDA-approved on December 18, 1996 and December 22, 2004, respectively. Like Pazeo, both products are indicated for the treatment of allergic conjunctivitis.[3,4] Like Pazeo, the recommended dosage for Pataday is one drop in each affected eye once daily; however, the recommended dosage for Patanol is one drop in each affected eye two times per day at an interval of 6-8 hours.[3,4] On April 15, 2019, the sponsor submitted a sNDA for a complete Rx to OTC switch of both Patanol (sNDA 020688/S-032) and Pataday (sNDA 021545/S-022), which were approved on February 14, 2020.[5]

1.2 RELEVANT PRODUCT LABELING

Pazeo is labeled under *Warnings and Precautions* for possible contamination and irritation with contact lens use.[1] The most commonly reported adverse events under *Adverse Reactions* include blurred vision, dry eye, superficial punctate keratitis, dysgeusia and abnormal sensation in the eye.[1] Select sections of the Pazeo product labeling are highlighted in **Appendix A**.

2 METHODS AND MATERIALS

2.1 FAERS

DPV searched the FAERS database with the strategies described in **Table 1**. Search 1 was a query of all serious adverse events with Pazeo, while search 2 was specifically performed to identify cases of misuse, as requested by ONDP.

Table 1. FAERS Search Strategies*

	Search 1	Search 2
Date of Search	December 23, 2019	
Time Period of Search	January 30, 2015† - December 22, 2019	
Search Type	FBIS Quick Query	
Product Terms	Product Name‡: Pazeo Product Verbatims‡: Pazeo 0.7% Alcon, Pazeo 0.7 0phth solution 2.5 mL, Pazeo olopatadine hydrochloride ophthalmic solution 0.7%, Pazeo dro 0.7%, Pazeo 0.7 percentage, Pazeo 0.7%, Pazeo (eye drops), Pazeo, Pazeo dro, Pazeo 0.7% ophthalmic solution, Pazeo eye drops, Pazeo eye drops lorazepam	Product Active Ingredient: Olopatadine, Olopatadine hydrochloride
MedDRA Search Terms (Version 22.1)	All	*Drug abuse and dependence (SMQ) Broad search*
Serious Outcome	Serious	N/A

* See **Appendix B** for a description of the FAERS database.
† U.S. Approval date
‡ ONDP clarified that the request was for FAERS data specific to the Pazeo 0.7% product, and not the Patanol 0.1% or Pataday 0.2% products.
N/A=Not applicable

2.2 SPONSOR'S DATA

In addition to the FAERS data, DPV reviewed the following data submitted by the Sponsor:

- Summary of Clinical Safety for Olopatadine Ophthalmic Solution 120-Day Safety Update Report for the period January 1, 2019 to October 31, 2019.[6,7] Of note, the Summary of Clinical Safety was submitted as two separate documents.
- Periodic Adverse Drug Experience Report (PADER) submission for the period January 30, 2018 to January 29, 2019.[8]

2.3 CASE DEFINITION

We included FAERS cases involving Pazeo and excluded cases that were associated with Patanol or Pataday, or did not report adverse events. We excluded Patanol and Pataday reports because the concentration of drug is lower in both of these formulations, compared to Pazeo.

To capture cases of misuse[a], we used the following inclusion criteria.

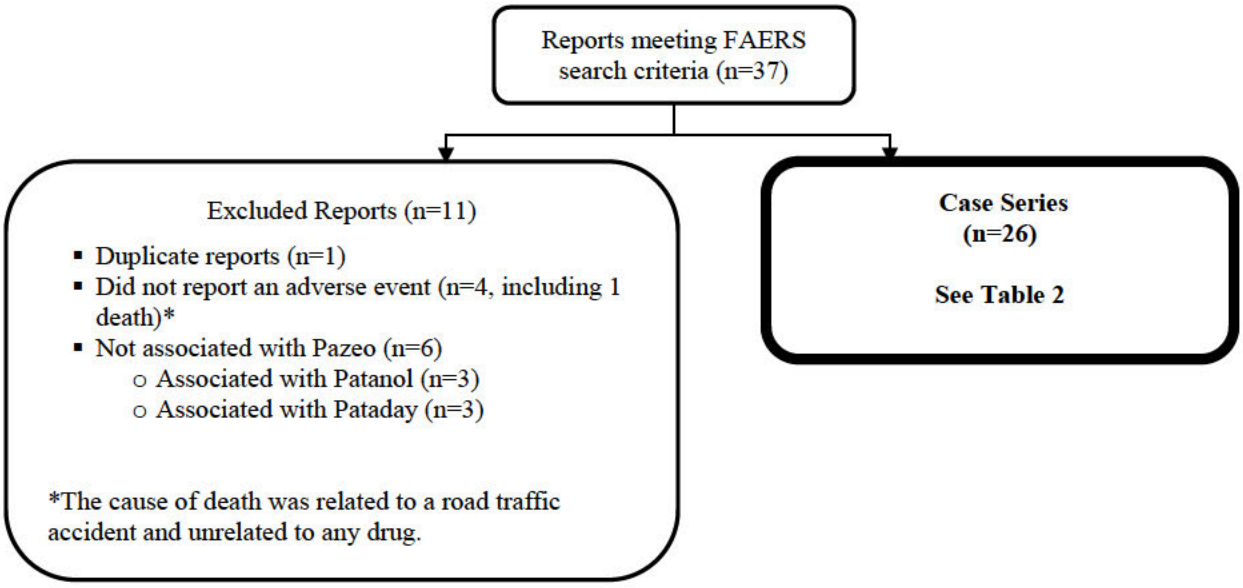
A case that reports one or more of the following criteria (#1 OR #2):

1. A term(s) describing "drug misuse" is stated in the narrative with or without clinical manifestations associated with drug misuse of Pazeo.
2. Clinical assessment by the reviewer of drug misuse based on the provided case details [e.g., National Institute on Drug Abuse (NIDA) criteria[9] such as intentionally taking higher than prescribed doses or for an indication other than its intended use].

3 RESULTS

The FAERS searches 1 and 2 described in **Table 1** retrieved a total of 37 reports, including 29 reports from the FAERS search 1 (all SAEs) and eight reports from the FAERS search 2 (misuse). After accounting for one duplicate and excluding cases that were not associated with Pazeo or did not report adverse events, 26 cases were included for analysis (see **Figure 1**).

Figure 1. FAERS Case Selection



[a] "Drug misuse" is defined by the National Institute on Drug Abuse as follows: Taking a medication in a manner or dose other than prescribed; taking someone else's prescription, even if for a legitimate medical complaint such as pain; or taking a medication to feel euphoria (i.e., to get high).

Table 2 summarizes the characteristics of the 26 FAERS cases with Pazeo received by FDA through December 22, 2019. **Appendix C** contains a line listing of the 26 FAERS cases.

Table 2. Descriptive Characteristics of FAERS Cases Reporting Serious Adverse Events or Misuse with Pazeo, Received by FDA through December 22, 2019 N=26		
Sex	Female	19
	Male	6
	Not reported	1
Age (years)	17-64	12
	≥65	2
	"Elderly"	1
	Not reported	11
Country	United States	25
	Foreign	1
Report type	Expedited	17
	Non-expedited	3
	Direct	6
Serious outcomes (n=25)*	Death	1
	Hospitalization	2
	Other serious	24
All SAEs	**Death**	**1**
	Ocular SAEs†	**19**
	Blindness	2
	Blindness transient	1
	Corneal abrasion	2
	Hypersensitivity‡	3
	Drug hypersensitivity	1
	Eye irritation	3
	Glaucoma	3
	IOP increased	1
	Iridocyclitis	1
	Ocular hypertension	1
	Periorbital swelling	1
	Vision blurred	2
	Misuse§	**2**
	Intentional Product Misuse	1
	Incorrect Dose Administered	1
	Non-Ocular SAEs	**4**
	Lung disorder	1
	Metal poisoning	1
	Migraine	1
	Tachycardia	1

* The following outcomes qualify as serious: death, hospitalization (initial or prolonged), and other serious important medical events. A report may have one or more outcome.
† There were 19 cases involving ocular SAEs that reported multiple PTs. A case may contain one or more PTs.
‡ One of the cases reported hypersensitivity related to the eye. The remaining two cases did not provide sufficient detail to determine whether the hypersensitivity was related to the eye.

Table 2. Descriptive Characteristics of FAERS Cases Reporting Serious Adverse Events or Misuse with Pazeo, Received by FDA through December 22, 2019 N=26
§ One case of misuse, which did not report serious outcomes, was captured under the PT *Intentional Product Misuse* (n=1). The second case was not coded for misuse and was captured under the PT *Incorrect Dose Administered* (n=1). Definitions: IOP = intraocular pressure

Table 3 contains the reported MedDRA preferred terms (PTs) of interest (death, blindness, corneal abrasion, hypersensitivity, and misuse) and ocular PTs per ONDP's consult request and the respective labeling status in the Pazeo product label.[1] Four cases were excluded due to no adverse event reported, and those PTs were not included in the table below. **Appendix D** contains a listing of all reported PTs and their respective labeling status in the Pazeo product label. The PTs of interest are characterized in **Section 3.1.1, 3.1.2, and 3.1.3**. Other non-ocular PTs are characterized in **Appendix E**.

Table 3. MedDRA PTs of Interest and Ocular PTs associated with Pazeo, Received by FDA through December 22, 2019, Sorted by Decreasing Number of FAERS Reports per PT*

	MedDRA PT	Number of FAERS Reports	Labeled (Yes/No), Location or Other Category†
1	Eye irritation	3	N
2	**Hypersensitivity**	3	N
3	Ocular hyperaemia	3	N
4	Glaucoma	3	N
5	Eye pain	3	N
6	Vision blurred	2	Y, AR
7	Lacrimation increased	2	N
8	**Blindness**	2	N
9	Visual impairment	2	N
10	**Corneal abrasion**	2	N
11	Swelling of eyelid	2	N
12	Eye pruritus	1	N
13	Periorbital swelling	1	N
14	Erythema of eyelid	1	N
15	Visual acuity reduced	1	N
16	Eye discharge	1	N
17	Ocular hypertension	1	N
18	Eye inflammation	1	N
19	Punctate keratitis	1	Y, AR
20	Uveitis	1	N
21	Ciliary hyperaemia	1	N
22	**Blindness transient**	1	N
23	Eye swelling	1	N
24	Eyelids pruritus	1	N
25	Periorbital pain	1	N
26	**Death**	1	N
27	Conjunctivochalasis	1	N
28	Blepharospasm	1	N
29	Instillation site pain	1	N
30	Intraocular pressure decreased	1	N
31	**Drug hypersensitivity**	1	N
32	Intraocular pressure increased	1	N

Table 3. MedDRA PTs of Interest and Ocular PTs associated with Pazeo, Received by FDA through December 22, 2019, Sorted by Decreasing Number of FAERS Reports per PT*			
33	Iridocyclitis	1	N
34	Cataract	1	N
35	**Intentional product misuse**	1	N
* A report may contain more than one MedDRA PT. The PTs in bold are the PTs of interest per ONDP's consult request. † SAEs of interest are characterized in **Section 3.1.1, 3.1.2, and 3.1.3**. Other non-ocular SAEs are characterized in **Appendix E**. Definitions: AR=Adverse Reactions			

3.1 FAERS

The FAERS searches 1 and 2 described in **Table 1** retrieved 26 cases of SAEs with Pazeo. The cases describing adverse events of interest, including misuse (n=2), death (n=1), and ocular SAEs (n=19) are characterized below in **Sections 3.1.1, 3.1.2, and 3.1.3**. The remaining cases describing non-ocular SAEs (n=4) are characterized in **Section 3.1.4** and **Appendix E**.

3.1.1 Summary of Misuse Adverse Events (N=2)

FAERS Case # 12126628, USA, Non-expedited, 2016
PTs: Corneal abrasion, Device physical property issue, Intentional product misuse, Scleral disorder
A 38-year-old male with allergic rhinitis and conjunctivitis received Pazeo for atopic conjunctivitis at a dose of one drop once daily. On an unknown date, he used Pazeo "with his contact lens" (intentional product misuse), which caused damage to the contact lens (lenses fragmented) and led to a corneal abrasion from the fragmented contact lens. On an unknown date within two months of starting Pazeo the patient developed "ulcerations" of the sclera (scleral disorder). Treatment with Pazeo was discontinued after 51 days. Concomitant medications were not reported. The events resolved on an unknown date. The physician states that the event was related to the use of Pazeo.

Reviewer's Comments: The contributory role of Pazeo cannot be excluded given that the corneal abrasion occurred with the misuse of Pazeo while wearing contact lens. Although the event corneal abrasion is unlabeled, this event occurred secondary to the misuse of Pazeo. We also note that the product label advises against the concomitant use of soft contact lens under Warnings and Precautions and Patient Counseling Information.[1]

FAERS Case # 15596279, Foreign, Expedited, 2018
PTs: Cataract, Concomitant disease aggravated, Drug ineffective, Eye pain, Incorrect dose administered, Vision blurred
A female of unspecified age with pre-existing eye pain received Pazeo eye drops twice daily for the treatment of itchy eyes from an unknown date at an unknown dose. Past medical history and concomitant medications were not reported. She instilled Pazeo "three or four times a day" and felt it was not working. She stopped taking the product for three weeks but still complained of blurry vision. She believes she was "using it too much/too many times" (incorrect dose administered). She was told that itchiness and blurred vision were expected side effects of Pazeo and that if she stopped the product, the side effects should subside with time. Pazeo was discontinued on an unknown date. The outcomes of the events incorrect dose administered, eye

pain, concomitant disease aggravated, drug ineffective and cataract were not reported. The outcome of the event vision blurred was reported as unchanged. Further investigation yielded no manufacturing-related cause for the reported lack of efficacy of the Pazeo product.

Reviewer's Comments: The contributory role of Pazeo cannot be determined given the lack of information on temporal association, past medical history, concomitant medications, and clinical outcome. Additionally, it is unknown to what extent the overuse of Pazeo contributed to the ocular symptoms. We also note that Pazeo is labeled for blurred vision under Adverse Reactions.[1] Of note, although misuse was not included in the MedDRA coding, this case described the misuse of Pazeo eye drops at a frequency of three to four times the recommended frequency.

3.1.2 Summary of Death

3.1.2.1 Death

FAERS Case # 16921599, USA, Expedited, 2019
PTs: Death
A 77-year-old male received octreotide and Pazeo for an unknown indication from an unknown date. Past medical history and concomitant medications were not reported.
The patient died. It was unknown if an autopsy was performed. No additional information was provided.

Reviewer's Comments: The contributory role of Pazeo cannot be determined given the lack of information on temporal association, past medical history, concomitant medications, clinical course, and cause of death.

3.1.3 Summary of Ocular Serious Adverse Events (N=19)

3.1.3.1 Blindness, Blindness transient

FAERS Case # 13333654, USA, Expedited, 2017
PTs: Blindness, Drug ineffective, Erythema, Eye irritation, Eye pruritus, Ocular hyperaemia, Periorbital pain, Vision blurred, Visual acuity reduced
A 57-year-old male received Pazeo eye drops for an unknown indication from an unknown date at a dose of one drop twice daily for 14 days. On an unknown date, Pazeo alleviated the redness and irritation in his eyes with the morning dose but a few hours later, the eye became cloudy (vision blurred) and irritated (eye irritation) again. The night dose alleviated the symptoms but his eye became red (ocular hyperaemia), irritated, painful, and itchy in the morning. It was also painful behind the eye socket. The patient stated he was considered legally blind and could see shapes only but could not focus on anything (visual acuity reduced). Treatment with Pazeo was stopped on an unknown date and switched to a new medication (unspecified). The outcome of the events was not reported. Past medical history and concomitant medications were not reported.

Reviewer's Comments: The contributory role of Pazeo cannot be excluded based on a temporal association of "a few hours" from Pazeo exposure to the onset of the ocular symptoms.

However, the time to onset from Pazeo exposure to the onset of visual acuity reduced and blindness is unclear. We note that potential alternate etiologies cannot be excluded, as information on past medical history, concomitant medications, clinical outcome, and contact lens use or presence of trauma is lacking. Additionally, several of the reported ocular symptoms are commonly associated with allergic conjunctivitis.

FAERS Case # 14119738, USA, Expedited, 2017
PTs: Blindness, Product quality issue
An 83-year-old male with the concurrent conditions of unspecified "vision problems", hypertension (HTN), diabetes (DM), and hypercholesterolemia received Pazeo (lot number 247048F) for the treatment of itchy eyes. Concomitant medications included "blood thinners and multiple medications for HTN, DM, and hypercholesterolemia". He administered Pazeo for about 4-5 days, at which time the Pazeo solution looked clear. Because he wanted to ensure easy access to the eye drops, he stored the bottle upside down with the top tightly sealed, after which the appearance of the eye drops became milky white in color (product quality issue). The patient reported that he "was blind", stating that he "has had vision problems". The outcome of the event blindness and action taken with Pazeo were not reported. The Pazeo sample was provided to the manufacturer's quality assurance (QA) department for analysis; however, because the sample was open and did not contain any ophthalmic solution, a conclusive root cause could not be determined. Additionally, no manufacturing-related root causes were found during the investigation. The QA department noted that consumer perception and consumer mishandling could not be eliminated as a potential root cause for this complaint. Review of the complaint history and chemical/microbial release data found no issues which could have contributed to this complaint. A total of one complaint was identified for lot 267048F reporting an issue with the color of the solution.

Reviewer's Comments: The contributory role of Pazeo cannot be determined given the lack of information on temporal association, clinical course, concomitant medications, clinical outcome, the action taken the Pazeo, and contact lens use or presence of trauma. The case narrative describes a change in the color of the Pazeo solution, which alludes to the possibility of contamination, which is a labeled event under the Warnings and Precautions section.[1] Additionally, further assessment by the sponsor's QA department did not identify a root cause and could not exclude mishandling of the product.

FAERS Case # 12416649, USA, Expedited, 2016
PTs: Blindness transient
Two patients of unspecified age and gender received Pazeo (batch/lot number unknown) for an unknown indication and experienced "lost vision for a short period of time" (blindness transient). Past medical history and concomitant medications were not reported. No other information was provided.

Reviewer's Comments: The contributory role of Pazeo cannot be determined given the lack of information on temporal association, past medical history, concomitant medications, clinical course, clinical outcome, the action taken with Pazeo, and contact lens use or presence of trauma.

3.1.3.2 Corneal abrasion

FAERS Case # 12491906, USA, Direct, 2016
PTs: Corneal abrasion, Eye inflammation, Eye pain, Eye swelling, Instillation site pain, Lacrimation increased, Ocular hyperaemia, Product quality issue
A 56-year-old female received a new prescription for Pazeo for "eye allergy" and applied one drop in each eye at 7:30 am. The first drop placed in the right eye caused severe burning immediately. The patient unsuccessfully tried to flush it out with copious amounts of water. She described the pain as "something in my eye as the pain moved around and was similar to a corneal abrasion but not as severe." She contacted the prescribing ophthalmologist but was unable to reach her. The right eye was inflamed around the tear duct and lower inside lid. The right eye pain (4/10 on the pain scale) continued for approximately four hours with profuse tearing and subsided thereafter. The right eye was itchy, swollen and watery until bedtime and "oozed most of the night". By the next morning, the redness was mostly resolved with minimal swelling and itchiness. The left eye was unaffected. The patient decided not to see the doctor the day after and to continue monitoring.

Reviewer's Comments: The contributory role of Pazeo cannot be excluded based on the immediate temporal association from Pazeo exposure to the onset of severe burning. However, we note that potential alternate etiologies cannot be excluded, as information on past medical history, concomitant medications, and information on contact lens use[b] or presence of trauma is lacking.

FAERS Case # 13792262, USA, Expedited, 2017
PTs: Corneal abrasion
A female patient of unspecified age instilled Pazeo into her eye for an unknown indication right before going to sleep and woke up with a "ripped cornea (corneal abrasion)". It was treated with "placing a (bandage) contact lens" and healed after about a month. The action taken with Pazeo was not reported. Past medical history and concomitant medications were not reported.

Reviewer's Comments: The contributory role of Pazeo cannot be excluded based on the temporal association of several hours from Pazeo exposure to the onset of the corneal abrasion. However, we note that potential alternate etiologies cannot be excluded, as information on past medical history, concomitant medications, and information on contact lens (non-bandage) use or presence of trauma is lacking.

3.1.3.3 Hypersensitivity

FAERS Case # 16018100, USA, Direct, 2019
PTs: Drug hypersensitivity, Erythema of eyelid, Eyelids pruritus, Swelling of eyelid
A 35-year-old female instilled one drop of Pazeo in each eye for "pollen allergy". On the second day, within 15 minutes of Pazeo instillation, both eyelids swelled and became red and itchy. Past medical history includes environmental and drug allergies to pollen, trees, mold, dust mites, tetracycline, blue dye, and acetaminophen/tramadol (Ultracet), and sensitivities to wheat, corn,

[b] Pazeo is labeled under *Warnings and Precautions* for possible contamination and irritation with contact lens use.

soy, sodium metabisulfite, kale, avocado, bananas, cow's milk, barley, cane sugar, cantaloupe, blue #1, blue #2, yellow #5, lentils, monosodium glutamate, pecan, pistachio, and cucumber. Concomitant medications, outcome of the aforementioned adverse events, and action taken with Pazeo were not reported.

Reviewer's Comments: The contributory role of Pazeo cannot be excluded based on a temporal association and 15 minute onset from Pazeo exposure to the onset of drug hypersensitivity, described as eyelid swelling, erythema, and pruritis. We note that exposure to benzalkonium chloride in Pazeo solution has been associated with allergic contact sensitivity.[2] We also cannot exclude potential alternate etiologies related to environmental factors, concomitant medications, contamination of the Pazeo solution, contact lens use, or the presence of trauma, as this information was not provided.

FAERS Case # 11246237, USA, Direct, 2015
PTs: Blepharospasm, Hypersensitivity, Swelling of eyelid, Urticaria, Visual impairment
A 59-year-old healthy female with no known drug allergies or concomitant medications received Pazeo eye drops from a nurse practitioner (the reporter) for allergic conjunctivitis (day 0). On day 1, within one minute of Pazeo self-instillation, the patient experienced swelling of the bilateral lower eyelids with twitching of the lower eye muscles and one large welt on the outer aspect of her right eye without pruritis. These symptoms improved throughout the day but did not resolve. Pazeo was discontinued. On day 2, the patient complained of slightly swollen lower eyelids and continuous twitching of the left lower eyelid, which were also observed at her follow-up appointment on day 3. She described her vision to be "like a film over her left eye". She did not experience any shortness of breath. The nurse practitioner advised her not to use this product again in the setting of a new allergic reaction. No information was provided on the treatment of the adverse event or the clinical outcome.

Reviewer's Comments: The contributory role of Pazeo cannot be excluded based on the temporal association and one minute onset from Pazeo exposure to the onset of blepharospasm, hypersensitivity, and visual impairment. We note that exposure to benzalkonium chloride in Pazeo solution has been associated with allergic contact sensitivity and corneal neurotoxicity and inflammation.[2,10] Notably, this case does not describe any potential alternate etiologies given the absence of comorbid conditions or concomitant medications. The presence or absence of contact lens use, however, was not reported.

FAERS Case # 15515654, USA, Expedited, 2018
PTs: Asthma, Hypersensitivity
A 38-year-old female received Pazeo for an unknown indication from an unknown date at an unknown dose and frequency. Past medical history and concomitant medications were not reported. On an unknown date, the patient had allergies (hypersensitivity) and asthma. The outcome of the events asthma and hypersensitivity and the action taken with Pazeo were not reported. No additional information was provided. This case was lost to follow-up.

Reviewer's Comments: The contributory role of Pazeo cannot be determined given the lack of information on temporal association, past medical history, concomitant medications, clinical course, clinical outcome, and the action taken with Pazeo. It is also unclear whether the eye was

affected by the hypersensitivity. We note that exposure to benzalkonium chloride in Pazeo solution has been associated with allergic contact sensitivity.[2]

FAERS Case # 16244604, USA, Expedited, 2019
PTs: Hypersensitivity, Syncope
An adult female of unspecified age received Pazeo for the treatment of an unknown indication on an unknown date at an unknown dose and frequency. Past medical history and concomitant medications were not reported. On an unknown date, the patient reported "being on the medication and recently hospitalized due to bad allergies (hypersensitivity)" and also said she fainted (syncope). The action taken with Pazeo was not reported. The outcome of the events hypersensitivity and syncope was not reported. No additional information was provided.

Reviewer's Comments: The contributory role of Pazeo cannot be determined given the lack of information on temporal association, past medical history, concomitant medications, clinical course, clinical outcome, and the action taken with Pazeo. It is also unclear whether the eye was affected by the hypersensitivity. We note that exposure to benzalkonium chloride in Pazeo solution, has been associated with allergic contact sensitivity.[2]

3.1.3.4 Eye irritation[c]

FAERS Case # 14240111, USA, Direct, 2017
PTs: Eye irritation, Lacrimation increased, Rhinorrhoea
A 55-year-old female instilled Pazeo eye drops in both eyes and experienced stinging and burning in the left eye a few minutes later. Because the left eye began to tear more, this caused the "left nostril to run". No additional information was provided.

Reviewer's Comments: The contributory role of Pazeo cannot be excluded based on the temporal association of "a few minutes" from Pazeo exposure to the onset of eye irritation, lacrimation increased, and rhinorrhea. However, we note that potential alternate etiologies cannot be excluded, as information on past medical history, concomitant medications, clinical outcome, contact lens use, and presence of trauma is lacking.

FAERS Case # 15434230, USA, Expedited, 2018
PTs: Eye irritation
A female of unspecified age received Pazeo for an unknown indication from an unknown date. On an unknown date, she reported the feeling of burning in her eye (left or right unspecified). She inquired about the stability of Pazeo drops at temperatures above 90 degrees and was informed that Pazeo should be stored at 36 to 77 degrees Fahrenheit and that the bottle should be tightly closed when not in use. Past medical history and concomitant medications were not reported. The outcome and action taken with Pazeo were unknown.

Reviewer's Comments: The contributory role of Pazeo cannot be determined given the lack of information on temporal association, past medical history, concomitant medications, clinical course, clinical outcome, the action taken with Pazeo, contact lens use, and presence of trauma.

[c] One additional case (#15728796) of eye irritation is included under section 3.1.3.5.

Additionally, the extent to which temperature-related storage issues possibly contributed to this event is unknown.

3.1.3.5 Glaucoma

FAERS Case # 13537488, USA, Expedited, 2017
PTs: Ciliary hyperaemia, Conjunctivochalasis, Depression, Eye pain, Glaucoma, Inappropriate schedule of product administration, Intraocular pressure decreased, Meibomian gland dysfunction, Punctate keratitis, Uveitis, Visual impairment
A 61-year-old female with chronic uveitis, glaucoma, shunt in left eye, allergic conjunctivitis, surgical diode in left eye, phacoemulsification with posterior chamber intraocular lens implantation in both eyes, double vision (caused by shunt), bilateral cataract surgery, "losing eye sight", asthma, gastroesophageal reflux disease, hypothyroidism, depression, and partial hysterectomy was prescribed cyclosporine 0.5mg/mL ophthalmic drops (Restasis) at a dose of two drops twice daily for extremely dry eyes, which she "sometimes used up to four times a day". She also started using Pazeo at the same time as the Restasis for dry eyes due to allergy. Dryness improved in both eyes. On an unspecified date after starting Restasis, she complained that her underlying glaucoma and uveitis were sometimes improved and sometimes worse. She experienced a dull ache in her left eye and her visual acuity fluctuated. After 1-2 years (exact timeframe unspecified), the pressure in her left eye "went up to 20 something and she had to have a laser surgery to correct it". Ocular exam showed pupils equal round and reactive in both eyes, no afferent pupillary defect, confrontation fields full to finger counting, equal ocular movement in both eyes, normal adnexa of both eyes. In the right eyelid, only papillary reaction of conjunctiva improved from previous Meibomian glandular dysfunction. Slit lamp examination showed bilateral eye conjunctiva chalasis follicles and mild ciliary flush. Both corneas had decreased tear film with interior superficial punctate keratitis foamy tears. The iris in both eyes was normal. Interior chamber: "right eye was deep and quiet, left eye tube shunt trace fell". Treatment included Bruder Mask, lid hygiene, brinzolamide/brimonidine (Simbrinza), mineral oil (Retaine) ophthalmic emulsion, difluprednate (Durezol), prednisone, HydroEye® nutritional formulation for dry eyes, and blinking exercises. In the same month, the patient recovered from intraocular pressure (IOP) increased. The dull ache in the left eye, visual acuity fluctuation, glaucoma, uveitis, and depression aggravated were ongoing. Restasis was continued and Pazeo was discontinued four months after the event due to affordability issues. Concomitant medications included chlordiazepoxide, desvenlafaxine, fluticasone/salmeterol, lansoprazole, levothyroxine, prednisolone ophthalmic (Pred Forte), and theophylline. The manufacturing site quality investigation for lot number 93644 was completed and was within specification.

Reviewer's Comments: The contributory role of Pazeo with glaucoma cannot be determined in the setting of compelling potential alternate etiologies, including underlying glaucoma and multiple concomitant medications that are labeled for increased IOP or the development of glaucoma, including desvenlafaxine (Warnings and Precautions),[11] fluticasone/salmeterol (Warnings and Precautions),[12] prednisolone ophthalmic (Warnings and Precautions),[13] and lansoprazole (Adverse Reactions).[14] We are unable to assess the contributory role of Pazeo with the PTs Eye pain/Visual impairment as it is unclear if the events were ongoing after the product was discontinued. The reported PTs Depression, Glaucoma, Meibomian gland dysfunction, and

Uveitis do not describe new adverse events, but rather the patient's underlying diseases. The reported PTs Ciliary hyperaemia, Conjunctivochalasis, Intraocular pressure decreased, describe ocular exam findings; however, it is difficult to determine whether Pazeo had a contributory role in their development given the patient's numerous underlying ocular conditions, age, and chronic use of Pazeo at an unknown frequency. The patient had existing risk factors for conjunctivochalasis, which is not uncommon and hypothesized to be associated with delayed tear clearance, unstable tear film, and dry eye and related to factors such as old age and female sex.[15] The reported PT Intraocular pressure decreased was likely coded to describe the patient's response to the brinzolamide/brimonidine treatment for glaucoma. With regard to the reported PT Punctate keratitis, we note that Pazeo is labeled for superficial punctate keratitis under Adverse Reactions.[1]

FAERS Case # 15427233, USA, Expedited, 2018
PTs: Glaucoma
An elderly female patient (age unspecified) received Pazeo, travoprost (Travatan Z), and betaxolol (Betoptic S) for an unknown indication from an unknown date. Past medical history and concomitant medications were not reported. On an unknown date, the patient developed "glaucoma". The outcome of the event glaucoma and the action taken with Pazeo, travoprost, and betaxolol were not reported.

Reviewer's Comments: The contributory role of Pazeo cannot be determined given the lack of information on temporal association, past medical history, concomitant medications, clinical course, clinical outcome, and the action taken with Pazeo.

FAERS Case # 15728796, USA, Expedited, 2018
PTs: Eye irritation, Glaucoma
An adult female of unspecified age received Pazeo and brinzolamide/brimonidine (Simbrinza) for an unknown indication from an unknown date. On an unknown date, she had glaucoma and burned eyes (eye irritation). On an unknown date, she underwent cataract surgery. Past medical history and concomitant medications were not reported. The outcomes of the events glaucoma and eye irritation and the action taken with brinzolamide/brimonidine and Pazeo were not reported. No additional information was provided.

Reviewer's Comments: The contributory role of Pazeo cannot be determined given the lack of information on temporal association, past medical history, concomitant medications, clinical course, clinical outcome, the action taken with Pazeo, contact lens use, and presence of trauma. We note that this patient exposure to benzalkonium hydrochloride in Pazeo solution has been associated with allergic contact sensitivity and corneal neurotoxicity and inflammation.[2,10] We also note that this case is confounded by the concomitant use of brinzolamide/brimonidine, which is indicated for the treatment of glaucoma and labeled for eye irritation under Adverse Reactions.[16]

3.1.3.6 IOP increased

FAERS Case # 12439878, USA, Expedited, 2016
PTs: Intraocular pressure increased
A 64-year-old male received Pazeo (lot number 257359F) one drop in each eye once daily for the treatment of itchy eyes. Past medical history and concomitant medications were not reported. Nine days later, during a follow up appointment, he discovered his IOP increased from 22 to 28 in his left eye, at which time he was instructed to discontinue Pazeo. The IOP reading was not reported for his right eye. The patient stated that he was instilling unspecified steroid drops in his right eye only, which could have contributed to the increased IOP in his right eye. He was prescribed brimonidine/timolol (Combigan) for the treatment of IOP increased. The outcome of the event IOP increased was not reported. Further information requested, but not received.

Reviewer's Comments: The contributory role of Pazeo cannot be excluded based on a temporal association and an onset within nine days of initial Pazeo exposure to the onset of IOP increased. However, we note that potential alternate etiologies cannot be excluded, as information on past medical history, baseline IOP, and concomitant medications is lacking.

3.1.3.7 Iridocyclitis

FAERS Case # 16475926, USA, Expedited, 2019
PTs: Iridocyclitis
A female in her mid-50's (exact age unspecified) received Pazeo for the treatment of ocular itch associated with allergic conjunctivitis from an unknown date at a dose of one drop once daily. Past medical history and concomitant medications were not reported. On an unknown date, she developed bilateral anterior uveitis (iridocyclitis). It was reported that she discontinued Pazeo and was started on a steroid for inflammation. The outcome of the event iridocyclitis was not reported.

Reviewer's Comments: The contributory role of Pazeo cannot be determined given the lack of information on temporal association, past medical history, concomitant medications, clinical course, clinical outcome, and contact lens use or presence of trauma. We note that exposure to benzalkonium hydrochloride in Pazeo solution has been associated with allergic contact sensitivity and corneal neurotoxicity and inflammation.[2,10]

3.1.3.8 Ocular hypertension

FAERS Case # 16283267, USA, Non-expedited, 2019
PTs: Ocular hypertension
An adult female of unspecified age received Pazeo for the treatment of chronic allergic conjunctivitis from an unknown date. Past medical history was not reported. Concomitant medications included ketotifen fumarate (Alaway), loteprednol etabonate (Lotemax), and hydrocortisone cream (Cortisone). On an unknown date, she developed "ocular hypertension due to OTC steroid cream". The outcome of the event ocular hypertension and the action taken with Pazeo and hydrocortisone were not reported. No additional information was provided.

Reviewer's Comments: The contributory role of Pazeo cannot be determined given the lack of information on temporal association, past medical history, clinical course, clinical outcome, the action taken with Pazeo, and the presence of trauma. We also note that this case is confounded by the concomitant use of ophthalmic and topical steroids, including loteprednol, which is labeled for increased IOP under Warnings and Precautions.[17] The patient also reported "ocular hypertension due to OTC steroid cream", which is not typically applied to the eye. Of note, the drug facts label for hydrocortisone cream contains a warning to "avoid contact with eyes".[18]

3.1.3.9 Periorbital swelling

FAERS Case # 16651375, USA, Direct, 2019
PTs: Periorbital swelling
A 53-year-old male instilled Pazeo in one eye (left or right unspecified) for four days. On day 4, the skin around and below the eye became very swollen, at which time he discontinued Pazeo. On day 5, the skin was still swollen. Past medical history, concomitant medications, and outcome of the event periorbital swelling were not reported. No additional information was provided.

Reviewer's Comments: The contributory role of Pazeo cannot be excluded based on the temporal association of within four days from initial Pazeo exposure to the onset of periorbital swelling. However, we note that potential alternate etiologies cannot be excluded, as information on past medical history, concomitant medications, clinical outcome, contact lens use, and presence of trauma is lacking.

3.1.3.10 Vision blurred

FAERS Case # 13865532, USA, Non-expedited, 2017
PTs: Vision blurred
A female of unspecified age received Pazeo for an unknown indication from an unknown date and developed blurriness (vision blurred). Past medical history and concomitant medications were not reported. She fully recovered from vision blurred on an unknown date. The action taken with Pazeo was not reported. No additional information was provided.

Reviewer's Comments: The contributory role of Pazeo cannot be determined given the lack of information on temporal association, past medical history, concomitant medications, clinical course, the action taken with Pazeo, contact lens use, and presence of trauma. Additionally, we note that blurred vision is labeled under Adverse Reactions as one of the most commonly reported adverse events with Pazeo.[1]

3.1.4 Summary of Non-ocular Serious Adverse Events (N=4)

The non-ocular SAEs include *Tachycardia* (n=1), *Metal poisoning* (n=1), *Migraine* (n=1), *and Lung disorder* (n=1). In all four cases, the contributory role of Pazeo cannot be determined given the lack of clinical information, including temporal association, past medical history, concomitant medications, and clinical outcome. See **Appendix E** for full case narratives.

3.2 SPONSOR'S DATA

Summary of Clinical Safety for Olopatadine Ophthalmic Solution 120-Day Safety Update Report for Patanol, Pataday, and Pazeo, January 1, 2019 – October 31, 2019[6,7]

- Pazeo-associated SAEs from the Alcon Internal Argus Safety Database
    - The sponsor identified five cases reporting SAEs containing the following PTs; however, case narratives were not provided.
        - *Eye disorders* (n=2)
            - *Iridocyclitis (n=1)*
            - *Ocular hypertension (n=1)*
        - *Nervous system disorders* (n=2)
            - *Headache (n=1)*
            - *Syncope (n=1)*
        - *Immune system disorders* (n=1)
            - *Hypersensitivity (n=1)*

Reviewer's Comments: *The five cases identified from Alcon's Postmarketing Safety Database contain PTs that are identical to those identified from our FAERS search. However, the lack of case narratives precludes our ability to compare case-level data. Additionally, the sponsor did not provide an assessment of these cases.*

PADER for Pazeo 0.7%, January 30, 2018 - January 29, 2019[8]

- The sponsor received four expedited reports (three domestic and one foreign) that reported serious unlisted events, including one initial and three follow-ups, none of which had a fatal outcome. No serious listed reports were received during this reporting period.
    - Two cases (#PHEH2018US039847, PHHY2018CA142147) reported the events *Cataract* and *Eye irritation*, both of which provided insufficient information for meaningful assessment by the sponsor.
    - One case (#PHEH2018US000551) reported the event *Feeling abnormal*; however, it contained insufficient information for meaningful assessment by the sponsor.
    - One case (#PHEH2018US032257) reported the event *Metal poisoning*; however, it contained insufficient information for meaningful assessment by the sponsor.

Reviewer's Comments: *The four cases identified by the sponsor were also captured in our FAERS search (case #s 14371556, 15596279, 15434230, 15256866). Case # 14371556 was excluded from our case series because it did not report an adverse event. The remaining three cases are described in* ***Sections 3.1.1*** *and* ***3.1.3*** *and* ***Appendix E***.

4 SUMMARY AND CONCLUSION

- We identified 26 FAERS cases associated with Pazeo 0.7% ophthalmic solution use that reported misuse (n=2), death (n=1), ocular SAEs (n=19), and non-ocular SAEs (n=4).
    - The top five reported PTs among all PTs were *Eye irritation*, *Hypersensitivity*, *Ocular hyperaemia*, *Glaucoma*, and *Vision blurred*.
- **Misuse (2 of the 26 cases)**
    - The contributory role of Pazeo **cannot be excluded** in one case of corneal abrasion associated with the concomitant use of Pazeo and contact lens. The second case did not provide sufficient information for assessment.
- **Death (1 of the 26 cases)**
    - The contributory role of Pazeo was indeterminate due to the lack of clinical information provided.
- **Ocular SAEs (19 of the 26 cases)**
    - The contributory role of Pazeo **cannot be excluded** in eight cases; the PTs described in these cases include *Blindness* (n=1), *Corneal abrasion* (n=2), *Hypersensitivity* (n=2), *Eye irritation* (n=1), *IOP increased* (n=1), and *Periorbital swelling* (n=1). We note that exposure to benzalkonium chloride in Pazeo solution has been associated with allergic contact sensitivity and corneal neurotoxicity and inflammation; although the extent of its contribution to the aforementioned ocular events is unclear.[2,9]
    - The contributory role of Pazeo was indeterminate in 11 cases due to the lack of clinical information provided.
- **Non-ocular SAEs (4 of the 26 cases)**
    - In all cases, which include *Tachycardia* (n=1), *Metal poisoning* (n=1), *Migraine* (n=1), *and Lung disorder* (n=1), the contributory role of Pazeo was indeterminate given the lack of clinical information, including temporal association, past medical history, concomitant medications, and clinical outcome.

Our review of the sponsor's data confirms that the SAEs reported in the PADER and Summary of Clinical Safety are consistent with those reported in FAERS.

In DPV's opinion, the limited FAERS cases we identified are not sufficient to predict the misuse potential of Pazeo. Therefore, if a concern for potential misuse remains, DPV recommends that ONDP consider requesting the sponsor provide in their annual periodic reports a summary of worldwide experience of all misuse cases.

5 REFERENCES

1. Pazeo (olopatadine hydrochloride ophthalmic solution 0.7%) [Package Insert]. Fort Worth, TX: Alcon Laboratories, Inc; January 2015. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206276s000lbl.pdf

2. Fisher AA, Stillman MA. Allergic Contact Sensitivity to Benzalkonium Chloride. *Arch Dermatol*. 1972 Aug;106(2):169-71.

3. Pataday (olopatadine hydrochloride ophthalmic solution 0.2%) [Package Insert]. Fort Worth, TX: Alcon Laboratories, Inc; December 2010. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021545s013lbl.pdf

4. Patanol (olopatadine hydrochloride ophthalmic solution 0.1%) [Package Insert]. Fort Worth, TX: Alcon Laboratories, Inc; April 2003. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/20688slr016_patanol_lbl.pdf

5. NDA 020688 and 021545, Supplemental New Drug Application, Alcon Research, LLC. April 15, 2019. Available at: \\cdsesub1\evsprod\nda020688\0018\m1\us\cover.pdf

6. NDA 206276, 020688, and 021545, Summary of Clinical Safety for Olopatadine Ophthalmic Solution 120-Day Safety Update Report, Alcon Research, LLC. November 20, 2019. Available at: \\cdsesub1\evsprod\nda020688\0025\m2\27-clin-sum\summary-clin-safety.pdf

7. NDA 206276, 020688, and 021545, Appendix 1 – Alcon's Internal Argus Safety Database, Alcon Research, LLC. November 20, 2019. Available at: \\cdsesub1\evsprod\nda020688\0025\m2\27-clin-sum\summary-clin-safety-appendix1.pdf

8. NDA 206276, Novartis Pharmaceuticals Corporation. Periodic Adverse Drug Experience Report. Dated March 7, 2019.

9. National Institute on Drug Abuse. Misuse of Prescription Drugs: Overview. Updated December 2018. Retrieved from: https://www.drugabuse.gov/publications/misuse-prescription-drugs/overview

10. Sarkar J, Chaudhary S, Namavari A, et al. Corneal Neurotoxicity Due to Topical Benzalkonium Chloride. *Invest Ophthalmol Vis Sci*. 2012 Apr 6;53(4):1792-802.

11. Pristiq (desvenlafaxine succinate) [Package Insert]. Philadelphia, PA: Wyeth Pharmaceuticals LLC, a subsidiary of Pfizer; November 2019. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0f43610c-f290-46ea-d186-4f998ed99fce

12. Advair (fluticasone/salmeterol) [Package Insert]. Research Triangle Park, NC: GlaxoSmithKline LLC; January 2019. Available at:

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4eeb5f6a-593f-4a9e-9692-adefa2caf8fc

13. Pred Forte (prednisolone acetate suspension) [Package Insert]. Madison, NJ: Allergan, Inc.; July 2019. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=00a5aa88-e361-4ea7-8922-530c738b726e

14. Prevacid (lansoprazole) [Package Insert]. Deerfield, IL: Takeda Pharmaceuticals America Inc.; February 2019. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=71ba78cb-7e46-43eb-9425-fa130f537f84

15. Meller D, Tseng SC. Conjunctivochalasis: Literature Review and Possible Pathophysiology. *Surv Ophthalmol.* 1998 Nov-Dec;43(3):225-32.

16. Simbrinza (brinzolamide/brimonidine) [Package Insert]. Fort Worth, TX: Alcon Laboratories, Inc; November 2015. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/204251s006lbl.pdf

17. Lotemax (loteprednol etabonate ophthalmic solution 0.5%) [Package Insert]. Tampa, FL: Bausch & Lomb Pharmaceuticals, Inc; March 1998. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/20583lbl.pdf

18. Cortisone Cream (hydrocortisone cream) [Package Insert]. Research Woonsocket, RI: CVS Pharmacy; December 2009. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4e0637db-b17b-4b25-9718-afc0ca4343a0

6 APPENDICES

6.1 APPENDIX A. RELEVANT PAZEO PRODUCT LABELING

5 WARNINGS AND PRECAUTIONS	*5.1 Contamination of Tip and Solution* *As with any eye drop, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle to prevent contaminating the tip and solution. Keep bottle tightly closed when not in use.* *5.2 Contact Lens Use* *Patients should not wear a contact lens if their eye is red. The preservative in PAZEO solution, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses and whose eyes are not red, should be instructed to wait at least five minutes after instilling PAZEO before they insert their contact lenses.*
6 ADVERSE REACTIONS	*6.1 Clinical Trials Experience* *Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In a randomized, double-masked, vehicle-controlled trial, patients at risk for developing allergic conjunctivitis received one drop of either PAZEO (N=330) or vehicle (N=169) in both eyes for 6 weeks. The mean age of the population was 32 years (range 2 to 74 years). Thirty-five percent were male. Fifty-three percent had brown iris color and 23% had blue iris color. The most commonly reported adverse reactions occurred in 2-5% of patients treated with either PAZEO or vehicle. These events were blurred vision, dry eye, superficial punctate keratitis, dysgeusia and abnormal sensation in eye.*
16 HOW SUPPLIED/STORAGE AND HANDLING	*PAZEO (olopatadine hydrochloride ophthalmic solution) 0.7% is supplied in a white, oval, low density polyethylene DROP-TAINER* dispenser with a natural low density polyethylene dispensing plug and a white polypropylene cap. Tamper evidence is provided with a shrink band around the closure and neck area of the package. PAZEO is supplied in a 4 mL bottle that contains 2.5 mL of olopatadine hydrochloride ophthalmic solution [7.76 mg of olopatadine hydrochloride in one mL of solution (0.7%)]:NDC 0065-4273-25* *Storage: Store at 2°C to 25°C (36°F to 77°F). Keep bottle tightly closed when not in use.*

6.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

6.3 APPENDIX C. FAERS LINE LISTING OF MISUSE AND SERIOUS ADVERSE EVENTS ASSOCIATED WITH PAZEO CASE SERIES (N=26)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
1	7/6/2015	11246237	1	N/A	Direct	59	Female	USA	OT
2	2/29/2016	12126628	2	ALCN2016US001553	Non- Expedited	NR	Male	USA	Non-serious
3	5/30/2016	12416649	1	ALCN2016US003710	Expedited	NR	NR	USA	OT
4	6/6/2016	12439878	1	ALCN2016US003888	Expedited	64	Male	USA	OT
5	6/22/2016	12491906	1	N/A	Direct	56	Female	USA	OT
6	3/14/2017	13333654	2	ALCN2017US001880	Expedited	57	Male	USA	OT
7	5/11/2017	13537488	3	US-ALLERGAN-1709534US	Expedited	61	Female	USA	OT
8	7/26/2017	13792262	1	PHEH2017US022748	Expedited	NR	Female	USA	OT
9	8/14/2017	13865532	1	PHEH2017US025257	Non- Expedited	NR	Female	USA	OT
10	10/24/2017	14119738	2	PHEH2017US034038	Expedited	83	Male	USA	OT
11	11/29/2017	14240111	1	N/A	Direct	55	Female	USA	OT
12	4/11/2018	14773110	1	N/A	Direct	45	Female	USA	OT
13	8/8/2018	15256866	1	PHEH2018US032257	Expedited	NR	Female	USA	OT
14	8/29/2018	15331132	2	PHHY2018US081482	Expedited	NR	Female	USA	HO,OT
15	9/25/2018	15427233	4	PHEH2018US039173	Expedited	“Elderly”	Female	USA	OT
16	9/27/2018	15434230	1	PHEH2018US039847	Expedited	NR	Female	USA	OT
17	10/17/2018	15515654	1	PHEH2018US042922	Expedited	38	Female	USA	OT
18	11/7/2018	15596279	1	PHHY2018CA142147	Expedited	NR	Female	Canada	OT
19	12/17/2018	15728796	2	PHEH2018US051715	Expedited	NR	Female	USA	OT
20	2/28/2019	16018100	1	N/A	Direct	35	Female	USA	OT
21	4/26/2019	16244604	1	PHEH2019US017271	Expedited	NR	Female	USA	HO,OT
22	5/7/2019	16283267	1	PHEH2019US018515	Non- Expedited	NR	Female	USA	OT
23	6/25/2019	16475926	1	PHEH2019US026154	Expedited	“Mid-50's”	Female	USA	OT
24	7/30/2019	16651375	1	N/A	Direct	53	Male	USA	OT
25	10/15/2019	16921599	1	NVSC2019US000694	Expedited	77	Male	USA	DE
26	10/16/2019	16927194	1	NVSC2019US003273	Expedited	63	Female	USA	OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, inpatient hospitalization or prolongation of existing hospitalization, and other serious important medical events. A case may have more than one serious outcome.
Abbreviations: N/A=Not applicable, NR=Not reported, DE=Death, HO=Hospitalization, OT=Other Medically Significant

6.4 APPENDIX D. ALL REPORTED MEDDRA PTS FOR PAZEO 0.7% OPHTHALMIC SOLUTION

Table 4. All Reported MedDRA PTs for Pazeo, Received by FDA through December 22, 2019, Sorted by Decreasing Number of FAERS Reports per PT[*]

	MedDRA PT	Number of FAERS Reports	Labeled (Yes/No), Location or Other Category[†]
1	Eye irritation	4	N
2	Hypersensitivity	4	N
3	Ocular hyperaemia	3	N
4	Glaucoma	3	N
5	Vision blurred	2	Y, AR
6	Eye pain	3	N
7	Lacrimation increased	2	N
8	Blindness	2	N
9	Visual impairment	2	N
10	Corneal abrasion	2	N
11	Lung disorder	2	N
12	Cough	2	N
13	Swelling of eyelid	2	N
14	Headache	2	N
15	Drug ineffective	2	U
16	Product quality issue	2	Y, WP (captured under “contamination of tip and solution”)
17	Eye pruritus	1	N
18	Periorbital swelling	1	N
19	Tachycardia	1	N
20	Migraine	1	N
21	Erythema	1	N
22	Rhinorrhoea	1	N
23	Erythema of eyelid	1	N
24	Visual acuity reduced	1	N
25	Eye discharge	1	N
26	Meibomian gland dysfunction	1	N
27	Ocular hypertension	1	N
28	Eye inflammation	1	N
29	Punctate keratitis	1	Y, AR
30	Depression	1	N
31	Breast cancer	1	N
32	Uveitis	1	N
33	Ciliary hyperaemia	1	N

Table 4. All Reported MedDRA PTs for Pazeo, Received by FDA through December 22, 2019, Sorted by Decreasing Number of FAERS Reports per PT*			
34	Blindness transient	1	N
35	Eye swelling	1	N
36	Malaise	1	N
37	Eyelids pruritus	1	N
38	Metal poisoning	1	N
39	Fatigue	1	N
40	Periorbital pain	1	N
41	Death	1	N
42	Conjunctivochalasis	1	N
43	Blepharospasm	1	N
44	Inappropriate schedule of product administration	1	N
45	Syncope	1	N
46	Instillation site pain	1	N
47	Urticaria	1	N
48	Intraocular pressure decreased	1	N
49	Intraocular pressure increased	1	N
50	Iridocyclitis	1	N
51	Asthma	1	N
52	Cataract	1	N
53	Concomitant disease aggravated	1	N
* A report may contain more than one MedDRA PT. † Definitions: WP=Warnings/Precautions, AR=Adverse Reactions, or Other Categories: U=Uninformative			

6.5 APPENDIX E. SUMMARY OF NON-OCULAR SAES (N=4)

Tachycardia (n=1)

FAERS Case # 14773110, USA, Direct, 2018

PTs: Fatigue, Headache, Tachycardia

A 45-year-old female started Pazeo for seasonal allergies and experienced extreme fatigue, acutely painful headache, and a rapid heartbeat. The time to onset was not reported. She did not attribute it to Pazeo immediately and continued administering it for a total of six days. On day 6, she experienced disorientation and a resting heart rate of 130. She reported that she will stop administering Pazeo. Past medical history, concomitant medications, and clinical outcome were not reported. No additional information was provided.

Reviewer's Comments: The contributory role of Pazeo cannot be determined given the lack of information on temporal association, past medical history, concomitant medications, and clinical outcome.

Metal poisoning (n=1)

FAERS Case # 15256866, USA, Expedited, 2017

PTs: Metal poisoning

A female of unspecified age received Pazeo in both eyes for an unknown indication on an unknown date and was diagnosed with mercury poisoning (metal poisoning). Past medical history and concomitant medications were not reported. The outcome of the event metal poisoning and the action taken with Pazeo was not reported. No additional information was provided.

Reviewer's Comments: The contributory role of Pazeo cannot be determined given the lack of information on temporal association, past medical history, concomitant medications, clinical course, clinical outcome, and the action taken with Pazeo.

Migraine (n=1)

FAERS Case # 16927194, USA, Expedited, 2019

PTs: Headache, Malaise, Migraine

A 63-year-old female received Pazeo in both eyes for an unknown indication from an unknown date. Past medical history and concomitant medications were not reported. On an unknown date, she developed a headache and "felt it down through her neck, she gets migraines, and not feeling well (malaise)". The outcome of the events headache, migraine and malaise and the action taken with Pazeo were not reported. No additional information was provided.

Reviewer's Comments: The contributory role of Pazeo cannot be determined given the lack of information on temporal association, past medical history, concomitant medications, diagnosis, clinical course, clinical outcome, and the action taken with Pazeo.

Lung disorder (n=1)

FAERS Case # 15331132, USA, Expedited, 2018

PTs: Breast cancer, Cough, Eye discharge, Lung disorder, Ocular hyperaemia

An adult female of unspecified age received Pazeo for an unknown indication on an unknown date and was hospitalized for "some issue with her lung" (lung disorder). She was advised that her “bad cough” was due to her “lung issues”. She also reported that her eyes were red (ocular hyperaemia), “eyes were stuck together” (eye discharge), and that she had breast cancer. Past medical history and concomitant medications were not reported. The outcome of the events lung disorder and cough and the action taken with Pazeo were not reported.

Reviewer’s Comments: The contributory role of Pazeo cannot be determined given the lack of information on temporal association, past medical history, concomitant medications, diagnosis, clinical course, clinical outcome, and the action taken with Pazeo.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

REGINA LEE
02/18/2020 03:42:52 PM

LYNDA V MCCULLEY
02/18/2020 03:47:52 PM

STEVEN C JONES
02/18/2020 05:31:03 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	January 7, 2020
Requesting Office or Division:	Division of Nonprescription Drug Products (DNDP)
Application Type and Number:	NDA 020688/S-032 NDA 021545/S-022 NDA 206276/S-005
Product Name, Dosage Form, and Strength:	Pataday Twice Daily Relief (olopatadine) ophthalmic solution, 0.1% Pataday Once Daily Relief (olopatadine) ophthalmic solution, 0.2%, 0.7%
Product Type:	Single Ingredient Product
Rx or OTC:	Over-the-Counter (OTC)
Applicant/Sponsor Name:	Alcon Research, LLC
FDA Received Date:	June 20, 2019, November 25, 2019, and January 3, 2020
OSE RCM #:	2019-923 and 2019-2003
DMEPA Safety Evaluator:	Grace P. Jones, PharmD, BCPS
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

As part of the review process, the Division of Nonprescription Drug Products (DNDP) requested that we review the proposed Pataday Twice Daily Relief (NDA 020688) and Pataday Once Daily Relief (NDA 021545 and NDA 206276) container labels and carton labeling for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

Patanol (olopatadine HCl) ophthalmic solution, 0.1%, Pataday (olopatadine HCl) ophthalmic solution, 0.2%, and Pazeo (olopatadine HCl) ophthalmic solution, 0.7%, are currently marketed as prescription products by Novartis Pharmaceuticals Corp (Novartis), under NDA 020688, NDA 021545, and NDA 206276, respectively. Novartis has granted Alcon the rights for the full Rx-to-OTC switch of these 3 NDAs. Alcon has also proposed the following proposed proprietary names for OTC marketing: Pataday Twice Daily Relief for the 0.1% strength product, and Pataday Once Daily Relief for the 0.2% and 0.7% strengths.

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 FINDINGD OF THE MATERIALS REVIEWED

Our review finds that the proposed Pataday Twice Daily Relief (NDA 020688) and Pataday Once Daily Relief (NDA 021545 and NDA 206276) container labels and carton labeling may be improved to ensure safe use of the proposed products and to minimize potential medication errors.

5 RECOMMENDATIONS FOR ALCON RESEARCH, LLC

We recommend the following be implemented prior to approval of the supplements:

A. Container Labels and Carton Labeling

1. For the proposed Pataday Twice Daily Relief (NDA 020688/S-032) and Pataday Once Daily Relief (NDA 021545/S-022 and NDA 206276/S-005), to help consumers easily recognize the proposed products' dosing administration and to clearly communicate the proposed products' dosing interval, increase the prominence of "Twice Daily Relief" (for NDA 020688/S-032) and "Once Daily Relief" (for NDA 021545/S-022 and NDA 206276/S-005) in the proposed proprietary names, Pataday Twice Daily Relief and Pataday Once Daily Relief on the proposed container labels and carton labeling. To increase the prominence of the modifiers without reducing font size of other texts, reduce the size of the red and blue graphic on the carton labeling to provide real estate.

   As currently presented, other information on the container labels and carton labeling appear more prominent than the modifiers, "Twice Daily Relief" and "Once Daily Relief" in the proposed proprietary names.

B. Carton Labeling

1. For the proposed Pataday Once Daily Relief (NDA 206276/S-005), revise the statement "(b) (4) to read "Eye Allergy Itch Relief" to be consistent with the container label, as well as the labels and labeling of other proposed olopatadine HCl products for OTC marketing.

2. For the proposed twin pack (Two x 2.5 mL bottles) Pataday Once Daily Relief (NDA 206276/S-005), revise the top of the principal display panel so it is clear that "Extra Strength" is (b) (4) As currently presented, it appears this packaging configuration is (b) (4) (b) (4).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information received from Alcon Research, LLC. on June 20, 2019, for Pataday Twice Daily Relief (NDA 020688/S-032), November 25, 2019, for Pataday Once Daily Relief (NDA 021545/S-022), and November 25, 2019, for Pataday Once Daily Relief (NDA 206276/S-005).

Table 2. Relevant Product Information for Olopatadine Ophthalmic Products

Product Name	Pataday Twice Daily Relief	Pataday Once Daily Relief	Pataday Once Daily Relief
Application	NDA 020688	NDA 021545	NDA 206276
Initial Approval Date	12/18/1996	12/22/2004	1/30/2015
Active Ingredient	Olopatadine	Olopatadine	Olopatadine
Indication	Temporarily relieves itchy and red eyes due to pollen, ragweed, grass, animal hair and dander	Temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair and dander	Temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair and dander
Route of Administration	Ophthalmic	Ophthalmic	Ophthalmic
Dosage Form	Ophthalmic Solution	Ophthalmic Solution	Ophthalmic Solution
Strength	0.1%	0.2%	0.7%
Dose and Frequency	**Adults and children 2 years of age and older:** Put 1 drop in the affected eye(s) twice daily, every 6 to 8 hours, no more than twice per day. **Children under 2 years of age:** Consult a doctor	**Adults and children 2 years of age and older:** Put 1 drop in the affected eye(s) once daily (b) (4) **Children under 2 years of age:** Consult a doctor	**Adults and children 2 years of age and older:** Put 1 drop in the affected eye(s) once daily, (b) (4) **Children under 2 years of age:** Consult a doctor
How Supplied	5 mL bottle	0.5 mL sample bottle 2.5 mL bottle 2 x 2.5 mL bottles	0.5 mL sample bottle 2.5 mL bottle 2 x 2.5 mL bottles
Storage	Store between 4°-25°C (39°-77°F)	Store between 2°-25°C (36°-77°F)	Store between 2°-25°C (36°-77°F)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Pataday labels and labeling submitted by Alcon Research, LLC.

- Container label and carton labeling received on January 3, 2020, for NDA 020688/S-032
- Container label and carton labeling received on January 3, 2020, for NDA 021545/S-022
- Container label and carton labeling received on November 25, 2019, for NDA 206276/S-005

G.2 Label and Labeling Images

Container Labels

NDA 020688/S-032

5 mL Bottle

(b) (4)

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GRACE JONES
01/07/2020 11:32:28 AM

CHI-MING TU
01/07/2020 03:02:54 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

0206276Orig1s005

PROPRIETARY NAME REVIEW(S)

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	February 6, 2020
Application Type and Number:	NDA 021545/S-022 NDA 206276/S-005
Product Name and Strength:	Pataday Once Daily Relief (olopatadine HCl) ophthalmic solution, 0.2% and 0.7%
Product Type:	Single Ingredient Product
Rx or OTC:	Over-the-counter (OTC)
Applicant/Sponsor Name:	Alcon Research, LLC (Alcon)
Panorama #:	2019-35994628 2019-35994150
DMEPA Safety Evaluator:	Grace P. Jones, PharmD, BCPS
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS
DMEPA Deputy Director:	Danielle Harris, PharmD, BCPS

Contents

1 INTRODUCTION

This review evaluates the proposed proprietary name, Pataday Once Daily Relief, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed proprietary name are outlined in the reference section and Appendix A respectively. Alcon did not submit an external name study for this proposed proprietary name.

1.1 REGULATORY HISTORY

Alcon has obtained from Novartis the rights for full Rx-to-OTC switch for olopatadine ophthalmic solution products. Alcon seeks to market all three strengths of the olopatadine ophthalmic solution under the root name Pataday, thus creating a Pataday product line in the OTC marketplace (See Table 1).

Alcon previously submitted the proposed proprietary name, Pataday Once Daily Relief, for the proposed full Rx-to-OTC switch of Pataday (olopatadine) ophthalmic solution, 0.2%, under NDA 021545/Supplement-022 on April 15, 2019. On July 9, 2019, we found the name, Pataday Once Daily Relief, acceptable.[a] Subsequently, on September 24, 2019, Alcon withdrew the name, Pataday Once Daily Relief, and submitted a new proprietary name, (b) (4)

On September 13, 2019, Alcon submitted NDA 206276/Supplement-005, for the proposed full Rx-to-OTC switch of Pazeo (olopatadine) ophthalmic solution, 0.7%, and submitted the proposed proprietary name, (b) (4) for review.

On November 13, 2019, we held a teleconference with Alcon to discuss preliminary concerns with the proposed proprietary name, (b) (4) and the totality of the proposed proprietary names for the proposed olopatadine products in the Pataday product line. There was preliminary concern with the proposed proprietary name (b) (4) (b) (4) (b) (4).[b]

On November 22, 2019, Alcon withdrew the proposed proprietary names, (b) (4) (b) (4) for the 0.2% strength, and (b) (4) for the 0.7% strength. On November 25, 2019, Alcon submitted the proposed proprietary name, Pataday Once Daily Relief, for both 0.2% and 0.7% strengths. Alcon plans to differentiate the two strengths via the labeling the descriptor, Extra Strength, for 0.7% strength product.

---

[a] Jones, G. Proprietary Name Review for Pataday Once Daily Relief (NDA 021545/S-022). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUL 09. Panorama No. 2019-30833224.

[b] Olagundoye-Alawode, A. General Advice Letter (Teleconference Meeting Minutes) for NDA 206276 and NDA 021545. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JAN 13.

Table 1. Proposed Pataday product line for OTC marketing

Rx Product Name	Proposed Proprietary Name (PN)	Product Strength	Application Number
Pazeo	Pataday Once Daily Relief	0.7%	NDA 206276/S-005
Pataday	Pataday Once Daily Relief	0.2%	NDA 021545/S-022
Patanol	Pataday Twice Daily Relief[c]	0.1%	NDA 020688/S-032

1.2 PRODUCT INFORMATION

The following product information is provided in the proprietary name submission received on November 25, 2019.

- Intended Pronunciation: Pat-Ah-Day
- Active Ingredient: olopatadine HCl
- Indication of Use: Temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair and dander.
- Route of Administration: ophthalmic
- Dosage Form: ophthalmic solution
- Strength: 0.2% and 0.7%
- Dose and Frequency:
    - Adults and children 2 years of age and older: Put 1 drop in the affected eye(s) once daily, (b) (4)
    - Children under 2 years of age: Consult a doctor
- How Supplied: 0.5 mL sample bottle, 2.5 mL bottle, and 2 x 2.5 mL bottles
- Storage: store between 2°-25°C (36°-77°F)

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name, Pataday Once Daily Relief.

[c] The proposed proprietary name Pataday Twice Daily Relief was found conditionally acceptable on July 9, 2019 in OSE RCM# 2019-30833213.

2.1 MISBRANDING ASSESSMENT & INITIAL COMMENTS

At the initial phase of the review, in response to our initial OSE, December 2, 2019 email, the Division of Nonprescription Drug Products (DNDP) had no comments or concerns related to the proposed proprietary name, Pataday Once Daily Relief, except they inquired if the words "Extra Strength" is a modifier in the proposed proprietary name or a descriptor for the olopatadine 0.7% product. Following clarification that the words "Extra Strength" is a descriptor on labels and labeling, DNDP maintained that they have no concerns with the proposed proprietary name, Pataday Once Daily Relief. DMEPA concurs with DNDP's assessment at initial review and finds that the proposed proprietary name, Pataday Once Daily Relief, would not misbrand the proposed product.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the proposed proprietary name, Pataday Once Daily Relief.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proposed proprietary name[d].

2.2.2 Components of the Proposed Proprietary Name

Alcon indicated in their submission that the proposed proprietary name, Pataday Once Daily Relief, is derived with the root name, Pataday, which has been a prescription product for 14 years with familiarity from doctors and patients as a product that provides temporary ocular relief from indoor and outdoor allergies. This proprietary name is comprised of the root name, Pataday, and the modifiers, Once Daily Relief. We further discuss the modifiers, Once Daily Relief, in Section 2.2.5.

2.2.3 FDA Name Simulation Studies

Eighty-seven practitioners participated in DMEPA's prescription studies for Pataday Once Daily Relief. The responses did not overlap with any currently marketed products nor did the responses sound or look similar to any currently marketed products or any products in the pipeline. We excluded the interpretation "Kynmobi"***, as it was mistakenly entered and is the intended response to another name in the name simulation study. Appendix B contains the results from the verbal and written prescription studies.

[d] USAN stem search conducted on December 3, 2019.

2.2.4 Medication Error Data Selection of Cases

On January 6, 2020, we searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 2 (see Appendix A1 for a description of FAERS database) for name confusion errors involving *Pataday* that would be relevant for this review.

Table 2. FAERS Search Strategy	
FAERS Field:	Search Terms:
Initial FDA Receive Dates	June 1, 2019* to January 1, 2019 *Last FAERS search was conducted on June 3, 2019 for OSE review 2019-30833224 (NDA 021545) dated July 9, 2019[a]
Product Name	Pataday
Drug Role	Suspect
Event	DMEPA Official PNR Name Confusion Search Terms
Country (derived)	USA

The search did not yield any reports.

2.2.5 Evaluation of the Proposed Modifiers, Once Daily Relief

The root name, Pataday, appears first in the proposed proprietary name followed by the modifiers, Once Daily Relief. Alcon indicates in its request for proprietary name review submissions that the modifiers Once Daily Relief, are used to connote the differences in dosing administration for olopatadine 0.2% and 0.7% products from the olopatadine 0.1% product that's dosed twice daily. In the proposed 0.2% and 0.7% products, the modifiers, Once Daily Relief, refers to the products' dosing administration. The proposed Drug Facts Label (DFL) *Directions* section for both olopatadine 0.2% and olopatadine 0.7% states, "Put 1 drop in affected eye(s) once daily", and the proposed product should not be used more than once per day according to the *Directions*. Additionally, Alcon indicates that the incorporation of the labeling descriptor, Extra Strength, for the olopatadine 0.7% product, serves to connote the differences in strength between the olopatadine 0.2% and 0.7% products.

While we did not identify any application OTC products that incorporate the modifier "Once Daily" in the proprietary name, frequency of dosing is commonly used in OTC nomenclature (e.g., Nasacort Allergy 24 Hour, Xyzal Allergy 24HR, Sudafed Sinus Congestion 12 Hour, etc.). The modifier "Relief" is also commonly used in OTC nomenclature (e.g., Flonase Allergy Relief, Advil Allergy and Congestion Relief, etc.). Because we typically see the modifier "Relief" in conjunction with the symptoms that the product provides relief for, it is unclear how consumers would interpret "Relief" when used in conjunction with the frequency of administration "Once Daily". However, from a medication error perspective, we do not anticipate the combination of the words "Once Daily Relief" to introduce any risk of confusion because the product is dosed once daily and will provide relief of the symptoms when used once daily.

Additionally, we learned from discussion with the review team that the safety margin for the 0.2% product is wide such that even if consumers were to use it more than recommended,

there is minimal risk of clinical harm. The local effect on the eye(s) from chronic administration at doses higher than recommended with the 0.7% product is unknown, thus, the safety profile for the 0.7% product and whether it is suitable for OTC marketing is an ongoing review issue. Should the review team determine that the 0.7% product is suitable for OTC marketing, DMEPA's evaluation finds that the modifier "Once Daily Relief" in the proposed proprietary name will aid in communicating to consumers that the 0.7% product should be used once daily. Likewise, the modifier "Once Daily Relief" will also aid in communicating to consumers that the 0.2% product should be used once daily. Thus, we do not object to the use of the modifiers, Once Daily Relief, and find the proposed proprietary name, Pataday Once Daily Relief, acceptable.

2.2.6 Communication of DMEPA's Analysis at Midpoint of Review

DMEPA communicated our findings to the Division of Nonprescription Drug Products (DNDP) via e-mail on January 29, 2020.

3 CONCLUSION

The proposed proprietary name, Pataday Once Daily Relief, is acceptable.

If you have any questions or need clarifications, please contact Abiola Olagundoye-Alawode, OSE project manager, at 301-796-3982.

3.1 COMMENTS TO ALCON RESEARCH, LLC

We have completed our review of the proposed proprietary name, Pataday Once Daily Relief, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your submission, received on November 25, 2019, are altered prior to approval of the marketing application, the name must be resubmitted for review.

Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns based on the draft Guidance for Industry entitled Best Practices in Developing Proprietary Names for Drugs available at:

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm398997.pdf

USAN Stems (https://www.ama-assn.org/about/united-states-adopted-names-approved-stems)

USAN Stems List contains all the recognized USAN stems.

Division of Medication Errors Prevention and Analysis proprietary name consultation requests

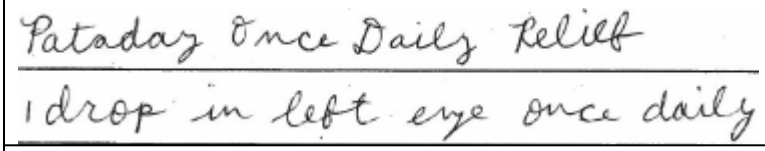
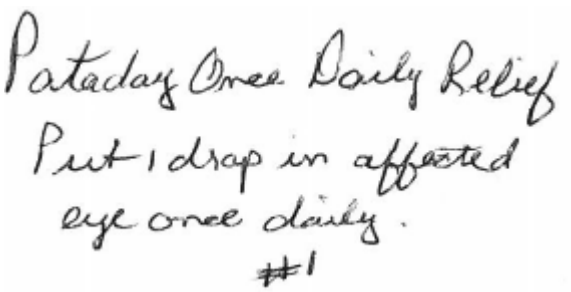
This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

Appendix A1: Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA' s Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

Appendix B: Prescription Simulation Samples and Results

Figure 1. Pataday Once Daily Relief Study (Conducted on December 6, 2019)

Handwritten Medication Order/Prescription	Verbal Prescription
Medication Order:  	Pataday Once Daily Relief Put 1 drop in affected eye once daily Dispense #1
Outpatient Prescription:  	
CPOE Study Sample (Font: sans-serif, 12 point, bold)	
Pataday Once Daily Relief	

FDA Prescription Simulation Responses (Aggregate Report)

210 People Received Study
87 People Responded

Study Name: Pataday Once Daily Relief

Total	16	18	20	33	
INTERPRETATION	OUTPATIENT	CPOE	VOICE	INPATIENT	TOTAL
KYNMOBI	1	0	0	0	1
PATADA ONCE DAILY RELIEF	0	0	0	1	1
PATADAY	2	0	0	19	21
PATADAY ONCE DAILY REFIEF	1	0	0	0	1
PATADAY ONCE DAILY RELEASE	0	0	1	0	1
PATADAY ONCE DAILY RELEIF	0	0	1	0	1
PATADAY ONCE DAILY RELIEF	11	18	10	11	50
PATADAY ONCE-DAILY RELEASE	0	0	1	0	1
PATADAY ONCE-DAILY RELIEF	0	0	1	0	1
PATADAY ONE DAY RELIEF	1	0	0	0	1
PATADAYONCE DAILY RELEIF	0	0	1	0	1
PATADAZ	0	0	0	1	1
PATADAZ ONCE DAILY RELIEF	0	0	0	1	1
PATADY ONCE DAILY	0	0	1	0	1
PATHADAY	0	0	1	0	1
TAFADEY	0	0	1	0	1
TAZADAY ONCE DAILY RELEASE	0	0	2	0	2

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GRACE JONES
02/06/2020 09:41:33 AM

CHI-MING TU
02/06/2020 09:43:58 AM

DANIELLE M HARRIS
02/06/2020 10:26:47 AM