

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021545s022

Trade Name: PATADAY ONCE DAILY RELIEF

Generic or Proper Name: olopatadine hydrochloride 0.2%

Sponsor: Alcon Research, LLC

Approval Date: February 14, 2020

Indication: Temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair, and dander.

CENTER FOR DRUG EVALUATION AND RESEARCH

021545s022

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021545s022

APPROVAL LETTER

NDA 020688/S-032
NDA 021545/S-022

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 applications (sNDAs) dated and received April 15, 2019 and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for:

- NDA 020688/S-032: Pataday Twice Daily Relief (olopatadine hydrochloride) ophthalmic solution, 0.1%
- NDA 021545/S-022: Pataday Once Daily Relief (olopatadine hydrochloride) ophthalmic solution, 0.2%

These “Prior Approval” supplemental new drug applications provide for the full prescription to over-the-counter switch of olopatadine hydrochloride 0.1% ophthalmic solution (NDA 020688) and olopatadine hydrochloride 0.2% ophthalmic solution (NDA 021545).

APPROVAL & LABELING

We have completed our review of these applications, as amended. They are 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.

In the Pataday® Twice Daily Relief 5 mL (0.17 Fl oz) carton label for NDA 020688/S-032, revise the “Purpose” statement to “Antihistamine and redness reliever” in Drug Facts. Revising to the lower-case letter “r” for “redness” and “reliever” is consistent with 21 CFR 201.66(d)(1). Include the above revision when you submit your FPL, or in your next annual report, or in your next supplement, whichever is soonest.

NDA 020688/S-032:

Submitted Draft Labeling	Date Submitted
Pataday® Twice Daily Relief 5 mL (0.17 Fl oz) carton	1/22/2020
Pataday® Twice Daily Relief 5 mL (0.17 Fl oz) container	1/22/2020

NDA 021545/S-022:

Submitted Draft Labeling	Date Submitted
Pataday® ONCE DAILY RELIEF 0.5 mL (0.017 Fl Oz) carton	1/22/2020
Pataday® ONCE DAILY RELIEF 0.5 mL (0.017 Fl Oz) container	1/22/2020
Pataday® ONCE DAILY RELIEF 0.5 mL (0.017 Fl Oz) pouch	1/22/2020
Pataday® ONCE DAILY RELIEF 2.5 mL (0.085 Fl Oz) carton	1/22/2020
Pataday® ONCE DAILY RELIEF 2.5 mL (0.085 Fl Oz) container	1/22/2020
Pataday® ONCE DAILY RELIEF two 2.5 mL (0.085 Fl Oz each) carton	1/22/2020

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 these submissions “**Final Printed Labeling for approved NDA 020688/S-032**” and “**Final Printed Labeling for approved NDA 021545/S-022**.” Approval of these submissions by FDA is not required before the labeling are 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.

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>

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 applications, you are exempt from this requirement.

REPORTING REQUIREMENTS

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

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

Sincerely,

{See appended electronic signature page}

Karen Murry Mahoney, MD, FACE
Deputy Director (Acting), Office of Nonprescription Drugs
Deputy Director (Acting), Division of Nonprescription Drugs II
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
02/14/2020 01:30:44 PM


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:


021545s022

LABELING


8 7 1 1



3 00654 27401 8



8 7 1 1



Drug Facts

Active ingredient Purpose
Olopatadine (0.1%)... Antihistamine and Redness Reliever (equivalent to olopatadine hydrochloride 0.111%)

Uses temporarily relieves itchy and red 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) twice daily, every 6 to 8 hours, no more than twice 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 4°-25°C (39°-77°F)

Inactive ingredients
benzalkonium chloride 0.01%, dibasic sodium phosphate, hydrochloric acid/sodium hydroxide (adjust pH), purified water, and sodium chloride

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

Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, Texas 76134
Country of Origin: Japan

NDC: 0065-4274-01
9017919-1219

NOW AVAILABLE without a prescription

Pataday®


TWICE DAILY RELIEF

Olopatadine hydrochloride ophthalmic solution 0.1%
Antihistamine and Redness Reliever

Eye Allergy Itch & Redness Relief

TWICE DAILY

Works in Minutes
Relief from Allergens:
• Pet Dander • Pollen
• Grass • Ragweed




STERILE

5 mL (0.17 FL OZ)

Pataday®

TWICE DAILY RELIEF

Eye Allergy Itch & Redness Relief
Works in Minutes



For Ages 2 and Older
30 DAY SUPPLY

TAMPER EVIDENT:

For your protection, this bottle has a seal imprinted with Alcon around the neck.

Fill Line

Do not use if seal is damaged or missing at time of purchase.

ACTUAL SIZE

1 1 4 8



LOT: EXP:



1 1 4 8



Only for use in the eye.
Store between 4° – 25°C
(39° – 77° F)

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.

Pataday.

TWICE DAILY RELIEF

Olopatadine hydrochloride
ophthalmic solution 0.1%
Antihistamine and Redness Reliever
Eye Allergy Itch & Redness Relief
5 mL (0.17 FL OZ) **STERILE**

Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, TX 76134

01

187

H15723-1219

6511



Pataday
ONCE DAILY RELIEF
Olopatadine hydrochloride
ophthalmic solution 0.2% Antihistamine
Eye Allergy Itch Relief

6511



Drug Facts

Active ingredient Purpose
Olopatadine (0.2%)Antihistamine
(equivalent to olopatadine hydrochloride 0.222%)

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, no more than once 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 0.01%, dibasic sodium phosphate, edetate disodium, hydrochloric acid/sodium hydroxide (adjust pH), povidone, purified water, and sodium chloride

Questions?

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

SAMPLE-NOT FOR SALE

Pataday

ONCE DAILY RELIEF

Olopatadine hydrochloride
ophthalmic solution 0.2%
Antihistamine

Eye Allergy Itch Relief

ONCE DAILY

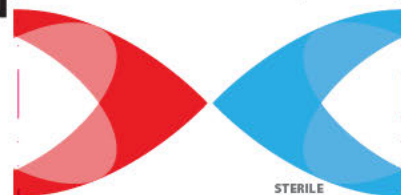
Works in Minutes
Relief from Allergens:
• Pet Dander • Pollen
• Grass • Ragweed

Pataday
ONCE DAILY RELIEF

Eye Allergy Itch Relief
Works in Minutes

For Ages 2 and Older

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.



Alcon

STERILE
0.5 mL (0.017 FL OZ)

Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, Texas 76134
Country of Origin: Japan

NDC: 0065-8150-04 9017951-1219

LOT:

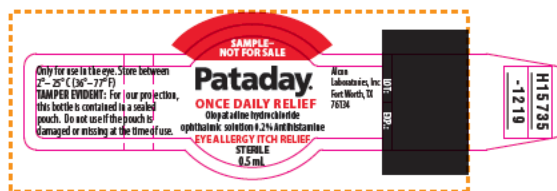
EXP.:

1159



1159







SAMPLE - NOT FOR SALE

Pataday[®]

ONCE DAILY RELIEF

Olopatadine hydrochloride
ophthalmic solution 0.2% Antihistamine

Alcon

STERILE

Eye Allergy Itch Relief 0.5 mL (0.017 FL OZ)

Alcon Laboratories, Inc.
6201 South Freeway, Fort Worth, TX 76134

9017658-1219
NDC: 0065-8150-04
See Carton for Use, Warnings and Directions

LOT:
EXP:

6 7 1 1



Pataday.

ONCE DAILY RELIEF

Olopatadine hydrochloride
ophthalmic solution 0.2% Antihistamine

Eye Allergy Itch Relief

**NOW AVAILABLE
without a prescription**

Pataday.

ONCE DAILY RELIEF

Olopatadine hydrochloride
ophthalmic solution 0.2%
Antihistamine

Eye Allergy Itch Relief

Works in Minutes
Relief from Allergens:
• Pet Dander • Pollen
• Grass • Ragweed



STERILE
Alcon 2.5 mL (0.085 FL OZ)

LOT:
EXP:

6 7 1 1



Drug Facts

Active ingredient	Purpose
Olopatadine (0.2%)	Antihistamine
(equivalent to olopatadine hydrochloride 0.222%)	

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, no more than once 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 0.01%, dibasic sodium phosphate, edetate disodium, hydrochloric acid/sodium hydroxide (adjust pH), povidone, purified water, and sodium chloride

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

3 00658 15001 1



Pataday.

ONCE DAILY RELIEF

Eye Allergy Itch Relief

Works in Minutes

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.



For Ages 2 and Older
30 DAY SUPPLY

— Fill Line —

Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, Texas 76134
Country of Origin: Japan
ACTUAL SIZE

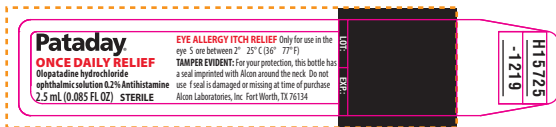
NDC: 0065-8150-01 9017921-1219

1 1 4 9





1 1 4 9



8 5 1 1

8 5 1 1

Pataday.

ONCE DAILY RELIEF
Olopatadine hydrochloride
ophthalmic solution 0.2% Antihistamine
Eye Allergy Itch Relief



Drug Facts

Active ingredient	Purpose
Olopatadine (0.2%)	Antihistamine (equivalent to olopatadine hydrochloride 0.222%)

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, no more than once 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 0.01%, dibasic sodium phosphate, edetate disodium, hydrochloric acid/sodium hydroxide (adjust pH), povidone, purified water, and sodium chloride

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

Country of Origin: Japan



Twin Pack
NOW AVAILABLE
without a prescription



Pataday.

ONCE DAILY RELIEF
Olopatadine hydrochloride
ophthalmic solution 0.2%
Antihistamine

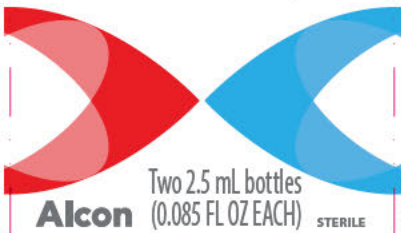
Eye Allergy Itch Relief

ONCE DAILY
Works in Minutes
Relief from Allergens:
• Pet Dander • Pollen
• Grass • Ragweed

Pataday.

ONCE DAILY RELIEF
Eye Allergy Itch Relief
Works in Minutes
For Ages 2 and Older

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.



Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, Texas 76134
NDC: 0065-8150-03 9017947-1219

LOT: _____ EXP: _____

1 1 5 8

1 1 5 8

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
02/14/2020 01:30:44 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021545s022

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	February 13, 2020
From	Francis E Becker, M.D., F.A.C.P.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 20688, S-32 PATANOL (olopatadine hydrochloride ophthalmic solution) 0.1% NDA 21545 S-22 PATADAY (olopatadine hydrochloride ophthalmic solution) 0.2%
Applicant	Alcon Research, LLC.
Date of Submission	April 15, 2019
PDUFA Goal Date	February 15, 2020
Proprietary Name	NDA 20688: Pataday Twice Daily Relief NDA 21545: Pataday Once Daily Relief
Established or Proper Name	Olopatadine Hydrochloride
Dosage Form(s)	Ophthalmic Solution 0.1%; 0.2%
Applicant Proposed Indication(s)/Population(s)	NDA 20688: Temporary relief of itchy and red eyes due to pollen, ragweed, grass, animal hair and dander. NDA 21545: Temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair and dander
Applicant Proposed Dosing Regimen(s)	NDA 20688: Adults and children 2 years of age and older: Put one 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 NDA 21545: Adults and children 2 years of age and older: Put one drop in the affected eye(s) once daily, no more than once per day. Children under 2 years of age: Consult a Doctor
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Adults and children 2 years of age and older (Children under 2 years of age: Consult a doctor)
Recommended Dosing Regimen(s)	<i>Same as above.</i>

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

I recommend approval of the prescription (Rx)-to-nonprescription (over-the-counter or OTC) switch of olopatadine hydrochloride ophthalmic solution 0.1% for the temporary relief of itchy and red eyes, and olopatadine hydrochloride 0.2% 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. Approval of these products for OTC use will provide an additional safe and effective therapeutic option for consumers to treat these symptoms of allergic conjunctivitis. The less frequent dosing regimen (once daily for olopatadine 0.2%, twice daily for olopatadine 0.1%) 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 for olopatadine 0.1% and 12 weeks for olopatadine 0.2% 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. Although not life-threatening, 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.

In multiple controlled clinical trials (environmental studies and conjunctival allergen challenge studies), olopatadine hydrochloride

ophthalmic solution 0.1% and 0.2% demonstrated statistically significant reduction of symptoms associated with allergic conjunctivitis and offers the benefits of a rapid acting, and highly specific, topical antihistamine, providing relief while remaining free from central nervous system depressive effects. The safety profile of olopatadine products has been well characterized through clinical trials and postmarketing experience. Over 10,000 patients have been exposed to olopatadine in completed clinical trials, and over 350 million patient months have been exposed cumulatively to olopatadine ophthalmic formulations in over 100 countries. Most adverse events involve eye disorders (eye irritation, eye pruritis, eye swelling, eye pain, eye disorder), and, in many cases, are likely related to the underlying disease (allergic conjunctivitis). Hypersensitivity is also a known adverse event, may be related to the preservative (benzalkonium chloride) and not olopatadine, and could easily be confused with allergic symptoms. Nevertheless, the proposed Drug Facts labeling for both products will include the Warning **Do Not Use** "if you are sensitive to any ingredient in this product."

During the review cycle, an additional safety consideration involved the potential for consumer confusion between the two products. The Applicant proposed to market the products OTC under the names Pataday Twice Daily Relief (olopatadine hydrochloride 0.1%) for ocular itching and redness, and Pataday Once Daily Relief (olopatadine hydrochloride 0.2%) for ocular itching. Therefore, a concern was raised that consumers might take both products at the same time or sequentially. The Applicant has addressed this issue by differences in carton and container design (color scheme, etc.) to help consumers distinguish between the two products. In addition, the review team agrees that the safety margin of olopatadine is such that these two products could be administered at the same time or sequentially without altering safety or efficacy. Olopatadine eye drops have been demonstrated to be safe and effective up to a concentration of 0.7% in clinical trials, so if a consumer were to mistakenly administer 0.2% twice a day (or every 16 hours), the exposure would still be less than a dose of 0.7%, which we know is safe when used as directed. The benefit-risk profile for olopatadine eye 0.1% and 0.2% is favorable for approval for OTC use.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p>Analysis of Condition</p>	<ul style="list-style-type: none"> • 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 allergy¹. • Although not life-threatening, profound effect on quality of life. ² • 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. • 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. • Associated with headache, fatigue, impaired concentration and learning, loss of sleep, reduced productivity, somnolence, functional impairment. 	<ul style="list-style-type: none"> • 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.

¹ O'Brien TP 2013. Curr Opin Allergy Clin Immunol; 13(5):543-9.

² Bielory L 2008. Ocular Allergy Overview. Immunol Allergy Clin North Am; 28(1):1-23.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p>Current Treatment Options</p>	<ul style="list-style-type: none"> • 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. 	<ul style="list-style-type: none"> • Pharmacotherapy has been the mainstay of treatment for conjunctival irritation. • Frequency of dosing required and potential adverse events may limit consumer use.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	<ul style="list-style-type: none"> • Olopatadine is a topical antihistamine with selective H1-receptor antagonist activity and mast cell stabilizing effects. • In controlled clinical trials, olopatadine hydrochloride ophthalmic solution 0.1% and 0.2% demonstrated statistically significant reduction of symptom(s) associated with allergic conjunctivitis with acceptable side effects. • Results from an environmental study demonstrated that olopatadine 0.1% eye drop solution was effective when dosed twice daily for up to 6 weeks • Results from clinical studies of up to 12 weeks duration demonstrated that olopatadine 0.2% eye drops solution when dosed once daily is effective in the treatment of ocular itching. • Olopatadine hydrochloride ophthalmic solution 0.1% and 0.2% offers the benefits of a rapid-acting, and highly specific, topical antihistamine, providing relief while remaining free from central nervous system depressive effects. • The efficacy of olopatadine eye drops 0.1% and 0.2% is well-established in numerous clinical trials conducted for approval for prescription use. • 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. 	<ul style="list-style-type: none"> • Olopatadine eye drops will provide consumers with an additional option for OTC use. • This eye drop has both antihistamine and mast cell stabilizing properties. • Less frequent dosing compared to other OTC allergy eye drops will prove of benefit to consumers. • Olopatadine eye drops will remain effective and safe if used over several weeks.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p>Risk and Risk Management</p>	<ul style="list-style-type: none"> • The most common adverse events (eye irritation, eye pruritis, eye swelling, ocular discomfort, dry eye, dysgeusia) are related to the site of administration and the underlying condition. • Overall numbers of reported adverse events (AEs) and SAEs are low. • Safety in pediatric patients ≤ 2 years of age has not been established. • Potential consumer confusion among the two proposed olopatadine-containing eye drops does not appear to introduce significant safety concerns. 	<ul style="list-style-type: none"> • Olopatadine hydrochloride has a satisfactory safety profile in the prescription environment based on 23 years of clinical use and 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, eye symptoms. • Safety of 0.1% and 0.2% olopatadine hydrochloride eye drop products is supported by clinical trial data submitted with the original applications and postmarketing data • Warnings provided in the proposed OTC labeling may help mitigate the risk of serious adverse events. • Potential misuse of the 0.1% or 0.2% olopatadine eye drops (in combination or dosing up to twice a day) exposes a consumer to a total of 0.4%, less than the amount from a 0.7% eye drop which is known to be safe.

2. Background

Alcon Research, LLC (the Applicant), a subsidiary of Novartis until 9 April, 2019 and acting as an agent for Novartis, simultaneously submitted two supplemental New Drug Applications (sNDAs) for a full prescription (Rx) to over-the-counter (OTC) switch of: Patanol (olopatadine hydrochloride) Ophthalmic Solution 0.1% (**NDA 20688**) for use as an antihistamine to temporarily relieve itchy and red eyes, and Pataday (olopatadine hydrochloride) Ophthalmic Solution 0.2% (**NDA 21545**) to temporarily relieve itchy eyes, due to pollen, ragweed, grass, animal hair and dander. Novartis continues to own the applications. To support approval for the two switches, the Applicant intends to rely on FDA's prior finding of safety and efficacy for Patanol (**NDA 20688**) and Pataday (**NDA 21545**) for olopatadine at multiple doses and routes of administration via cross-reference to the approved NDAs for Patanol (**NDA 20688**), Pataday (**NDA 21545**), Pazeo (**NDA 206276**), and Patanase (**NDA 21861**). As the proposed OTC products are unchanged from the current Rx products, except for the proposed labeling, no new clinical, preclinical, or chemistry, manufacturing, and controls (CMC) data are submitted in the two sNDAs, as agreed upon during a Type B Teleconference with FDA on 3 April 2019.

Olopatadine is a topical antihistamine with selective histamine-1 (H1)-receptor antagonist activity and mast cell stabilizing effects. It is available in the United States (Rx only) as Patanol 0.1% (1 mg/mL), Pataday 0.2% (2 mg/mL) and Pazeo 0.7% (7 mg/mL) eye drops; and as Patanase 0.6% (6.65 mg/mL) intranasal spray. Olopatadine 0.1% ophthalmic solution (Patanol) was approved by the FDA on 18 December 1996 for the treatment of signs and symptoms (including itching and redness) associated with allergic conjunctivitis. Once daily ophthalmic formulations of olopatadine 0.2% (Pataday) and olopatadine 0.7% (Pazeo) were approved on 22 December 2004 and 30 January 2015, respectively, for the treatment of ocular itching associated with allergic conjunctivitis. In addition, olopatadine nasal spray 0.66% (Patanase) was approved for the treatment of symptoms of seasonal allergic rhinitis in adults and pediatric patients 12 years of age and older in April 2008 and in children 6 to 11 years of age in December 2009.

In addition to **sNDAs 20688** and **21545** which were submitted concurrently on 15 April 2019 and which are the subject of this cross-discipline team leader (CDTL) Review, Alcon submitted an sNDA seeking approval for a full Rx-to-OTC switch of Pazeo (olopatadine hydrochloride) 0.7% (**NDA 206276**) on 13 September 2019. At the time of this writing, **NDA 206276** is still under evaluation (PDUFA date: 13 July 2020) and is not the subject of this review.

The Applicant initially submitted **sNDA 20688** Patanol (olopatadine hydrochloride) Ophthalmic Solution 0.1% for the indication of relief of itchy eyes due to pollen, ragweed, grass, animal hair and dander. Thus, the initial proposed indication would be identical to the proposed indication for the Pataday (olopatadine hydrochloride) 0.2% product (**NDA 21545**). However, FDA questioned whether

this would constitute a partial rather than a full Rx-to-OTC switch, since the redness indication would presumably remain Rx only. While internal FDA discussion regarding this matter continued, the concern was conveyed to the Applicant in informal telephone conversation on 11 June, 2019³. Subsequently, the Applicant submitted an amendment to the sNDA with revised draft labeling to add back the “redness” indication to the 0.1% product (NDA 20688, SD-408; 20 June 2019).

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 chemosis⁴. 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 mediators⁵. 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.

³ sNDA 20688 Memorandum to File; DARRTS, 6/20/2019.

⁴ Singh K, Axelrod S, Bielory L 2010. J Allergy Clin Immunol; 126(4):778-783.

⁵ O’Brien TP 2013. Curr Opin Allergy Clin Immunol; 13(5):543-9.

Current Treatment Options

According to the American Academy of Ophthalmology⁶, 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.

Table 1 below lists approved NDA OTC ophthalmic products currently marketed to treat allergy symptoms (there are also numerous ANDAs not included in the table). Note that naphazoline is a vasoconstrictor; therefore, labeling for OTC naphazoline products contains the warning 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. One NDA-approved ophthalmic drug product (Lumify, **NDA 208144**) has an indication of “relief of redness” only; its active ingredient is brimonidine. In addition, there are numerous “generally recognized as safe and effective” (GRASE) active ingredient ophthalmic vasoconstrictors marketed under Final Monograph (part 349) with an indication for “relief of redness of the eye” (not other allergy symptoms). For example, for tetrahydrozoline HCl 0.05% eye drops, directions for use state: 1-2 drops up to four times daily. There are also eyewash drug products under the monograph that have “relief of itching” as an indication.

⁶ Au, A. and Grigorian, P. et al; Allergic Conjunctivitis; https://eyewiki.aaopt.org/Allergic_conjunctivitis; accessed 7/29/2019.

Table 1: Current NDA Ophthalmic Solutions to Treat Allergy Symptoms

NDA and Brand Name	Indication	Active Ingredient(s)	Dosage	Approval Date (OTC)
020485 Visine A	Temporarily relieves itchy, red eyes due to pollen, ragweed, grass, animal hair, and dander	0.025% naphazoline HCl, 0.3% pheniramine maleate		1/31/1996
020065 Opcon-A	Temporarily relieves itchy, red eyes due to pollen, ragweed, grass, animal hair, and dander	0.02675% naphazoline HCl, 0.315% pheniramine maleate	1 or 2 drops up to qid \geq 6 yo	6/8/1994
020226 Naphcon A	Temporarily relieves itchy, red eyes due to pollen, ragweed, grass, animal hair, and dander	0.025% naphazoline HCl, 0.3% pheniramine maleate		6/8/1994
021066 Zaditor	Temporarily relieves itchy, red eyes due to pollen, ragweed, grass, animal hair, and dander	0.025% ketotifen fumarate	1 drop bid, \geq 3 yo	10/19/2006 [now ANDA only]
021996 Alaway	Temporarily relieves itchy, red eyes due to pollen, ragweed, grass, animal hair, and dander	0.025% ketotifen fumarate		12/1/2006

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Regulatory Background

The Applicant had the following important interactions with FDA regarding the proposed OTC development program for its olopatadine products.

A Type B pre-sNDA Meeting was held between FDA and the Applicant on 30 November 2010 (Patanol: **PIND 107178**). Important discussions at the meeting included the following:

- FDA agreed that it was acceptable for the Applicant to propose labeling down to 2 years of age without doing additional studies in 2-year olds. At the time of Patanol approval in 1996, safety and efficacy studies were conducted down to age 3 years, and this was therefore reflected in prescription labeling. However, FDA has determined since a 26 June 2009 Advisory Committee that there is essentially no difference in maturity of the eyes between ages 2 and 3, so 2-year olds may be considered as the same population as 3-year olds.
- FDA agreed that no chemistry, manufacturing, and controls (CMC) or nonclinical safety studies need to be conducted to support approval of an Rx-to-OTC switch. The Applicant may rely on the nonclinical safety findings that were reviewed and approved under the original NDA submission for prescription Patanol (**NDA 20688**).

A Type B pre-sNDA teleconference was held between FDA and the Applicant on 3 April 2019 (Pataday: **PIND 142363**). Important discussions at the teleconference were as follows:

- 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.”

In addition, during the current review cycle for **NDA 208288** and **21545**, to clarify or expand upon the submitted data, the Applicant responded to several Information Requests (IRs) which are described in detail by the DNPD II Medical Officer, Elizabeth Donohoe, M.D., in her clinical review.

3. Product Quality

Chemistry Manufacturing and Controls (CMC) review for both products was conducted by Ping Jiang-Baucom, PhD, and Ramash Raghavachari, PhD of the Office of Pharmaceutical Quality (OPQ). For both NDAs, the CMC Team recommends “approval from CMC perspective.”^{7,8}

The Applicant is referencing the original **NDA 20688** and **NDA 21545** submissions for prescription use for CMC data as the proposed products are unchanged from the current Rx products. The OTC products will have the same strength, dose, duration of use, dosage form, population, and route of administration as the approved Rx products. Therefore, no new CMC data were submitted. For Patanol, prescription labeling states that each mL of Patanol (olopatadine 0.1%) contains the active ingredient olopatadine hydrochloride 1.11 mg, which is equivalent to 1 mg of olopatadine. For Pataday, prescription labeling states that each mL of Pataday (olopatadine 0.2%) contains the active ingredient olopatadine hydrochloride 2.22 mg, which is equivalent to 2 mg of olopatadine. Both formulations contain benzalkonium chloride 0.01% as a preservative.

The CMC Team notes that there are no drug substance or drug product changes from the current prescription NDAs. The Alcon DROP-TAINER container closure system is approved for both Patanol and Pataday, and the CMC Team concludes that the container closure system is appropriately designed for the desired delivery of the two products. There will be no change to the container closure system, except the addition of new outer (carton) packaging for the OTC products. Stability data for both Patanol and Pataday have been updated and provided in the Annual Reports to the respective NDAs.

⁷ NDA 20688 S-032 Review of Chemistry, Manufacturing and Controls; 31 December 2019.

⁸ NDA 21545 S-022 Review of Chemistry, Manufacturing and Controls; 31 December 2019.

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. Therefore, no new nonclinical safety data were submitted.

5. Clinical Pharmacology

No additional information regarding clinical pharmacology was submitted as the Applicant is referencing previous Clinical Pharmacology findings from the original NDA applications (**NDA 20688** Patanol and **NDA 21545** Pataday). Prescription labeling for both Patanol (olopatadine 0.1%) and Pataday (olopatadine 0.2%) describes pharmacokinetic studies conducted for NDA approval as follows:

Two studies in normal volunteers (totaling 24 subjects) dosed bilaterally with olopatadine 0.15% ophthalmic solution once every 12 hours for 2 weeks demonstrated plasma concentrations to be generally below the quantitation limit of the assay (<0.5 ng/mL). Samples in which olopatadine was quantifiable were typically found within 2 hours of dosing and ranged from 0.5 to 1.3 ng/mL. The elimination half-life in plasma following oral dosing was 8 to 12 hours, and elimination was predominantly through renal excretion. Approximately 60-70% of the dose was recovered in the urine as parent drug. Two metabolites, the mono-desmethyl and the N-oxide, were detected at low concentrations in the urine.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The proposed olopatadine products will have the same strength, dose, duration of use, dosage form, indication, and route of administration as the approved prescription (Rx) products. Therefore, the Applicant relies on the previous clinical trials conducted for NDA approval of the Rx products to support the efficacy of olopatadine for OTC use. The completed clinical trials which supported the approval of prescription Patanol (**NDA 20688**) and Pataday (**NDA 21545**) are summarized in the **Table 2** and **Table 3** below:

Table 2: 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-mediated 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

Electronically copied and reproduced from Dr. Boyd’s clinical review (Source: NDA 20688/S-032 Module 2.5).

Table 3: 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 olopatadine 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
Total Subject Exposure to Pataday							858
#	Protocol	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing Duration	Total # Subjects Exposed to Active Drug
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

*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.

Electronically copied and reproduced from Dr. Boyd’s clinical review (Source: NDA 20688/S-032 Module 2.5).

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. 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.”⁹ 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: I agree with Dr. Boyd’s assessment that the clinical trials were adequate and support the efficacy and safety of the olopatadine 0.1% and 0.2% products when used once or twice daily. The Applicant is proposing twice daily OTC dosing for the 0.1% product and once daily OTC dosing for the 0.2% product. 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 either product is only indicated for relief of itching and not redness. Regarding safety (see also Section 8 below), it is noted that the clinical trials evaluated doses up to olopatadine 0.7% (7 mg/ml). 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. Assessment of the efficacy and safety of the 0.7% product is ongoing and is not the subject of this review.

8. Safety

Clinical Trial Safety

The clinical trial population includes healthy normal subjects and subjects with allergic conjunctivitis, ranging from 3 to >65 years of age. A total of 98 completed clinical studies across all olopatadine formulations is included in the Integrated Summary of Safety (ISS).

⁹ Ophthalmic clinical review NDA 20688/S-032 PATANOL (olopatadine ophthalmic solution) 0.1%; NDA 21545/S-022 PATADAY (olopatadine ophthalmic solution) 0.2%; NDA 206276/ S-005 PAZEO (olopatadine ophthalmic solution) 0.7%. 11 January 2020.

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 70), as shown in **Table 4** below:

Table 4: Tabular Summary of Completed Clinical Trials

Formulation	Phase I	Phase II	Phase III	Phase IV*	Total
	N	n	n	n	
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.

Electronically copied and reproduced from Dr. Boyd’s clinical review (Source: NDA 20688/S-032 Module 5.3.5.3).

Approximately 10,814 patients received olopatadine treatment in marketing authorization holder sponsored investigational clinical trials cumulatively. There were no ongoing interventional trials during the reporting interval of the most recent periodic safety update report (PSUR) and no trials ongoing at the time of this submission, as shown in **Table 5** below:

Table 5: 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.

Electronically copied and reproduced from Dr. Boyd's clinical review (Source: NDA 20688/S-032 Module 5.3.5.3).

In his clinical review, Dr. Boyd noted that a total of 132 serious adverse events (SAEs) was reported in the combined olopatadine development programs. Of these, a total of 11 SAEs was 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 who 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. Importantly, no patient exposed to olopatadine in any clinical study experienced an SAE assessed as related to study treatment. Dr. Boyd concluded that there were no safety issues identified in the clinical trials that would preclude the safe administration of olopatadine ophthalmic solution 0.1%, 0.2% or 0.7% as an OTC product.

Patanol Prescription Labeling (revised April 2018) identifies the most common adverse events (AEs) for olopatadine 0.1% (Patanol) from the clinical trials as follows:

Adverse Reactions:

Headaches have been reported at an incidence of 7%. The following adverse experiences have been 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.

Pataday Prescription Labeling (revised December 2010) identifies the most common AEs for olopatadine 0.2% from the Clinical Trials as follows:

Adverse Reactions:

Symptoms similar to cold syndrome and pharyngitis were reported at an incidence of approximately 10%. The following adverse experiences have been 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.

CDTL Comment: *I agree with Dr. Boyd's assessment. Importantly, as noted in prescription labeling for both products, some of the reported adverse events were likely symptoms of the underlying disease and not related to olopatadine.*

Postmarketing Safety

Postmarketing safety review was performed by Elizabeth Donohoe, M.D., Medical Officer, Division of Nonprescription Drugs II (DNPDI). Dr. Boyd also performed a review of the postmarketing safety data.

Postmarketing Exposure

Dr. Boyd reported that 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 per patient; therefore, it is difficult to give an exact number of patients exposed. An estimation based on patient-months was calculated. Estimated postmarketing exposure is shown in the Table 6 below:

Table 6: Estimated Postmarketing (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)

Electronically copied and reproduced from Dr. Boyd’s clinical review (Source: NDA 20688/S-032 Module 5.3.5.3).

Dr. Donohoe correctly noted that there are limitations of postmarketing adverse drug event reporting as reports are submitted voluntarily and the magnitude of underreporting is unknown. In addition, Dr. Donohoe observed that the total numbers for adverse event (AE) reports for any one product between databases also vary as do the respective years included in queries. The raw numbers of “reports” for “cases” also vary widely. Overall, the total numbers of reported AEs are low so the number of AEs, as opposed to percentage of total, has been used. Dr. Donohoe’s review references information related to all three eye drops containing olopatadine hydrochloride [Patanol (0.1%), Pataday (0.2%) and Pazeo (0.7%)] for ease of presenting information submitted by the

Applicant as all three sNDAs are currently under review for proposed Rx-to-OTC switch. Furthermore, the postmarketing data submitted encompassed all three products, and the Integrated Summary of Safety is identical for the three applications.

Olopatadine 0.1% eye drops solution is marketed as a prescription drug in 112 countries and OTC in 5 countries. Olopatadine 0.2% eye drops solution is marketed as a prescription drug in 42 countries and OTC in 1 country. The cumulative number of units sold from 2000 through 30 April 2018 was (b) (4) with (b) (4) units OTC, as shown in Table 7 below.

Table 7: Distribution of Nonprescription Olopatadine for Ophthalmic Use, March 2013 to December 2018

olopatadine-nonprescription (OTC) (Ophthalmic use)	
COUNTRY	Sum of units_March_2013 to December_2018
Amer. Central & Carib.	(b) (4)
Hong Kong	
Italy	
Malaysia	
Singapore	
South Africa	
TOTAL OTC	

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The Applicant provided the table below (Table 8), which shows units sold OTC worldwide by brand from 2000 to the end of 2018.

Table 8: Estimated Postmarketing Exposure (Cumulative by Brand to 31 Dec2018)

Brand	Cumulative Sales to 31-Dec-2018 (Units Sold)
Patanol (olopatadine 0.1% eye drops, solution)	(b) (4)
Pataday (olopatadine 0.2% eye drops, solution)	
Pazeo (olopatadine 0.7% eye drops, solution)	
TOTAL	

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Postmarketing Databases

In the Integrated Summary of Safety (ISS), the Applicant submitted the following in support of olopatadine safety:

- Applicant’s Pharmacovigilance Database from 1996 to 2018
- FDA Adverse Events Reporting System (FAERS) database search from 1997 to 2018 with break-outs by year of reporting, patient age, duration of use, and brand
- World Health Organization (WHO) search from 1996 to 2019
- National Poison Data System (NPDS) database from 2000 to 2019
- Published medical literature for safety issues associated with use of olopatadine

Applicant’s Database (Novartis and Alcon/Argon)

The Applicant’s safety database was the only source of data by marketing status. For the time period of 2012-2018, a total of 4,072 adverse events (AEs) was reported for Patanol; however, only 54 (1.3%) were related to OTC use, as shown in the **Table 9** below.

Table 9: Frequency of Postmarket AEs for Olopatadine-containing Products, Stratified by Marketing Status

Dosage Strength	Total n	Marketing Status	
		Prescription n	Over the counter n
Patanol			
Serious adverse events	160	154	6
Non-serious adverse events	3912	3864	48
Total adverse events (serious + non-serious)	4072	4018	54
Pataday			
Serious adverse events	55	55	0
Non-serious adverse events	1995	1991	4
Total adverse events (serious + non-serious)	2050	2046	4

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AEs (serious and nonserious) were reported to have occurred more frequently in individuals aged 12-65 years, commensurate with that being the largest category of consumers. However, Dr. Donohoe noted that age was not provided in approximately 42% of all reports, making it difficult to identify trends or draw definitive conclusions. **Table 10** below summarizes the total number of serious adverse events, nonserious adverse events, and all adverse events (serious and nonserious combined), with respect to the age of the subject for 0.1% and 0.2% olopatadine-containing products.

Table 10: Adverse Events by Age (Applicant’s Database)

Dosage Strength	Total n	Subject Age			
		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

Electronically copied and reproduced from Dr. Donohoe’s clinical review; Source: ISS Module 5.3.5.3 ISS, Table 13 (modified), page 32 of 66.

From Alcon’s internal database [1994-2018], the total number of events reported for Patanol (olopatadine 0.1%) was 3911 with 141 serious adverse events (SAEs). For Pataday (olopatadine 0.2%), there was a total of 1871 events with 37 SAEs. The most frequently reported SAEs and nonserious AEs for the three olopatadine ophthalmic products by system organ class (SOC) are shown in **Table 11** and **Table 12** below.

Table 11: The Five Most Frequently Reported SAE SOC for the Three Olopatadine Ophthalmic Products

Order	Patanol	Pataday	Pazeo
1	Eye disorders (N=54)	Eye disorders (N=9)	Eye disorders (N=7)
2	Skin and subcutaneous tissue disorders (N=18)	Nervous system disorders (N=6)	Injury, poisoning and procedural complications (N=3)
3	Nervous system disorders (N=14)	Gastrointestinal disorders (N=5)	Musculoskeletal and connective tissue disorders (N=3)
4	Immune system disorders (N=10)	General disorders and administration conditions (N=4)	Respiratory, thoracic and mediastinal disorders (N=3)
5	General disorders and administration conditions (N=9)	Infections and infestations (N=4)	Investigations (N=2)

Source data: Tables 1-3; 7-9; 13-15 [Source Data Tables Q4]

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Table 12: The Five Most Frequently Reported AE SOCs for the Three Olopatadine Ophthalmic Products

Order	Patanol	Pataday	Pazeo
1	Eye disorders (N=1699)	Eye disorders (N=706)	Eye disorders (N=408)
2	General disorders and administration conditions (N=936)	General disorders and administration conditions (N=659)	General disorders and administration conditions (N=104)
3	Injury, poisoning and procedural complications (N=276)	Injury, poisoning and procedural complications (N=102)	Injury, poisoning and procedural complications (N=42)
4	Nervous system disorders (N=240)	Nervous system disorders (N=86)	Nervous system disorders (N=38)
5	Skin and subcutaneous tissue disorders (N=153)	Respiratory, thoracic and mediastinal disorders (N=60)	Product Issues (N=36)

Source data: Tables 4-6: 10-12: 16-18 [Source Data Tables O4]

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For Patanol and Pataday, the most common SAEs by preferred Term (PT) are listed in **Table 13** and **Table 14** below.

Table 13: Patanol (olopatadine 0.1%) Most Frequent SAEs (n≥3) by PT

All events	141
Eye disorders	54
Eye irritation	4
Eye pain	4
Eye pruritus	3
Eye swelling	3
Punctate keratitis	3
Ulcerative keratitis	3
Skin and subcutaneous tissue disorders	18
Swelling face	5
Nervous system disorders	14
Headache	3
Immune system disorders	10
Anaphylactic reaction	3
Hypersensitivity	3

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Table 14: Patanol (olopatadine 0.1%) Most Frequent SAEs (n≥3) by PT

All events	37
Eye disorders	9
Blindness	3

Electronically copied and reproduced from Dr. Donohoe’s clinical review; Source: Applicant’s submission of 9/16/19, Data Tables Q4, page 8 of 175.

The SAEs of “blindness” are discussed in the **Significant Adverse Events** section of this review. Regarding postmarketing safety data specific to OTC use, the total number of reported AEs is listed in the **Table 15** below.

Table 15: OTC Olopatadine Eye Drops, All Reported AEs with PT n ≥3

All events	57
Eye irritation	5
Accidental exposure to product by child	3
Eye pruritus	3
Ocular hyperaemia	3
Wrong product administered	3

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As pointed out by Dr. Donohoe, the relatively low frequency of OTC AEs compared to the total AEs reported may reflect the very small number of units of OTC olopatadine ophthalmic solution products sold worldwide. Currently, Patanol is only marketed OTC in

five countries (Italy, Myanmar, Namibia, South Africa, and Zimbabwe), and Pataday is only marketed OTC in one country (Hong Kong). In addition, as observed by Dr. Donohoe, the Applicant noted that “While there is a very small number of units of OTC olopatadine eye drop solution products sold worldwide, an analysis of most frequently reported AEs for OTC products by Preferred Term is not possible in the external databases since the OTC products share identical names as the Rx products, and the WHO database does not distinguish whether a primary suspect olopatadine eye drop solution is an Rx or OTC entity. OTC data from Alcon’s internal database were produced by tabulating those events that were reported from countries that have an OTC product.”

Dr. Donohoe concluded that, overall, the findings are consistent with the known safety profile and identified risks on current prescription labeling of olopatadine eye drop products. I agree.

FAERS Database

A search of the FAERS database from the fourth quarter of 1997 to the fourth quarter of 2018 returned 7,390 cases in which olopatadine was reported. Of these, 3,787 (51.2%) originated from the United States, and 3,603 (48.3%) originated from outside of the United States. Broken out by brand, there were 1,924 cases for Patanol, 1,527 cases for Pataday, 501 cases for Pazeo, 821 cases for Patanase, and 2,719 cases for unknown olopatadine brand. **Table 16** below 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 nonserious; and there were 5 deaths, one of which was reported as a road traffic accident and another as a homicide.

Table 16: 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)

Electronically copied and reproduced from Dr. Boyd’s Clinical Review (Source: NDA 20688/S-032 Module 5.3.5.3).

The five most frequently reported SAE SOC for all three olopatadine eye drop products from the FAERS database are shown in **Table 17** below:

Table 17: Five Most Frequently Reported SAEs by SOC for Olopatadine Eye Drop Products (FAERS Database)

Order	Patanol	Pataday	Pazeo
1	Eye disorders (N=20)	Nervous system disorders (N=16)	Eye disorders (N=11)
2	Immune system disorders (N=20)	Eye disorders (N=13)	Nervous system disorders (N=6)
3	Nervous system disorders (N=15)	Vascular disorders (N=9)	General disorders and administration conditions (N=5)
4	General disorders and administration conditions (N=10)	General disorders and administration conditions (N=7)	Injury, poisoning and procedural complications (N=4)
5	Skin and subcutaneous tissue disorders (N=10)	Immune system disorders (N=6)	Respiratory, thoracic and mediastinal disorders (N=4)

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Table 18 below shows SAEs by Preferred Term where use of olopatadine 0.1% was considered to be the primary suspect.

Table 18: Patanol Cases with SAEs and Preferred Term n≥3 [1997-2018] (FAERS Database)

Total Number of CASES	38
Eye Irritation	4
Eye Pain	4
Headache	4
Hypersensitivity	4
Anaphylactic Reaction	3
Anaphylactoid Reaction	3
Eye Disorder	3
Ocular Hyperaemia	3
Pyrexia	3
Visual Impairment	3

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Table 19 below shows SAEs by Preferred Term where use of olopatadine 0.2% was considered to be the primary suspect.

Table 19: Pataday Cases with SAEs and Preferred Term n≥3 [1997-2018] (FAERS Database)

Total Number of CASES	30
Eye Irritation	4
Headache	4
Back Pain	3
Blindness	3
Diarrhoea	3
Hypersensitivity	3
Migraine	3

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Dr. Donohoe observed that the number of FAERS reports for Pataday compared to Patanol seems fairly high, considering that Patanol was approved for marketing 8 years prior to Pataday, and also expressed concern about the high number of cases of “unknown brand.” Nevertheless, Dr. Donohoe concludes that this information is consistent with findings from the Applicant’s database and reflects the known safety profile of the olopatadine eye drops. I agree with Dr. Donohoe’s conclusion. It is difficult to make further comparisons between olopatadine products based on the FAERS data provided.

WHO Database

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. **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 nonserious; and there were 9 deaths, one of which was reported as a road traffic accident. Note that Olopat, Patanol/Patanol S, and Opatanol all represent 0.1% olopatadine.

Table 20: Summary of Cases with Olopatadine Reported as the Primary Suspect (WHO Database)

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)

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SAEs by Preferred Term for Patanol and Pataday are shown in the **Table 21** and **Table 22**, respectively, below:

Table 21: Patanol SAEs with Preferred Term n≥3 (WHO Database)

Total Number of EVENTS	119
Alopecia areata	6
Contusion	5
Death	5
Eye pain	4
Muscle spasticity	4
Pain	4
Cerebrovascular accident	3
Eye disorder	3
Eye irritation	3
Head injury	3
Muscle rigidity	3
Visual impairment	3

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Table 22: Pataday SAEs with Preferred Term n≥3 (WHO Database)

Total Number of EVENTS	146
Eye irritation	5
Diarrhoea	4
Headache	4
Hypersensitivity	4
Back pain	3
Blindness	3
Blood pressure abnormal	3
Diabetes mellitus	3
Migraine	3
Vision blurred	3

Electronically copied and reproduced from Dr. Donohoe’s clinical review. Source: Applicant’s submission of 9/16/19, Clinical Information Amendment, Data Tables Q4, 165/175

Dr. Donohoe reports that, overall, adverse events reported by WHO were similar to FAERS, with the most common events related to eye disorders. Dr. Donohoe noted that SAE reports for “cerebrovascular accidents” related to use of olopatadine eye drop products

would be highly unlikely as there does not appear to be a plausible mechanism of action. In order to verify information from the WHO database, Dr. Donohoe searched Mercado for nervous system disorders for the past year (to 10 October 2018) with zero results. For further discussion of the “cerebrovascular accidents” SAEs, please see the **Significant Adverse Events** section of this review.

Dr. Donohoe also searched Mercado (FAERS data) for reports of alopecia during the past year and found three expedited reports associated with Patanol; there were none with Pataday. One case involved a 5 year old girl who was actually taking Allelock (available in China and Japan) tablets (not Patanol), one case was a 34 year old female taking Patanol and an oral antihistamine where the case report stated that the reporting physician told the patient that use of antihistamines should be avoided as the patient had a family history of autoimmune disease (mother with Hashimoto’s thyroiditis and brother with Type 1 diabetes mellitus), and a third case in a 9 year old boy using Patanol who had pre-existing alopecia areata. Dr. Donohoe also did a PubMed search and identified one study¹⁰ that suggested that olopatadine may be used to treat alopecia areata. For further details, please see Dr. Donohoe’s clinical review. Dr. Donohoe concluded that “as there does not appear to be a plausible mechanism of action for olopatadine cause alopecia, reports of alopecia do not pose safety concerns.” I agree.

Deaths

The Applicant submitted a Clinical Information Amendment on 17 October 2019 to address FDA concern that data submitted for the WHO database (submitted on 16 September 2019; Data Tables Q4) for Patanol were not consistent with information in the accompanying 10-page narrative. In the Applicant’s pharmacovigilance database, there was a total of 6 cases that resulted in death, 4 of which were olopatadine was primary suspect product. The numbers of deaths reported from differing external safety databases are: FAERS = 5 Deaths; WHO data = 9 deaths. Four deaths were associated with the use of Allelock, a tablet available in China and Japan, and thus not included in FAERS. In addition, the WHO database reports 2 deaths attributable to olopatadine while FAERS codes them as Patanase (nasal spray approved in the U.S.). Thus, the differing attribution to brand between WHO and FAERS appears to be the result of WHO coding the cases as “olopatadine” and FAERS coding them as “Patanase.” **Table 23** 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 Medical Dictionary for Regulatory Activities (MedDRA) preferred terms.

¹⁰ T. Ito, et al; Antihistaminic drug olopatadine downmodulates T cell chemotaxis toward CXCL10 by reducing CXCR3 expression, F-actin polymerization and calcium influx in patients with alopecia areata; Letters to the Editor; *Journal of Dermatological Science*; 72 (2013) 61–77 69.

Table 23: 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

Electronically copied and reproduced from Dr. Boyd’s clinical review (Source: NDA 20688/S-032 Amendment 17 October 2019 Module 1.11.3).

The reader is referred to Dr. Boyd’s and Dr. Donohoe’s clinical reviews for details of the individual case reports. Dr. Donohoe reported that 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.

The “Patanol” death was in a 49-year old female whose medical history was not reported. She was on additional multiple medications including: Ritalin, Singulair, Lyrica, Dilaudid, Xyrem, Imitrex, Lidocaine patch and potassium chloride. Cause of death was not reported, it was not known if an autopsy was performed. The patient was on Patanol for “years”.

One of the deaths associated with “Pataday” listed “Patanol S Sol” in the report; this death was a homicide. The other death associated with “Pataday” was in an elderly male, age and medical history not reported. He was also using other eye drops: travoprost and brinzolamide [for presumptive glaucoma]. Unknown cause of death and unknown if autopsy was performed.

Dr. Donohoe concluded that the information from the WHO database has limited value, especially in respect to brand attribution for olopatadine products. Nevertheless, she further noted that “reports of ‘death’ do not raise any safety concerns.” I agree.

NPDS

The NPDS database search included 512 exposures from 2000-2019. The database was searched for the following terms: olopatadine; Pataday; Patanol; Patanase; Pazeo; Opatanol; Olopat; Allelock. The five top SOC categories were: ocular = 262 (48%); miscellaneous = 91 (17%); neurological = 82 (15%); gastrointestinal = 59 (11%); and dermal = 38 (7%). No deaths were reported. Although 43% of the reports of exposure were in individuals age 13-69 years old, children ≤ 5 years old represented the second largest age group (117 [21%]). This is not surprising given that NPDS is a poison control center database. Dr. Donohoe concluded that, “given the significant limitations with this database (including the inability to identify brand, varying years product may have entered market, and the unlikelihood that reports related to events seen with olopatadine drug products would be in a database for “poison control”), specific conclusions cannot be made in regard to these findings beyond a general impression that findings are consistent with the known safety profile of the drug product.” I agree.

Summary of Postmarket Data from Databases

In summary, as noted by Dr. Donohoe in her review, postmarket database searches of products with olopatadine 0.1% and olopatadine 0.2% provided valuable information though had limitations. Multiple IRs were sent to the Applicant to clarify information. Eye-related events accounted for most of all adverse events reported in the Applicant and FAERS databases. Data collected from the WHO database were somewhat similar but of less value. Information from NPDS did not provide additional insight into the known safety profile of Patanol and Pataday. The adverse events reported in the searched databases are consistent with the known safety profile of olopatadine and no new trends or patterns were identified. Most AEs for both Patanol and Pataday involve eye disorders and, in general, are similar to AEs listed in Rx labeling. Where reported, most AEs are for the 12–64 years and >65 years age groups; this pattern is consistent with higher volume of use in these age groups relative to the other groups.

Literature

The Applicant conducted a PubMed search and retrieved relevant publications from two scientific databases, Medline and Embase, from 1 May 2015 through 30 April 2018. In March 2019, an updated search was done, retrieving additional literature from two scientific databases, PubMed/Medline and Google Scholar, for the period of 1 January 2018 through March 2019. Subsequently, the

Applicant submitted a 120-day Safety Update which covered the period from 1 January 2019 to 31 October 2019. Dr. Donohoe also performed a PubMed search herself. From the period of 1 January 2019 through March of 2019, publication-reported treatment emergent adverse events with use of olopatadine 0.1% included oropharyngeal discomfort (6.1%), headache (7%), and burning sensation of eyes (3%).¹¹ An additional article¹² involved “an evaluation of 126 subjects (age range, 3-17) that revealed no clinically relevant treatment-related changes in visual acuity, intraocular pressure, slit-lamp assessments, fundus examinations, or cardiovascular parameters. All adverse events reported were mild or moderate” and it was concluded that “olopatadine 0.2% administered once daily for 6 weeks is safe and well tolerated in children and adolescent patients.”

For further detailed summaries of the literature search, please see Dr. Donohoe’s clinical review. Dr. Donohoe concluded that, “literature provided does not alter the known safety profile of 0.1% olopatadine eye drops.” I agree.

Significant Adverse Events

The following significant adverse events were identified either by the Applicant or the review team.

Blindness

Narratives for three SAE cases with the Preferred Term “blindness” were reported under Pataday, noted in the Argon database (as well as FAERS and WHO), and were submitted in the Clinical Information Amendment of 16 September 2019. Please see Dr. Donohoe’s and Dr. Boyd’s reviews for detailed narratives. In his clinical review, Dr. Boyd points out that the limited information available on the three cases with the preferred term “blindness” precludes a meaningful causality assessment. Dr. Boyd notes that 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. Dr. Boyd concludes that there were no safety issues identified that would preclude the safe administration of olopatadine ophthalmic solution 0.1% or 0.2% as an OTC product.

Dr. Donohoe observes that there may be a plausible mechanism of action for olopatadine eye drop products to cause “blindness”, as “keratitis” and “punctate keratitis” (inflammation of the cornea, a known adverse reaction), if left untreated, may result in loss of

¹¹ NDA 206288 submission of 15 April 2019; ISS, page 56 of 66.

¹² Lichtenstein, SJ et al; Safety and tolerability of olopatadine 0.2% in children and adolescents. *J Ocul Pharmacol Ther.* 2007 Aug;23(4):366-71.

vision¹³. In addition, the presence of the preservative benzalkonium chloride may, in itself, result in corneal toxicity¹⁴, as the Applicant also noted in its Benefits and Risks Conclusion¹⁵, and contact lens overwear may also result in keratitis¹⁶. However, Dr. Donohoe agrees that, as described above in the case reports, information is limited in all three cases; two patients were elderly and in one, age was not reported. None of the three cases had a medical history reported or information about concomitant medication but all three included reports of “legally blind”. Dr. Donohoe concludes that insufficient information is included to establish causality. I agree.

Corneal Damage

The Applicant identified “corneal damage” as an important potential risk. According to the Applicant¹⁷, corneal disorders, keratitis and punctate keratitis are listed adverse events as per the current Core Company Data Sheet for olopatadine 0.1% and 0.2% eye drops, solution. Only a few serious cases of corneal disorders have been reported through postmarketing surveillance. Dr. Donohoe reports 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 (benzalkonium chloride) rarely result in hospitalization.

Cerebrovascular Accident

Regarding the three 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). However, the Applicant’s internal database and the FAERS database confirmed that the two cases where Pataday was the primary suspect product are identical in both databases. Therefore, narratives for two Pataday cases of cerebrovascular accident (Internal Alcon Database and FAERs) were submitted in the Clinical Information Amendment of 9/16/2019. Please see Dr. Boyd’s review for detailed narratives of these two cases. Dr. Boyd concludes that the limited information available on the two Pataday 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. Therefore, Dr. Boyd

¹³ Merck Manual, Superficial Punctate Keratitis <https://www.merckmanuals.com/professional/eye-disorders/corneal-disorders/superficial-punctate-keratitis?query=keratitis>; accessed 10/21/2019.

¹⁴ Baudouin, C. et al; Preservatives in eyedrops: The good, the bad and the ugly; *Progress in Retinal and Eye Research* 29 (2010) 312-334.

¹⁵ Sponsor’s submission of 7/03/2019, Benefits and Risks Conclusion, p. 12/19.

¹⁶ Merck Manual [see above footnote].

¹⁷ Applicant’s Submission of 07/03/2019, response to Information Request, SDN 410, Module 2.5 Clinical Overview

writes, “there are no safety issues identified that would preclude the safe administration of Patanol, Pataday, or Pazeo as an OTC product.” Dr. Donohoe concludes that SAE reports for “cerebrovascular accidents” related to use of olopatadine eye drop products would be highly unlikely as there does not appear to be a plausible mechanism of action. I agree.

Hypersensitivity

The Applicant identified “hypersensitivity” as an important identified risk. Hypersensitivity can range from mild local reactions to life-threatening anaphylactic reactions, is a known adverse event (see **Tables 13, 18, 19, and 22** above), and is identified in prescription labeling under **Adverse Events** for both Patanol and Pataday. No serious cases of hypersensitivity associated with olopatadine have been reported in clinical studies. However, cases have been reported through postmarket surveillance. For Patanol, under **Contraindications**, prescription labeling states, “PATANOL (olopatadine hydrochloride solution) 0.1% is contraindicated in persons with a known hypersensitivity to olopatadine hydrochloride or any components of PATANOL.” However, Pataday Prescription labeling contains no such contraindications. The Applicant reports that, “based on the incidences found in the Novartis safety databases, the potential for a significant impact on public health is expected to be low.”¹⁸

*CDTL Comment: No new safety signals were identified in the postmarketing review or in the literature that would preclude use of olopatadine 0.1% or 0.2% in the OTC setting. The adverse events reported are consistent with the known safety profile of olopatadine. Most AEs for both Patanol and Pataday involve eye disorders (eye irritation, eye pruritis, eye swelling, eye pain, eye disorder), and are similar to AEs listed in Rx labeling, and, in many cases, are likely related to the underlying disease (allergic conjunctivitis). Hypersensitivity is also a known adverse event, and may be related to the preservative (benzalkonium chloride) and not olopatadine, and could easily be confused with allergic symptoms. Nevertheless, the proposed Drug Facts labeling for both products will include the Warning **Do Not Use** “if you are sensitive to any ingredient in this product.” Regarding postmarketing reports of deaths, cerebrovascular accidents, and alopecia, review of the case reports provides no compelling evidence of an association with olopatadine eye drops. Furthermore, there is no plausible mechanism of action for these events, and the systemic absorption of olopatadine eye drops is so minimal (See **Section 5 Clinical Pharmacology**) that it would be extremely unlikely for these products to cause systemic effects. Reports of blindness and corneal damage are perhaps more plausible; however, the case reports did not support an association. For example, as Dr. Boyd pointed out, all three cases of blindness are in an elderly population which is susceptible to multiple reasons for decreased visual acuity risk including cataract, corneal disease, glaucoma, and macular degeneration. Lastly, it should be noted that the more severe forms of conjunctivitis, atopic keratoconjunctivitis (AKC) and vernal*

¹⁸ NDA 20688 and 21545 Module 2.5.6 Benefit and Risk Conclusion

keratoconjunctivitis (VKC), are considered more serious and may be associated with corneal scarring, neovascularization, ulceration, and other sequelae. Thus, it is possible that some of these cases may be associated with these more severe underlying diseases.

9. Advisory Committee Meeting

An advisory committee meeting was not held for this application as it is not a new class switch and does not raise significant public health issues.

10. Pediatrics

The two applications (**NDA 20688** and **NDA 21545**) do 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. Drug Facts labeling (DFL) for both products 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.

Pataday prescription labeling states, "Safety and effectiveness in pediatric patients below the age of 2 years have not been established." In contrast, Patanol prescription labeling states, "Safety and effectiveness in pediatric patients below the age of 3 years have not been established." However, as discussed in the **Regulatory Background** section above, at the Type B pre-sNDA Meeting held between FDA and the Applicant on 30 November 2010 (Patanol: **PIND 107178**), FDA agreed that it was acceptable for the Applicant to propose labeling down to 2 years of age without doing additional studies in 2 year olds. At the time of Patanol approval in 1996, safety and efficacy studies were conducted down to age 3 years, and this was therefore reflected in prescription labeling. However, FDA has determined since a 26 June 2009 Advisory Committee that there is essentially no difference in maturity of the eyes between ages 2 and 3, so 2-year olds may be considered as the same population as 3-year olds.

Pregnancy and Nursing

Patanol and Pataday Prescription Labeling both state the following:

***Pregnancy:** Olopatadine was found not to be teratogenic in rats and rabbits. However, rats treated at 600 mg/kg/day, or 93,750 times the MROHD and rabbits treated at 400 mg/kg/day, or 62,500 times the MROHD, during organogenesis showed a decrease in live fetuses. There are, however, no adequate and well controlled studies in pregnant women. Because animal studies are not always predictive of human*

responses, this drug should be used in pregnant women only if the potential benefit to the mother justifies the potential risk to the embryo or fetus.

Nursing Mothers: *Olopatadine has been identified in the milk of nursing rats following oral administration. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in the human breast milk. Nevertheless, caution should be exercised when...olopatadine hydrochloride ophthalmic solution...is administered to a nursing mother.*

Dr. Donohoe reviewed annual safety reports (2016-2019) and performed literature searches for information related to pregnancy and breastfeeding, and use of olopatadine. Please see Dr. Donohoe's clinical review for detailed description of the findings. In brief, during the reporting interval of the latest Periodic Safety Update Report (01 May 2015-30 April 2018), five cases of pregnancy associated with olopatadine eye drops were retrieved. 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 was retrieved. Analysis of these cases did not reveal any new safety information regarding use of olopatadine during breastfeeding. Literature searches did not reveal any significant safety findings. Based on information submitted to date regarding adverse events with use of olopatadine eye drops related to pregnancy and breastfeeding, Dr. Donohoe concluded that there are no safety signals of concern. There are no warnings for use when pregnant or breastfeeding in the proposed DFLs.

The three applications (**NDA 20688** Patanol; **NDA 21545** Pataday; and **NDA 206276** Pazeo) were discussed with the Division of Pediatric and Maternal Health (DPMH) to confirm that DPMH was in agreement that usage of olopatadine eye drop products is safe for use by pregnant and breastfeeding women in the OTC setting. This CDTL spoke directly to Miriam Dinatale, D.O., LCDR, USPHS, Team Leader, Maternal Health Team, DPMH. In email correspondence¹⁹, Dr. Dinatale reported that she performed a literature search in PubMed and LactMed and confirmed that "there do not seem to be any safety concerns with the use of topical olopatadine during pregnancy and lactation." She also noted that "it seems that systemic concentrations of olopatadine following topical administration of Pazeo were negligible."

¹⁹ Email correspondence of 10/25/2019 from Miriam Dinatale, Team Leader, Maternal Health Team, DPMH in response to inquiry by Francis Becker, Team Leader, DNNDP

***CDTL Comment:** I agree with the assessment of Drs. Donohoe and Dinatale. Importantly, systemic absorption of olopatadine eye drops appears to be negligible (see **Section 5 Clinical Pharmacology**), so effects on pregnancy or breastfeeding would be unlikely.*

11. Other Relevant Regulatory Issues

Not applicable.

12. Labeling

Proprietary Name Review

Proprietary name reviews^{20,21} were conducted by Grace P. Jones, PharmD, BCPS; Chi-Ming (Alice) Tu, PharmD; and Danielle Harris, PharmD, BCPS, of the Division of Medication Error Prevention and Analysis (DMEPA). The DMEPA team concluded that the proposed proprietary names, Pataday Twice Daily Relief for the olopatadine 0.1% product (NDA20688), and Pataday Once Daily Relief for the olopatadine 0.2% product (NDA 021545) are acceptable.

Upon initial review, the DMEPA team expressed concern about potential consumer confusion between the products because: 1) both products share the “Pataday” name; 2) the suffix “-aday” in the root name Pataday implies once daily, which may be confusing the proposed proprietary name Pataday Twice Daily Relief because both “a day” and “twice daily” are together in the product name; and 3) the proposed names Pataday Once Daily Relief and Pataday Twice Daily Relief imply the duration of efficacy or the frequency of administration. However, DNP II noted that clinical trials have established safety and efficacy up to a daily dose of one drop in each eye of olopatadine 0.7%. Therefore, as confirmed in internal discussions with the Division of Ophthalmology, the safety margin is such that 2 or 3 of these products could be administered at the same time or sequentially without altering safety or efficacy.

The DMEPA team also noted that, while they did not identify any application OTC products that incorporate the modifier “Once Daily” or “Twice 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.). DMEPA pointed out that, because we typically

²⁰ NDA 20688 Proprietary Name Review; 9 July 2019.

²¹ NDA 021545 Proprietary name Review; 9 July 2019.

see the modifier “Relief” in conjunction with the symptoms for which the product provides relief, it is unclear how consumers would interpret “Relief” when used in conjunction with the frequency of administration “Once Daily [Twice Daily]”. However, from a medication error perspective, the DMEPA team does not anticipate the combination of the words “Once Daily Relief [Twice 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.” The DMEPA team continued, “Per the review team, even if consumers were to take this product incorrectly, dose it more frequently, or use more than one olopatadine product at a time, there is no safety concern. Therefore, for these reasons, we do not object to the use of the modifiers, Once Daily Relief [Twice Daily Relief]. DMEPA concluded that proposed proprietary names are in totality acceptable.

DMEPA Labeling Review

The DMEPA team (Grace P. Jones, PharmD, BCPS; Chi-Ming (Alice) Tu, PharmD), also conducted a Labeling Review.²² Specifically, DNP II requested that DMEPA review the container labels and carton labeling for areas of vulnerability that may lead to medication errors. The team reviewed the Product Information/Prescribing Information, labels, and labeling. DMEPA concluded that “the proposed Pataday Twice Daily Relief (NDA 020688) and Pataday Once Daily Relief (NDA 021545 and NDA 206276) may be improved to ensure safe use of the proposed products and to minimize potential medication errors.”

DMEPA recommended the following to 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.

²² NDA 20688 and 021545 Label and Labeling Review; 7 January 2020.

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.”

Interdisciplinary Science Team Labeling Review

Labeling Reviews for Pataday Twice Daily Relief (NDA 20688)²³ and Pataday Once Daily Relief (NDA 21545)²⁴ were also conducted by Arlene Solbeck, MS (Team Leader: Sergio Coelho, PhD), Interdisciplinary Science Team, DNPD I.

Pataday Twice Daily Relief (NDA 20688)

As noted previously, on 20 June 2019, the Applicant submitted an amendment to sNDA 20688 with revised labeling to add back the “redness” indication to the labeling. On 27 December 2019, FDA submitted information requests for the carton and container labeling for Pataday Twice Daily Relief submitted on 20 June 2019. In addition to revisions in accordance with content and format specifications (see Ms. Solbeck’s reviews for details), important labeling requests included in the IR were as follows:

Overall

- Since Pataday TWICE DAILY RELIEF and Pataday ONCE DAILY RELIEF (NDA 021545/S-22; revised labeling submitted November 25, 2019 and reviewed under separate cover) have similar proprietary names but different indications, we recommend that you address potential consumer confusion between the products by revising the design elements on the Principal Display Panels (PDPs), e.g., by use of an alternate color scheme, graphic, or other strategy.

Carton Principal Display Panel (PDP)

- Revise the proposed Statement of Identity (SOI) from (b) (4) (b) (4) ” to read “Olopatadine hydrochloride ophthalmic solution 0.1% Antihistamine and Redness Reliever” by removing the word (b) (4) from the (b) (4)
- Revise the claim (b) (4) to read “Eye Allergy Itch and Redness Relief” to be consistent with products in this category.

²³ Labeling Review for Pataday Twice Daily Relief (Olopatadine hydrochloride) Ophthalmic Solution 0.1%; NDA 20688 S-32; 13 January 2020.

²⁴ Labeling Review for Pataday Twice Daily Relief (Olopatadine hydrochloride) Ophthalmic Solution 0.2%; NDA 21545 S-22; 13 January 2020.

Carton Side Panel

- Revise the claim (b) (4) to read “Eye Allergy and Itch and Redness Relief” to be consistent with products in this category.
- Delete or revise (b) (4).

Immediate Container (bottle)

- Revise the claim (b) (4) to read “Eye Allergy Itch and Redness Relief” consistent with products in this category.

The Applicant submitted revised labeling on 3 January 2020. Ms. Solbeck generally concluded that the Applicant adequately revised the labeling in compliance with the IR and found the submitted revisions acceptable.

Pataday Once Daily Relief (NDA 21545)

On 15 April 2019, the Applicant submitted a proprietary name review with the requested name of Pataday Once Daily Relief (see **Proprietary Name Review** section above). On 19 September 2019, the Applicant submitted a proposal to withdraw this name, and the Applicant proposed a new name of (b) (4).” However, after discussions with the FDA on the appropriateness of this name, the Applicant withdrew the name request on 22 November 2019 and, on 25 November 2019, submitted a labeling amendment with the originally proposed “Pataday Once Daily Relief.”

The information request of 27 December 2019 was similar in content as described above for Pataday Twice Daily Relief with the following important addition:

Carton Principal Display Panel (PDP)

- To be consistent and parallel with olopatadine hydrochloride 0.1% product, which states “twice daily relief”, delete the “(b) (4)” claim and replace with “ONCE DAILY”. We acknowledge that the sponsor (you) removed “(b) (4)” from the proposed proprietary name. However, the claim (b) (4).

Overall, the Applicant complied with the IR, and the submitted labeling was found to be acceptable.

CDTL Comment: The proposed (b) (4) was submitted shortly after the Applicant Submitted sNDA 206276 Pazeo for Rx-to-OTC switch and was an attempt to aid consumers in distinguishing between the 0.2% and 0.7% products, both of which are to be administered once daily for the same indication. According to the Division of Ophthalmology, (b) (4). However, DNPD II Clinical Team expressed concerns that consumers in the OTC setting would perhaps misunderstand and (b) (4). The concerns were conveyed to the Applicant who changed the name back to Pataday Once Daily Relief. NDA 206276 Pazeo review is ongoing and is not the subject of this review.

Outstanding Issues/Additional Comments

For both applications, the IDS Labeling Team identified the following two outstanding issues for which clinical feedback was requested:

1. The Applicant dropped the “(b) (4)” from the statement on the PDP, as shown below:

“Relief from (b) (4) allergens:

- Pet dander
- Pollen
- Grass
- Ragweed”



2. In the Drug Facts, the words “^{(b) (4)}” were deleted from the subheading of the section **Stop use and ask a doctor if**. Originally, it read “**Stop use and ask a doctor if** you experience ^{(b) (4)}” The latest submitted revised label now reads “**Stop use and ask a doctor if** you experience:”

IDS Labeling deferred these two issues to the clinical review team to determine if the Applicant needed to revise back to the original form from a clinical safety perspective.

CDTL Comment: The Clinical Team (Dr. Donohoe and I) agree that the proposed labeling changes above are acceptable and pose no clinical concern. The omitted word “^{(b) (4)}” and the omitted clause ^{(b) (4)} are not on other DFLs for OTC allergy eye drops.

In addition, the IDS team identified the following outstanding issues, which were conveyed to the Applicant on 17 January 2020:

1. Revise the SOI on the carton and container labeling so that there is no break between “ophthalmic” and “solution.” This might require the SOI to be three lines instead of two. This is to be consistent with other products in this category. To do this it may be necessary to reduce the size of the red and blue graphic on the carton labeling to provide real estate.
2. In Drug Facts, the hairlines should not extend to each end of the Drug Facts box. Applicant needs to revise this item.

3. In response to our request for the Applicant to confirm the font and format specifications using annotated labeling, the Applicant submitted specifications but failed to include bullet type size specifications. Applicant needs to submit type size for bullets in Drug Facts.
4. From DMEPA: Increase the prominence of the “ONCE DAILY RELIEF” in the proposed proprietary name. DMEPA requested this in their review dated 1/7/2020 to help consumers easily recognize the proposed product’s dosing administration and dosing interval. They are also recommending this for the “TWICE DAILY RELIEF” product, reviewed under separate cover. They suggest that the Applicant consider reducing the size of the red and blue graphic on the carton to provide real estate. DMEPA believes that the other information on the PDP appears more prominent than the modifiers.

Ms. Solbeck concluded that, “Issuing an APPROVAL letter could be acceptable after the Applicant addresses all outstanding issues.”

The labeling team also asked the Applicant to address potential consumer confusion between the two products because both products have similar proprietary names but different indications. The team suggested revising the design elements of the PDP by use of an alternate color scheme, graphic, or other strategy. Previously, both the 0.1% and 0.2% product used a white background on the entire carton. To address this, the Applicant revised the 0.1% product carton as follows (the two carton designs are shown below to highlight the differences:



Subsequently, the Applicant provided, in an email dated 8 January 2020, six additional options, shown below, to help consumers differentiate the twice daily product from other Pataday products, and the Applicant requested feedback from FDA. The IDS team conveyed to the Applicant that the middle option in the first row may be an acceptable option.



The Applicant responded to the January 17 IR on 22 January 2020 and addressed all remaining outstanding issues:

- The Drug Facts box was updated to ensure the horizontal hairlines do not extend on either side to each end of the Drug Facts box.
- The Applicant confirmed that the bullets in the Drug Facts were solid square bullets in 5-point type size.
- The Applicant confirmed the prominence of the naming modifier “TWICE DAILY RELIEF” (**NDA 20688**) and “ONCE DAILY RELIEF” (**NDA 21545**) were increased by increasing the font size on both the carton and container labels. In order to do this, the Applicant either shifted the red and blue graphic down (carton) or decreased the brand name “Pataday” (bottle for **NDA 20688**; bottle and pouch for **NDA 21545**)
- The Applicant confirmed that the SOI for Pataday Once Daily Relief was updated and “ophthalmic” and “solution” are on the same line.

The IDS Labeling team confirms that all of the outstanding labeling issues have been adequately addressed by the Applicant and are acceptable. In addition, the Applicant chose to use the FDA preferred option of the six possibilities above Pataday Twice Daily Relief, shown below:



Thus, final labeling for the two products is acceptable for approval and is illustrated below:

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

13. Postmarketing Recommendations

None.

14. Recommended Comments to the Applicant

None.

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
02/13/2020 12:41:48 PM

KAREN M MAHONEY
02/13/2020 02:32:09 PM

I concur with Dr. Becker's CDTL review, and with his recommendation for approval.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021545s022

CLINICAL REVIEW(S)

Clinical Review
 Elizabeth Donohoe, MD
 sNDA 020688 Pataday Twice Daily Relief

CLINICAL REVIEW

Application Type	505(b)(1)
Application Number(s)	sNDA 020688
Priority or Standard	Standard
Submit Date(s)	15 April 2019
PDUFA Goal Date	14 February 2020
Division/Office	Division of Non-prescription Drug Products (DNNDP)/Office of Drug Evaluation IV
Reviewer Name(s)	Elizabeth Donohoe, MD
Established/Proper Name	olopatadine hydrochloride, 0.1%
(Proposed) Trade Name	Pataday Twice Daily Relief ¹
Applicant	Alcon Research, LLC (Alcon)
Dosage Form(s)	ophthalmic solution
Applicant Proposed Dosing Regimen(s)	One drop in the affected eye(s) twice daily, every 6 to 8 hours, no more than twice per day
Applicant Proposed Indication(s)/Population(s)	Temporarily relieves itchy and red eyes due to pollen, ragweed, grass, animal hair and dander/adults and children 2 years of age and older
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Temporarily relieves itchy and red eyes due to pollen, ragweed, grass, animal hair and dander/adults and children 2 years of age and older

¹ Proposed proprietary name, Pataday Twice Daily Relief, is noted as acceptable in the Division of Medication Error Prevention and Analysis review by Grace P. Jones, PharmD, BCPS, submitted in DARRTS 7/9/2019.

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Glossary

AE adverse event
CMC chemistry, manufacturing, and controls
CVA cerebrovascular accidents
DNPD Division of Nonprescription Products
DTOP Division of Transplant and Ophthalmology Products
eCTD electronic common technical document
FAERS FDA Adverse Event Reporting System
FDA Food and Drug Administration
PIND preinvestigational new drug application
IR information request
ISS integrated summary of safety
NHANES National Health and Nutrition Examination Survey
NDA new drug application
NPDS National Poison Data System
OTC over-the-counter
PSUR periodic safety update report
PT preferred term
Rx prescription
SAE serious adverse event
sNDA supplemental NDA
SOC System Organ Class
WHO World Health Organization

1. Executive Summary

1.1. Product Introduction

Pataday Twice Daily Relief is composed of a 0.1% olopatadine hydrochloride solution for use as a topical ophthalmic agent indicated for treatment of signs and symptoms of allergic conjunctivitis (itching and redness); this product was initially approved in 1996 as a prescription drug product and is currently sold as “Patanol”. The Applicant proposes the same indication and dosing as stated in the prescription labeling; dosing instructions are adults and children 2 years of age and older: put 1 drop in the affected eye(s) twice daily, every 6-8 hours. For ease of reference, “Pataday Twice Daily Relief” is referred to as “Patanol” in this review.

Note that this review also references information related to 0.2% olopatadine hydrochloride solution (approved as “Pataday”, NDA 021545) as the Applicant submitted sNDA 020688 and sNDA 021545 at the same time. See Section 3 Regulatory Background.

Olopatadine

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 of ocular pruritus due to allergic conjunctivitis and as a nasal spray for the relief of the symptoms of seasonal allergic rhinitis. The ophthalmic solution is the first ophthalmic agent with both antihistamine and mast cell stabilizing effects. Olopatadine 0.1% ophthalmic solution (Patanol) was approved by the Food and Drug Administration (FDA) in December 1996. A once daily ophthalmic formulation of olopatadine 0.2% (Pataday) was approved by the FDA in December 2004. Olopatadine nasal spray (Patanase) was approved by the FDA in adults and pediatric patients 12 years of age and older in April 2008 and in children 6—11 years of age in December 2009. 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 seasonal allergic rhinitis. Olopatadine does not act upon alpha-adrenergic, dopaminergic, type 1 or type 2 muscarinic, or serotonergic receptors. There is minimal, often undetectable, systemic absorption with ophthalmic use. Following topical ocular administration, plasma concentrations of olopatadine were in the range of 0.5—1.3 ng/ml within 2 hours of dosing and were undetectable after 2 weeks of dosing in normal volunteers.²

²<https://www.clinicalpharmacologyip.com/Forms/Monograph/monograph.aspx?cpnum=2135&sec=mondesc&t=0;> accessed 7/30/2019.

The half-life in plasma is approximately 3 hours, and elimination is predominantly through renal excretion. Olopatadine is not extensively metabolized. Approximately 60-70% of the dose was recovered in the urine as parent drug. Two metabolites, the mono-desmethyl and the N-oxide, were detected at low concentrations in the urine. Results from an environmental study demonstrated that Patanol was effective in the treatment of the signs and symptoms of allergic conjunctivitis when dosed twice daily for up to 6 weeks. Results from conjunctival antigen (CAC) challenge studies demonstrated that Patanol, when subjects were challenged with antigen both initially and up to 8 hours after dosing, was significantly more effective than its vehicle in preventing ocular itching associated with allergic conjunctivitis.³ “Signs and symptoms of allergic conjunctivitis” include itching and redness.

Olopatadine hydrochloride 0.7% eye drops, a prescription drug marketed as Pazeo (NDA 206276), was approved by the FDA in 2015. The Applicant cross-references these additional olopatadine eye drop products (Pataday and Pazeo) in its submission. Of note, the Applicant has also submitted a supplemental NDA (sNDA) 021545 for a full-switch of Pataday 0.2% eye drops to over-the-counter (OTC) and a sNDA for a full-switch of Pazeo, 0.7% eye drops. The proposed indication for both Pataday and Pazeo is “temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair and dander/adults and children 2 years of age and older”. The proposed OTC names for Pataday and Pazeo are “Pataday Once Daily Relief” and “Pataday 24-Hour Relief”, respectively, but are under Agency review. Note that each of the three olopatadine-containing eye drops proposed for Rx-to-OTC switch all have “Pataday” in the name.

Multiple OTC products to treat eye allergy symptoms are marketed in the United States; some are approved through the new drug application (NDA) process or marketed via the monograph system.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Efficacy of Patanol was established under review of NDA 020688, approved in 1996 as a prescription drug product. In the sNDA submission, the Applicant states in the Summary of Clinical Efficacy: “Seven conjunctival allergen challenge (CAC) studies have demonstrated superior efficacy in reducing ocular itching and redness of olopatadine at concentration of 0.05% and 0.1%, compared with placebo. Four environmental trials were conducted to demonstrate and confirm efficacy of Patanol (olopatadine, 0.1%).”⁴

Efficacy of Pataday was established under review of NDA 021545, approved in 2004 as a prescription drug product. In the sNDA submission, the Applicant states in the Summary of

³ From prescription labeling for Patanol, NDA 020688; accessed at drugs@fda
https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/20688slr016_patanol_lbl.pdf; 9/26/2019.

⁴ sNDA 020688 submission of 4/15/2019 under Module 2.2, Section 2.7.3.

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Clinical Efficacy: “While much of the efficacy of olopatadine-containing ophthalmic solutions is supported by studies of the 0.1% Patanol formulation, there are a number of Pataday specific studies, including 858 patients, that were included in the original Pataday NDA. Three are CAC studies relevant for the evaluation of efficacy. In addition, there are also three environmental studies that further support the efficacy of the product. The overall objective of the clinical development was to demonstrate that Pataday (olopatadine 0.2%) is effective and well tolerated for the treatment of ocular itching associated with allergic conjunctivitis when dosed once-daily.”⁵

Refer to the review conducted by the Division of Transplant and Ophthalmology Products (DTOP) for a more comprehensive discussion of efficacy.

⁵ sNDA 021545 submission of 4/15/2009 under Module 2.2, Section 2.7.3.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

I recommend approval of the prescription (Rx)-to-Over-the-Counter (OTC) switch of 0.1% olopatadine hydrochloride ophthalmic solution for the temporary relief of itchy and red eyes due to pollen, ragweed, grass, animal hair and dander in adults and children 2 years of age and older.

There have been multiple OTC ophthalmic drops approved under an NDA to treat symptoms related to allergies on the market since 1994. It is long established that the symptoms and condition are readily diagnosed by consumers and treatment provides great benefit in daily quality of life issues. There may be additional benefit with this eye drop product as it has both antihistamine and mast-cell stabilizer properties; its twice a day dosing to treat both itchy and red eyes is also a benefit. The risks are negligible and would be adequately addressed in labeling.

Highlights of the Submission and Approval Recommendation:

The approval recommendation is from a clinical standpoint and for the indications and the intended populations the Applicant has requested.

This application is an efficacy supplement to the original NDA submission (sNDA 020688). This application relies on the Agency's prior findings of safety (including nonclinical safety) and efficacy for the approved listed drug product, Patanol 0.1% (olopatadine hydrochloride, 0.1%) which was approved in 1996 for the treatment of signs and symptoms of allergic conjunctivitis in adults and children 3 years of age and older. Meeting minutes under PIND 107178 discussing an Rx-to-OTC switch on 11/30/2010 note that the Applicant may propose labeling down to 2 years of age. See Section 3.2 Summary of Presubmission/Submission Regulatory Activity.

The Applicant revised its original indication "treatment of ocular itching" to reflect the full indication in the Rx product "relief of signs and symptoms of allergic conjunctivitis" following a teleconference with the Food and Drug Administration (FDA) on June 11, 2019 discussing a Full Switch vs. Partial Switch. For OTC purposes, the indication is "temporarily relieves itchy and red eyes due to pollen, ragweed, grass, animal hair and dander/adults and children 2 years of age and older".

The Applicant's summary of clinical safety, which included literature and postmarket safety from the Novartis/Alcon internal database, the FDA Adverse Event Reporting System (FAERS), the World Health Organization (WHO), and the National Poison Data System (NPDS) (through 2018), did not raise safety concerns.

An additional safety consideration for this review involved evaluation of the name(s) for both 0.1% and 0.2% olopatadine eye drop products and the potential for consumer confusion. This reviewer notes points made in the Division of Medical Error Prevention and Analysis review: “The safety margin of olopatadine is such that 2 or 3 of these products could be administered at the same time or sequentially without altering safety or efficacy. We met internally with the Division of Nonprescription Products (DNPP) and the Division of Transplant and Ophthalmology Products (DTOP) to discuss these comments and learned that if confusion occurs between the 2 proposed OTC olopatadine ophthalmic products (i.e., 0.1% and 0.2% strengths), there would be minimal public health safety concern and no harm to consumers.” The 0.7% olopatadine eye drop product (Pazeo, approved under NDA 206276) is currently marketed; if a consumer were to mistakenly “overdose” 0.2% twice a day (or every 16 hours), the exposure would still be less than a dose of 0.7%, which we know is safe when used as directed.

Table 1: Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> Allergic conjunctivitis is common Estimated frequency of allergic conjunctivitis ranges from 5% to 22% of the population depending on the area studied. Symptoms of eye itchiness and redness are common 	<ul style="list-style-type: none"> Relief of eye itchiness and redness due to allergic conjunctivitis is important to consumers for both physiologic and cosmetic reasons Relief of symptoms of allergic conjunctivitis improves quality of life for consumers
Current Treatment Options	<ul style="list-style-type: none"> Multiple antihistamine eye drop solutions are currently marketed OTC to treat allergic conjunctivitis Mechanisms of action for OTC eye drops include antihistamines, vasoconstrictors, and mast cell stabilizers 	<ul style="list-style-type: none"> Pharmacotherapy has been the mainstay of treatment for conjunctival irritation and the fact that most sufferers self-treat for minor eye irritations, highlight the importance of OTC treatments for control of some of the symptoms.
Benefit	<ul style="list-style-type: none"> 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 1996. 	<ul style="list-style-type: none"> 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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p>Risk and Risk Management</p>	<ul style="list-style-type: none"> The Applicant is relying on preclinical and toxicology data and clinical studies for prior NDA submissions to support efficacy and safety. For a risk assessment in this application, the Applicant submitted a Summary of Clinical Safety (ISS) and Postmarket safety data from 2000-2018 The proposed OTC labeling has the essential warnings translated from the current Patanol Rx label; warnings regarding pregnancy and breastfeeding are not warranted The most common adverse events are related to the site of administration (eye disorders) and the underlying condition Overall numbers of reported adverse events (AEs) and serious AEs are low Safety in pediatric patients \leq 2 years of age has not been established Potential consumer confusion between the two proposed olopatadine-containing eye drops (0.1% and 0.2%) does not appear to introduce significant safety concerns. 	<ul style="list-style-type: none"> This eye drop has both antihistamine and mast cell stabilizing properties Olopatadine hydrochloride has a satisfactory safety profile in the prescription environment based on 23 years of clinical use and 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, eye symptoms. Safety of 0.1% and 0.2% olopatadine hydrochloride eye drop products is supported by clinical trial data submitted with the original applications and postmarketing data Warnings provided in the proposed OTC labeling may help mitigate the risk of serious adverse events. Potential misuse of the 0.1% or 0.2% olopatadine eye drops (in combination or dosing up to twice a day) exposes a consumer to a total of 0.4%, less than the amount from a 0.7% eye drop which is known to be safe. Potential misuse with the 0.7% eye drop will be discussed under the review for sNDA 206276.

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1.4. Patient Experience Data

Clinical studies for this product began prior to 1996 when Patanol was approved. No patient experience data was collected to this reviewer's knowledge.

X Patient experience data was not submitted as part of this application.

2. Therapeutic Context

2.1. Analysis of Condition

Allergy

Allergy affects more than 15% of the world population, and some studies have shown that up to 30% of the United States' (U.S.) population has some form of allergy. Most of these patients have various target organs for their allergies, and most have ocular involvement. The ocular component may be the most prominent and sometimes disabling feature of their allergy. Some are affected for only a few weeks to months, whereas others have symptoms that last throughout the year.

The allergic inflammatory component in allergic rhinitis has been extensively studied because of the high incidence of this condition, the significant morbidity it imposes, and the accessibility of nasal tissue. However, ocular symptoms are less well studied as an independent entity, and much of the clinical information is commonly buried within the rhinoconjunctivitis literature.

Allergic disease affects approximately 25% of the general population; allergic diseases affecting the eye are very common. Allergic conjunctivitis is commonly associated with allergic rhinitis and numerous eye symptoms. In one study of 5000 allergic children, 32% had ocular disease as the single manifestation of their allergies; of those children symptoms included: itchy (88%), red (78%), sore (75%), swollen (72%), and stinging (65%) eyes. The importance of allergic conjunctivitis is more the result of its frequency than its severity, which ranges from 5% to 22% of the population depending on the area studied. Numerous recent reports indicate that the incidence and prevalence of allergic conditions have increased dramatically during the past 40 years and continue to rise.⁶

Ocular allergy includes a spectrum of disorders, such as seasonal allergic conjunctivitis, perennial allergic conjunctivitis, vernal keratoconjunctivitis, and atopic keratoconjunctivitis. Seasonal and perennial allergic conjunctivitis, collectively known as allergic conjunctivitis, are the most common forms of ocular allergy. The overall prevalence of ocular allergy is reported to be ~15%–25% in the U.S. Although not life threatening, symptoms of allergic conjunctivitis, such as ocular itching, redness, eyelid swelling, chemosis, and tearing, significantly impact quality of life, particularly in the pediatric population.⁷

⁶ Bielory, L., *Allergic and Immunologic Disorders of the Eye. Part II: Ocular Allergy*; J Allergy Clin Immunol 2000; 106:1019-32.

⁷ Meier, E. et al; *Pharmacokinetics and safety of olopatadine hydrochloride 0.77% in healthy subjects with asymptomatic eyes: data from 2 independent clinical studies*, Clinical Ophthalmology 2017: 11, 669-681.

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Allergic conjunctivitis is an acute, intermittent, or chronic conjunctival inflammation usually caused by airborne allergens. It is due to a type I hypersensitivity reaction to a specific antigen and the diagnosis is clinical. The different categories of allergic conjunctivitis are further defined below:

- Seasonal allergic conjunctivitis (hay fever conjunctivitis) is caused by airborne mold spores, or pollen of trees, grasses, or weeds. It tends to peak during the spring, late summer, or early fall and disappear during the winter months—corresponding to the life cycle of the causative plant.
- Perennial allergic conjunctivitis (atopic conjunctivitis, atopic keratoconjunctivitis) is caused by dust mites, animal dander, and other nonseasonal allergens. These allergens, particularly those in the home, tend to cause symptoms year-round.
- Vernal keratoconjunctivitis is a more severe type of conjunctivitis most likely allergic in origin. It is most common among males aged 5 to 20 who also have eczema, asthma, or seasonal allergies. Vernal keratoconjunctivitis typically reappears each spring and subsides in the fall and winter. Many children outgrow the condition by early adulthood. Treatment is with topical antihistamines and mast cell stabilizers.⁸

Epidemiology

In the article “The epidemiology of ocular and nasal allergy in the United States, 1988-1994”⁹, authors state: Allergies give rise to the fifth-leading group of chronic diseases. However, the specific prevalence of ocular allergy is poorly described. The analysis in this article provides the first representation of the epidemiology of ocular allergy in the United States. The analysis, based on a cross-sectional sample of the U.S. population, allowed the authors to estimate the epidemiology of ocular allergy. The analysis evaluated the prevalence of ocular allergy and nasal allergy symptoms in relation to skin prick testing, which was then extrapolated to reflect prevalence in the U.S. population. Authors analyzed a report from the National Health and Nutrition Examination Survey (NHANES) III studying the epidemiology of allergic conjunctivitis, where 6.4% and 29.7% of 20,010 patients reported ocular symptoms and combined ocular and nasal symptoms, respectively. 40% of the population reported experiencing at least 1 occurrence of ocular symptoms in the past 12 months. Up to 40% of the population experienced ocular symptoms at least once in their lifetime, with a peak of symptoms in the months of June and July.

The analysis of NHANES III demonstrates that there are 3 distinct populations with regard to ocular and nasal allergy symptoms and that each of these populations demonstrates

⁸ <https://www.merckmanuals.com/professional/eye-disorders/conjunctival-and-scleral-disorders/allergic-conjunctivitis?query=Allergic>; accessed 7/29/2019

⁹ Singh, K. et al; *The epidemiology of ocular and nasal allergy in the United States, 1988-1994*; J Allergy Clin Immunol 2010; 126:778-83.

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differences in epidemiology and skin reactivity profiles. At the time of NHANES III, 6% of the U.S. population, approximately 18.5 million (according to current U.S. population clock) persons, reported isolated ocular symptoms throughout the year, and up to 40% reported symptoms at least once during the 6-year period of the conducted study, the highest prevalence reported to date. Ocular symptoms tend to be prevalent throughout all decades of adult life in contrast to those with nasal symptoms alone or both ocular and nasal symptoms, which appear to be more common at younger ages. When comparing age group by symptom, older patients (>50 years old) have more frequent isolated ocular symptoms, whereas younger patients (<50 years old) have more frequent isolated nasal and combined nasal and ocular symptoms.

The article also cites an Allergies in America Survey which found that 38% of the U.S. population has nasal allergies, but up to 25% to 40% of these persons reported associated red, watery, itchy eyes.

Treatment

The American Academy of Ophthalmology¹⁰ provides the following in regard to treatment of ocular symptoms due to seasonal/perennial allergic conjunctivitis. It is noted that itching is the primary symptom and presentation is most often bilateral.

Topical drops for allergic conjunctivitis come in many different forms.

- First line: Over-the-counter antihistamine/vasoconstrictor agent. Vasoconstrictors: Inexpensive over-the counter are first line. Many brands are available containing antazoline phosphate 0.05%, naphazoline HCl 0.05%, oxymetazoline HCl, tetrahydrozoline HCl 0.05%, or phenylephrine 0.12%. Chronic use of vasoconstrictive agents can lead to rebound vasodilation when discontinued.
- Second line: Second-generation topical histamine H1-receptor antagonist. H-1 receptor antagonists: Considered more effective than the vasoconstrictors, but much more expensive. The three principal choices are pheniramine maleate 0.3% (Naphcon), emedastine (Emadine), and levocabastine HCl 0.05% (Livostin).
- Third line: recurrent/persistent - mast-cell stabilizers can be used. Mast cell stabilizers: cromolyn sodium 4% (Crolom), nedocromil 2% (Alocril), pemirolast 0.1% (Alamast), and lodoxamide tromethamine 0.1% (Alomide). These are FDA-approved only for vernal conjunctivitis. Use only if other classes of medications have failed.

¹⁰ Au, A. and Grigorian, P. et al; Allergic Conjunctivitis; https://eyewiki.aao.org/Allergic_conjunctivitis; accessed 7/29/2019.

Combined medications can also be used: Combined H-1 receptor antagonist and mast cell stabilizers are more effective than the mast cell stabilizers alone. Ketotifen fumarate 0.025% (Zaditor and Alaway) is both an anti-histamine and a mast-cell stabilizer and is marketed OTC.

Mast cells play a central role in allergic reactions and inflammation. Successful anti-allergic therapies have typically targeted mast cell mediators, particularly histamine. Antihistaminic compounds interact with the various histamine receptors found on many cells, whereas other compounds such as disodium cromoglycate, are referred to as mast cell stabilizers, as they inhibit degranulation.¹¹

The predominant forms of allergic conjunctivitis include perennial allergic conjunctivitis (typically year-round and caused by house dust or animal dander), and seasonal allergic conjunctivitis (typically appearing during pollen season). The pathogenesis common to both involves a local and systemic immunological hypersensitivity reaction; through multiple mechanisms, contact of the ocular surface with environmental (usually airborne) allergens leads to mast cell degranulation and release of chemical mediators such as histamine. This release sparks a cascade of molecular events that manifest clinically as the hallmark signs and symptoms of allergic conjunctivitis: itching, conjunctival hyperemia, tearing, eyelid edema, chemosis, and rhinitis. The clinical presentation may vary, depending on the weather (worse in warm, dry climate) and the patient's exposure to allergens. Current therapeutic modalities attempt to improve the patient's quality of life by removing the offending allergen and/or modifying the inflammatory response. Initial management combines cold compresses, lubrication and an avoidance of allergens. If conservative therapy fails, the use of topical and oral medications is considered.¹²

2.2. Analysis of Current Treatment Options

There are numerous OTC ophthalmic solution products currently marketed to treat allergy symptoms (topical antihistamines). "Allergy symptoms" generally include itchy eyes due to: pollen, ragweed, grass, animal hair and dander; some products also include treatment of red eyes. Table 2 lists approved NDA OTC products ophthalmic solution products currently marketed to treat allergy symptoms; there are also many ophthalmic abbreviated NDAs marketed to treat allergy symptoms which are not included in the table below.

¹¹ Cook, EB et al; Mechanisms of antihistamines and mast cell stabilizers in ocular allergic inflammation. [Abstract], *Curr Drug Targets Inflamm Allergy*. 2002 Jun;1(2):167-80.

¹² drugs@fda, Clinical Review NDA 021545, p. 5/14, 12/14/2004.

Table 2: Current NDA OTC Ophthalmic Solutions to Treat Allergy Symptoms

NDA and Brand Name	Indication	Active Ingredient(s)	Dosage	Approval Date (OTC)
020485 Visine A	Temporarily relieves itchy, red eyes due to pollen,	0.025% naphazoline HCl, 0.3% pheniramine maleate		1/31/1996
020065 Opcon-A	ragweed, grass, animal hair and dander	0.02675% naphazoline HCl, 0.315% pheniramine maleate	1 or 2 drops up to qid \geq 6 yo	6/8/1994
020226 Naphcon A	Temporarily relieves itchy eyes due to pollen,	0.025% naphazoline HCl, 0.3% pheniramine maleate		6/8/1994
021066 Zaditor	ragweed, grass, animal hair and dander.	0.025% ketotifen fumarate		10/19/2006 [now ANDA only]
021996 Alaway		0.025% ketotifen fumarate	1 drop bid, \geq 3 yo	12/1/2006

Source: Constructed from DARRTS search

Note: above eye drops with “redness relief” contain the active ingredient naphazoline, a vasoconstrictor with safety the concern “ask a doctor before use if you have: heart disease, high blood pressure, trouble urinating, narrow angle glaucoma”. Olopatadine-containing eye drops do not have vasoconstrictive properties. One NDA-approved ophthalmic drug product (Lumify, NDA 208144) has an indication of “relief of redness” only; its active ingredient is brimonidine. In addition, there are numerous GRASE active ingredient ophthalmic vasoconstrictors marketed under Final Monograph (part 349) with an indication for “relief of redness of the eye” (not other allergy symptoms); e.g., tetrahydrozoline HCl 0.05%; directions for use for these eye drops state: 1-2 drops up to four times daily. There are also eyewash drug products under the monograph that have “relief of itching” as an indication.

Patanol would be the only OTC eye drop for relief of itching and redness with bid dosing; other eye drops marketed under the monograph have more frequent dosing.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Patanol was approved on 18 December 1996 as a prescription (Rx) drug product for the treatment of signs and symptoms of allergic conjunctivitis; signs and symptoms include itching and redness. The Applicant has submitted this efficacy supplement as a switch from Rx-to-OTC drug product for persons 2 years of age and older. There are other OTC eye drops with the same indication (see Table 2 above) but with more frequent dosing.

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sNDA 020688 Pataday Twice Daily Relief

The Applicant has concurrently submitted a sNDA to seek approval of Pataday® (olopatadine hydrochloride) Ophthalmic Solution 0.2% (NDA 021545) switch from Rx-to-OTC status for the indication to “temporarily relieve itchy eyes due to pollen, ragweed, grass, animal hair and dander” for persons 2 years of age and older. Pataday was approved on 22 December 2004 for the treatment of ocular itching associated with allergic conjunctivitis.

Olopatadine ophthalmic solutions are marketed in the United States under the trade names Patanol 0.1%, Pataday 0.2%, and Pazeo 0.7%.

- Patanol was approved on December 18, 1996, as a prescription drug under NDA 20688 for the treatment of signs and symptoms associated with allergic conjunctivitis (itching and redness) dosed twice a day.
- Pataday was approved on December 22, 2004, as a prescription drug under NDA 21545, for the treatment of ocular itching associated with allergic conjunctivitis dosed once a day.
- Pataday’s active ingredient, olopatadine, is also available as an intranasal spray under the name Patanase 0.66%.
- Pazeo was approved on January 30, 2015, as a prescription drug under NDA 206276, for the treatment of ocular itching associated with allergic conjunctivitis dosed once a day.

This review references information related to all three eye drop products containing olopatadine hydrochloride [Patanol (0.1%), Pataday (0.2%) and Pazeo (0.7%)] for ease of presenting information submitted by the Applicant as all three NDAs are currently under review for a proposed Rx-to-OTC switch. This review also references information submitted by the Applicant under sNDA 020688 that often relates to review of the 0.2% drug product, “Pataday”; this review references “Pataday” where this is the case. However, this review provides analysis and recommendations related only to the 0.1% product, “Patanol”. Also, for simplicity, this reviewer refers to the drug products as “Patanol” and “Pataday” and often refers to these ophthalmic solution products as “eye drops”.

3.2. Summary of Presubmission/Submission Regulatory Activity

Regulatory Background

Note that information below relates to both sNDA 020688 (“Patanol”) and 021545 (“Pataday”) as much of the information submitted is the same, especially in response to Information Requests (IR). Also, the Applicant generally submitted IR responses under sNDA 020688 and referenced those submissions under sNDA 021545.

(1) Meeting Requests

- A Type B Pre-sNDA Meeting was held between Alcon and the Agency on November 30, 2010 under preinvestigational new drug application (PIND) 107178.

(2) Meeting Minutes

- November 30, 2010 Meeting Minutes
 - FDA informed the Applicant that it may propose labeling down to 2 years of age; It is not necessary to do additional studies in 2 year olds. At the time Patanol was approved in 1996 safety and efficacy studies were done down to age 3 years and the Agency made the determination of safety and efficacy based on this data. The Agency has determined since the June 26th, 2009 Advisory Committee that there is essentially no structural difference in maturity of the eyes between the ages of 2 and 3 years, and 2 year old patients can be considered in the same patient population as 3 year olds. You may propose labeling down to the age of 2 years, similar to and consistent with the Bepreve product
 - FDA agreed that no additional Chemistry Manufacturing and Controls (CMC) or nonclinical safety studies need to be conducted to support the approval of a prescription to over-the counter switch of Patanol (olopatadine hydrochloride) 0.1% ophthalmic solution. 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 Patanol (NDA 20688).
 - The NDA application should contain a summary of postmarketing safety information for olopatadine from databases (worldwide) and from review of published literature. A summary and analyses of postmarketing safety surveillance information should be submitted of the currently marketed olopatadine product (including all adverse events) from the following safety databases:
 - Applicant's pharmacovigilance database
 - FDA Adverse Events Reporting System (AERS)
 - World Health Organization's (WHO) International Drug Monitoring Program
 - National Poison Data System (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.

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- The following information also needs to be provided:
 - A list of countries where olopatadine is marketed either as an Rx or OTC product. Include 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.
 - Summary protocols, narratives and analyses of serious adverse events (SAEs), deaths and discontinuations due to adverse events (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.

(3) Teleconference on April 3, 2019 under PIND 142363 (sNDA 021545, olopatadine hydrochloride 0.2%)

- Meeting minutes indicated that:
 - FDA noted that there are no significant differences in the safety and efficacy profiles for olopatadine 0.1%, 0.2%, and 0.7%, yet the Applicant proposed to switch only olopatadine 0.1% and 0.2%. The Applicant explained that 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 also noted that the distinction in the indications between olopatadine 0.1%, 0.2% and 0.7% is 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 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 a day; 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 a day dosing for any of the concentrations. FDA stated the Applicant will need to address the differences in indications of its products in its submission(s).
 - At the time, the Applicant proposed names were 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, upon approval of future marketing applications. FDA expressed concerns that consumers may not be able to differentiate between the two olopatadine products, especially since both products share similar indications. The need for a label discernment study was considered.

Note: upon further internal discussion, FDA determined that as there were no safety concerns with the Applicant's proposed names, they were acceptable. No additional consumer studies were warranted.

(4) Submission sNDA 020688

- April 15, 2019

Under 1.18 Proprietary Names, the Applicant provided the following information:

- *In market research conducted by Directions Research, Inc. on behalf of Alcon, consumers were easily able to differentiate between the two dosage strengths of olopatadine and their frequency of use. This research was an 11-cell design conducted via a 20 minute online interview and fielded May 14-15, 2016. The names used in this research were Pataday® (for 0.1% olopatadine) and Pataday® Extra Strength (for 0.2% olopatadine). As a result of the research, the names have been further clarified to Pataday® Twice Daily Relief and Pataday® Once Daily Relief, respectively, to further enhance understandability, and do not affect the applicability of the findings.*

This reviewer notes that the above study was conducted without input from the Agency and without additional review by DNDP Social Science.

(5) Filing sNDA 020688

- June 20, 2019

No filing issues identified. The following was included in the correspondence to the Applicant:

Under the Pediatric Research Equity Act (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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because none of the criteria apply at this time to your application, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for electronic common technical document submissions) of your application.

(6) Amendment to sNDA 020688 submitted June 20, 2019

- The Applicant submitted an amendment to the sNDA to add back "relief of redness"

to the indication to the labeling following a teleconference¹³ on June 11, 2019 discussing a Full Switch vs. Partial Switch. FDA Participants included Dan Brum, PharmD, Chief, Project Management Staff and Jung Lee, MS, RPh, Senior Regulatory Project Manager.

Note: The Applicant had not been aware that removal of “redness” as initially planned would have resulted in a partial switch to OTC (leaving “redness relief” under a prescription drug product).

(7) Response to Information Request submitted July 3, 2019

- The Applicant submitted a “Benefits and Risks Conclusion” that had been omitted in the initial submission.

(8) Amendment to sNDA 020688 submitted September 16, 2019

- The Applicant submitted a Clinical Information Amendment to address the Information Request sent 9/6/2019 requesting the following [summarized]:
 - Clarify the time period covered by the submitted Integrated Summary of Safety (ISS).
 - On p. 13/66 of the ISS, it states: “Since the treatment with this product may be maintained for up to four months, if necessary...”. Provide justification.
 - Clarify the number of deaths reported, by database.
 - Submit a “summary and analysis” for data retrieved from each safety database
 - Submit, broken out by brand (Patanol [0.1%], Pataday [0.2%], Pazeo [0.7%]) of olopatadine ophthalmic solution:
 - For each database, tables with AEs reported where olopatadine product was primary suspect, broken out by age, year reported and duration of use:
 - Top 5 SOCs [by count and percentage] for Serious AEs and non-serious AEs
 - All frequently reported serious AEs > 1% [by count and percentage] by Preferred Term [U.S.]. If > 1% does not result in at least 6 listings, adjust cut-off to include at least six listings
 - OTC: Most frequently reported AEs > 1% [by count and percentage] by Preferred Term [understood this may be limited due to narrow OTC market worldwide]. If > 1% does not result in at least 6 listings, adjust cut-off to include at least six listings.
 - Clarify what is covered in the Appendices.

¹³ Discussion minutes submitted as “Memorandum to File” in DARRTS, 6/20/2019.

(9) Amendment to sNDA 020688 submitted September 27, 2019

- The Applicant submitted a Clinical Information Amendment to address the Information Request to provide:
 - Units sold by brand (broken out by 0.1%, 0.2% and 0.7% olopatadine hydrochloride)
 - Narratives for the three Serious Adverse Events cases with the Preferred Term “blindness” reported under Pataday as noted in the Amendment to sNDA 020688 submitted September 16, 2019

(10) Amendment to sNDA 020688 submitted October 17, 2019

- The Applicant submitted a Clinical Information Amendment to address the Information Request to provide:
 - clarification of “deaths” reported under Patanol as noted in the Amendment to sNDA 020688 submitted September 16, 2019
 - narratives for five Serious Adverse Events with Preferred Term “cerebrovascular accident” reported under Patanol as noted in the Amendment to sNDA 020688 submitted September 16, 2019

(11) Amendment to sNDA 206276 (Pazeo) submitted October 22, 2019

- The Applicant submitted a Clinical Information Amendment to address the Information Request to provide data related to conduction of consumer studies to assess the ability of consumers to differentiate between the three olopatadine eye drop products for proposed OTC use (Pataday, Patanol and Pazeo).
 - A “label discernment study” was conducted by the Applicant; the protocol or any other materials were not submitted for review prior to study conduction.
 - 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) (Pataday) and (b) (4) (Pazeo). However, the Division of Nonprescription Products’ (DNPP’s) social scientist noted that the Applicant did not submit the protocol, questionnaire, or dataset. An IR was sent to the Applicant to provide additional information; this study is under review by DNPP’s social scientist.
 - Multiple variations of proposed labeling for Twice Daily Relief were tested; as of the writing of this review the Applicant had yet to submit an updated version since the 6/20/2019 submission.

This review does not address this study in further detail. See the clinical review for Pazeo (sNDA 206276) for a more thorough assessment of this submission.

(12) Anticipated Amendment to sNDA 020688

- The Applicant had not submitted a 120-day safety update, as required under 21 CFR 314.50(d)(5)(vi)(b). The 120-day safety update is also referred to as a 4-month safety update.
- Safety data submitted to date included:
 - ISS from initial submission of 4/15/2019: through Dec. 31, 2018
 - Annual Safety Report (PADER) submitted 6/27/2019: through April 30, 2019
- An IR was sent requesting the Applicant to:
 - Submit a 120-day safety update to cover May 1, 2019 through August 31, 2019.
 - Provide safety data from the Applicant’s database (adverse events and serious adverse events) for 0.1% and 0.2% olopatadine hydrochloride eye drops. Also provide a summary and analysis of the related important findings from your safety database as well as literature.

Summary of Issues and Actions

The Applicant has submitted a supplemental NDA for Rx-to-OTC switch of olopatadine 0.1% eye drop solution, currently marketed as Patanol. Review of Patanol as a proposed OTC product does not pose any specific efficacy or safety issue. However, as the Applicant also submitted sNDAs for Rx-to-OTC switches of olopatadine 0.2% eye drop solution (currently marketed as Pataday, NDA 021545) and olopatadine 0.7% eye drop solution (currently marketed as Pazeo, NDA 206276), an issue arose related to consumers’ ability to differentiate appropriately between the three eye drops.

Although separate DNDP clinical reviews are being conducted for each olopatadine eye drop product, reference may be made to the other products in any one review. The indication for Patanol (relief of itching and redness) differs from Pataday and Pazeo (relief of itching) as does the dosing regimen (twice a day for Patanol versus once a day for Pataday and Pazeo). A consumer’s ability to differentiate between these eye drops is somewhat more of a concern with Pataday and Pazeo since the indication and dosing are the same; this issue is addressed in the DNDP clinical review for Pazeo.

3.3. Foreign Regulatory Actions and Marketing History

Olopatadine 0.1% eye drops solution is marketed as a prescription drug product in 112 countries and OTC in 5 countries.¹⁴ The first Alcon product containing olopatadine for ocular

¹⁴ Source: Applicant submission of 4/15/2019 Module 5.3.5.3, Appendix 14.

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use was first registered in Puerto Rico on 01 Dec 1996.¹⁵ Although an olopatadine eye drop product has been marketed since 1996, the Applicant provides distribution data from the year 2000 on.

Distribution¹⁶

The Applicant provided information for eye drops (solution) in the post-marketing setting (non-clinical trial). The cumulative number of units sold, from 2000 through 4/30/2018 was:

(b) (4). Cumulative exposure by units, with distribution among regions, was:

- Japan: (b) (4)
- U.S.A./Canada: (b) (4)
- European Economic Area: (b) (4)
- Rest of World: (b) (4)

The Table below shows worldwide distribution data for nonprescription use, ophthalmic use (global manufacturers and generics). During the same timeframe, the total number of Rx units sold was (b) (4)

¹⁵ Source: Safety Report submission under NDA 020688 of 6/30/2016

¹⁶ Source: Applicant submission of 4/15/2019 Module 5.3.5.3 ISS, p. 14/66

Table 3: Distribution of Nonprescription Olopatadine for Ophthalmic Use, March 2013 to December 2018

olopatadine-nonprescription (OTC) (Ophthalmic use)	
COUNTRY	Sum of units_March_2013 to December_2018
Amer.Central & Carib.	(b) (4)
Hong Kong	(b) (4)
Italy	(b) (4)
Malaysia	(b) (4)
Singapore	(b) (4)
South Africa	(b) (4)
TOTAL OTC	(b) (4)

Source: Applicant submission of 4/15/2019, Module 5.3.5.3, Appendix 14, Table 4

The Applicant noted that “OTC use during the reporting period was restricted to just a few countries with limited sales, as described in [Appendix 14]. Sales over the 5-year period amounted to approximately (b) (4) units. As such analysis by marketing status (Rx versus OTC) has not been conducted.”

In response to an Information Request, the Applicant provided the table below which shows units sold, by brand, from 2000 to the end of 2018.

Table 4: Estimated Post-Marketing Exposure (Cumulative by Brand to 31Dec2018)

Brand	Cumulative Sales to 31-Dec-2018 (Units Sold)
Patanol (olopatadine 0.1% eye drops, solution)	(b) (4)
Pataday (olopatadine 0.2% eye drops, solution)	(b) (4)
Pazeo (olopatadine 0.7% eye drops, solution)	(b) (4)
TOTAL	(b) (4)

Source: Applicant submission of 9/27/2019, Clinical Information Amendment, 1.11.3, p.1/3.

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

4.1. Office of Scientific Investigations

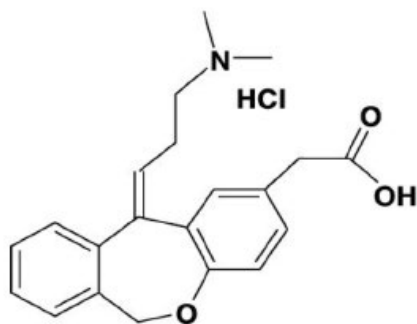
An Office of Scientific Investigations request was not submitted for this review.

4.2. Product Quality

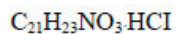
The Applicant is relying on FDA's previous findings under NDA 00688 in regard to CMC. There is no additional CMC review for this supplemental efficacy application. Below are the structural formula and the molecular formula for olopatadine hydrochloride.

Figure 1: Structural and Molecular Formula for Olopatadine Hydrochloride

- *Structural Formula:*



- *Molecular Formula:*



The prescription labeling for Patanol provides the following:

Each mL of Patanol contains: Active: 1.11 mg olopatadine hydrochloride equivalent to 1 mg olopatadine. Preservative: benzalkonium chloride 0.01 %. Inactives: dibasic sodium phosphate; sodium chloride; hydrochloric acid/sodium hydroxide (adjust pH); and purified water. It has a pH of approximately 7 and an osmolality of approximately 300 mOsm/kg.

The prescription labeling for Pataday provides the following:

Each mL of Pataday solution contains: Active: 2.22 mg olopatadine hydrochloride equivalent to 2 mg olopatadine. Inactives: povidone; dibasic sodium phosphate; sodium chloride; edetate disodium; benzalkonium chloride 0.01% (preservative); hydrochloric acid/sodium hydroxide (adjust pH); and purified water. It has a pH of approximately 7 and an osmolality of approximately 300 mOsm/kg.

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Reviewer Comment

The two olopatadine eye drop products contain different inactives with the same concentration of preservative, benzalkonium chloride 0.01 %, and the same pH and osmolality.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

To support the nonclinical safety of olopatadine, the Applicant is relying on FDA's previous findings of nonclinical safety for Patanol, submitted under NDA 020688.

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

4.5. Clinical Pharmacology

No additional information regarding clinical pharmacology issues were submitted with this supplemental efficacy application. As noted in both the Patanol and Pataday prescription labeling under Section 12.3, Pharmacokinetics:

Two studies in normal volunteers (totaling 24 subjects) dosed bilaterally with olopatadine 0.15% ophthalmic solution once every 12 hours for 2 weeks demonstrated plasma concentrations to be generally below the quantitation limit of the assay (< 0.5 ng/mL). Samples in which olopatadine was quantifiable were typically found within 2 hours of dosing and ranged from 0.5 to 1.3 ng/mL. The elimination half-life in plasma following oral dosing was 8 to 12 hours, and elimination was predominantly through renal excretion. Approximately 60 - 70% of the dose was recovered in the urine as parent drug. Two metabolites, the mono-desmethyl and the N-oxide, were detected at low concentrations in the urine.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

This review focuses on postmarket safety; this section is not applicable.

5.2. Review Strategy

The overall approach to this review is as follows:

- The DTOP team will review the efficacy and safety data from the clinical trials

submitted in support of this application. This information is covered in Sections 6, 7 and 8.1 through 8.6 and is not addressed in this review.

- The safety data from the postmarket setting and safety from the literature are reviewed in Section 8.7.

The submission relative to this review (sNDA 020688) is almost identical to the Applicant's companion submission (0.2% olopatadine hydrochloride, sNDA 021545); information under Modules 5.2 and 5.3.5.3 including appendices as well as the Benefit-Risk Summary are the same.

The following NDA submissions are included in this safety review:

- SDN 407, 04/15/2019 efficacy supplement
- SDN 408, 6/20/2019 multiple categories/subcategories (labeling)
- SDN 410, 07/03/2019 response to Information Request
- SDN 412, 09/16/2019 response to Information Request
- SDN 413, 09/27/2019 response to Information Request
- SDN 414, 10/17/2019 response to Information Request
- SDN 415, 11/20/2019 4 month safety update

6. Review of Relevant Trials Used to Support Efficacy

This review focuses on postmarket safety; as such, this section is not applicable to this review.

7. Integrated Review of Effectiveness

Not applicable. This review does not address efficacy; see review conducted by DTOP.

8. Review of Safety

8.1. Safety Review Approach

This review evaluates safety as it relates to postmarketing data and published literature submitted by the Applicant. As such, information normally found under Sections 8.1 through 8.6 is related to safety issues identified through clinical trial data and considered "Not applicable" to this review; clinical trial safety is addressed in a separate review by DTOP.

In this review Section 8.2 (Safety in the Postmarket Setting) pertains to postmarket safety and related published literature.

8.2. Safety in the Postmarket Setting

Risks Identified in Prescription Labeling

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

Adverse Reactions:

Headaches have been reported at an incidence of 7%. The following adverse experiences have been 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.

Contraindications:

Patanol (olopatadine hydrochloride ophthalmic solution) 0.1% is contraindicated in persons with a known hypersensitivity to olopatadine hydrochloride or any components of Patanol.

Warnings:

Patanol (olopatadine hydrochloride ophthalmic solution) 0.1% is for topical use only and not for injection or oral use.

Labeling also states “this drug 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”.

Risks Identified in Applicant’s Benefit/Risk Conclusions¹⁷

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 Core Company Data Sheet.

¹⁷ Applicant’s Submission of 07/03/2019, response to Information Request, SDN 410, Module 2.5 Clinical Overview

(1) Important identified risks: Hypersensitivity

(2) Important potential risks: Corneal damage

- Corneal disorders, keratitis and punctate keratitis are listed adverse events as per the current Core Company Data Sheet for olopatadine 0.1% and 0.2% eye drops, solution. 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 (benzalkonium chloride) rarely result in hospitalization.

(3) Missing information: Use during pregnancy and use during breastfeeding as this has not been studied in humans.

- During the reporting interval of the (latest Periodic Safety Update Report (PSUR), 01 May 2015-30 April 2018) five cases of pregnancy associated with olopatadine eye drops were retrieved. All the 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 6 cases related to breastfeeding were retrieved. Analysis of these cases did not reveal any new safety information regarding use of olopatadine during breast-feeding.

In the ISS, under Analysis of Medical Literature Relative to the Clinical Safety of Olopatadine¹⁸, no significant safety findings were identified; see “Literature” below.

Reviewer’s Comment

The risks of hypersensitivity and corneal damage are not unexpected with this class of eye drop drug products. Current OTC Antihistamine eye drops include no pregnancy/breastfeeding statement. DNDP asked colleagues in DTOP to make recommendations regarding some 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 drop 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). This reviewer identified an OTC eye drop (Lumify, NDA 208144) in which the Drug Facts Label states: If pregnant or breast-feeding,

¹⁸ Applicant’s submission of 4/15/2019, ISS, p. 56/66.

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ask a health professional before use. However, the active ingredient in Lumify is brimonidine, a selective alpha-adrenergic receptor agonist (redness reliever), not an anti-histamine.

Although labeling used outside the United States may not impact the agency's decision-making, this reviewer notes the following language from 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”*

This reviewer noted that the labeling submitted for Olopatanol (0.1%) marketed OTC in Italy was very cursory; it did not include any warnings but included the directive to “read package insert before use”, which was not provided.

This reviewer looked at recent Safety Reports (submitted 2016-2019) for data primarily related to pregnancy and use of olopatadine. Literature searches related to: ‘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”; preferred terms (PTs) “Forceps delivery”, “Failed forceps delivery”, “Vacuum extractor delivery”, “Exposure via body fluid”, and “Ectopic pregnancy under hormonal contraception”). In 2016, 4 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 Report 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 was identified under the SOC including “Pregnancy”, which was a serious unlisted event. The serious unlisted event identified was abortion. That case (PHHY2018MX190661), with event of interest ‘abortion’, was presented under the SOC related to ‘Nervous system disorders’ based on its lead event ‘brain edema.’

- **PHHY2018MX190661** (Clinical Trial, non-HCP): A 28-year-old female patient with a history of accident and current condition of blindness (initiated rehabilitation therapy

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for better vision) enrolled in a patient oriented program (POP00000846) received ophthalmic Patanol at a dose of 1 drop (in each eye) once daily for ocular hyperemia and eye pruritus. Concomitant medications were not reported. On an unspecified date post-initiation of Patanol, she got pregnant (maternal exposure during pregnancy) and had abortion (time frame not reported). Later on, her weight increased and she developed eye pruritus, ocular hyperemia and eye irritation aggravated. An unspecified period post-initiation of Patanol, she developed eye disorder and brain edema. Therapy with Patanol was ongoing. Outcome of all the events was not reported.

Applicant Comment: Due to absence of information regarding relevant systemic medical history, therapy details with temporal details, concomitant medication details, event details with final diagnosis, laboratory details, and clinical consequences, causality of the events brain edema and abortion was not assessable with olopatadine hydrochloride.

This reviewer did not identify any safety-related information related to use of antihistamines and “milk production” in lactating women, however, the following is in the full prescribing information for a different antihistamine nasal spray (Astelin, azelastine hydrochloride, NDA 020114, approved 1996):

Monitoring for Adverse Reactions

- Breastfed infants of lactating women treated with Astelin should be monitored for possible signs of milk rejection related to the bitter taste of azelastine hydrochloride.

Based on information submitted to date regarding adverse events with use of olopatadine eye drops related to pregnancy and/or breastfeeding, this reviewer does not believe there are safety signals of concern. This reviewer notes that under the review of the 0.7% olopatadine eye drop, Pazeo, DNDP requested input from colleagues in the Division of Pediatric and Maternal Health (DPMH) regarding these issues. DPMH concluded¹⁹: “there do not seem to be any safety concerns with the use of topical olopatadine during pregnancy and lactation. It seems that systemic concentrations of olopatadine following topical ocular administration of Pazeo were negligible.” See the DNDP clinical review under sNDA 206276 for details.

Other Noted Risks

Dysgeusia has also been reported with the ophthalmic solutions in 2 to 5% of patients. Ocular adverse reactions associated with olopatadine ophthalmic solution include ocular irritation (burning or stinging), foreign body sensation, hyperemia, keratitis, blepharedema, ocular pruritus, blurred vision, conjunctivitis, and xerophthalmia. These reactions were reported in less than 5% of the patients. Abnormal sensation in the eye was reported by patients receiving

¹⁹ Per email correspondence of 10/25/2019 from Miriam Dinatale, Team Leader, Maternal Health Team, DPMH in response to inquiry by Frank Becker, Team Leader, DNDP.

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olopatadine 0.7% ophthalmic solution. Keratitis, although with an incidence rate of < 5%, was the only adverse reaction noted to be severe.²⁰

Postmarket Data Submitted by Applicant in ISS

Applicant submitted postmarket support of olopatadine safety includes database and published literature searches:

- Applicant's Pharmacovigilance Database from 1996-2018
- FDA Adverse Events Reporting System (FAERS) database search from 1997-2018 with break-outs by year of reporting, patient age, duration of use, brand
- World Health Organization search from 1968-2019
- NPDS 2000-2019
- Published medical literature for safety issues associated with use of olopatadine

In the ISS, the Applicant made a statement:²¹ "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." In response to an IR inquiring about the context for this statement and if there is some duration of use recommendation, the Applicant stated:²² "This statement comes from the PSUR for olopatadine. The intent of the statement in the ISS/PSUR is for purposes of estimating post-market patient exposure and is not intended to make any recommendation regarding posology/duration of use. The correct instructions for dosing are found within the individual product labeling."

This reviewer notes that there are limitations of post-marketing adverse drug event reporting as reports 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 years included in queries. The raw numbers of "reports" for "cases" also vary widely; overall, the total numbers of reported AEs are low so use of the number, as opposed to percentage of total, has been used. Further, detailed comparisons between databases are not appropriate, however, general impressions of safety findings parallel.

Overall, the Applicant's ISS stated that the Novartis database (1996-2018) identified 8,144 AEs for Patanol. The Applicant's submission initially identified AEs from the external databases for all olopatadine products, not broken out by brand; FAERS (1997-2018): 7,390 cases, WHO

²⁰

<https://www.clinicalpharmacologyip.com/Forms/Monograph/monograph.aspx?cpnum=2135&sec=monadve&t=0;>
accessed 9/10/2019.

²¹ Source: Applicant submission of 4/15/2019, Module 5.3.5.3 ISS, page 13/66.

²² Source: Applicant submission of 9/16/2019, page 2/10.

(1968-2019): 3,427 cases, and NPDS (2000-2019): 512 exposures. There have been no withdrawals for safety or regulatory reasons.

This review references information related to all three eye drop products containing olopatadine hydrochloride [Patanol (0.1%), Pataday (0.2%) and Pazeo (0.7%)] for ease of presenting information submitted by the Applicant as all three sNDAs are currently under review for proposed Rx-to-OTC switch. This review, however, provides analysis and recommendations related only to the 0.1% product.

8.2.1. Adverse Events Identified in Postmarket Experiences

The Applicant’s reports of post-market adverse events (AEs) were coded with the Medical Dictionary for Regulatory Activities Version 21.1. In all data presentations, events were grouped by system organ class (SOC) first, and then preferred term (PT) within SOC. All SOCs and PTs were listed in alphabetic order. This reviewer notes that in Module 5.3.5.3 of the initial submission of 4/15/2019, data presented did not include a summary or analysis of safety findings or an assessment of Preferred Terms. Data was presented as total AEs and by System Organ Class (SOC); Appendices provided alphabetical listings of SOCs and PTs. An Information Request was sent 9/6/2019 requesting that the Applicant submit more detailed Tables by PT. The sources for information below are identified as ISS (4/15/2019), initial submission, or Clinical Information Amendment (9/16/2019), response to IR. Note that some data presented also includes information for Pataday, 0.2% olopatadine (sNDA 021545) and Pazeo, 0.7% olopatadine (sNDA 206276).

Applicant’s Database (Novartis and Alcon/Argon)

The Applicant provided postmarket safety data for olopatadine eye drop products broken out by various categories including year of reporting, age and duration of use.

Applicant’s Postmarket Data by Year of Reporting

The Table below illustrates no appreciable increasing or decreasing trends in adverse events reported between 1996 and 2018 given marketing considerations (i.e., approval dates).

Table 5: Frequency of Post-Market Adverse Events for Olopatadine-Containing Products, Stratified by Year of Reporting (Applicant Database)

Dosage Strength	Total n	Year of Reporting				
		1996-2000 n	2001-2005 n	2006-2010 n	2011-2015 n	2016-2018 n
Patanol						
Serious adverse events	160	2	7	31	65	55
Non-serious adverse events	3912	453	846	961	893	759
Total adverse events (serious + non-serious)	4072	455	853	992	958	814
Pataday						
Serious adverse events	55	0	0	2	18	35
Non-serious adverse events	1995	0	0	389	1164	442
Total adverse events (serious + non-serious)	2050	0	0	391	1182	477

Source: Integrated Summary of Safety, Mod 5.3.5.3, Table 12 (modified), p. 30/66

Applicant’s Postmarket Data by Age

AEs (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. The table below 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 0.1% and 0.2% olopatadine-containing products.

Table 6: Reports of AEs by Age (Applicant’s Database)

Dosage Strength	Total n	Subject Age			Other* n
		3y to <12y n	12y to 65y n	>65y 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

Source: Integrated Summary of Safety, Mod 5.3.5.3, Table 13 (modified), p. 32/66.

Reviewer Comment

No significant findings in regard to years of reporting or age, where available. Information submitted related to duration of use did not provide any helpful insights to the safety assessment of olopatadine.

Applicant’s Postmarket Data by Marketing Status

The Applicant’s safety database was the only source for data broken out by marketing status. Of interest is the numbers of AEs reported for Rx versus OTC drug products, shown in the Table below. Data represents Years 2012-2018.

Table 7: Frequency of Post-Market Adverse Events for Olopatadine-Containing Products, Stratified by Marketing Status (Applicant’s Database)

Dosage Strength	Total n	Marketing Status	
		Prescription n	Over the counter n
Patanol			
Serious adverse events	160	154	6
Non-serious adverse events	3912	3864	48
Total adverse events (serious + non-serious)	4072	4018	54
Pataday			
Serious adverse events	55	55	0
Non-serious adverse events	1995	1991	4
Total adverse events (serious + non-serious)	2050	2046	4

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Source: Applicant submission of 4/15/2019, Module 5.3.5.3 ISS, Table 10 (modified), p. 26/66.

Of a total of 4,072 AEs reported for Patanol, 54 (1.3%) were related to OTC use. Units sold by marketing status broken out by brand was not provided.

Applicant's Postmarket Data by SOC and PT

From Alcon's internal database [1994-2018], the total number of events reported for Patanol was 3911 with 141 SAEs; there were 1871 total events for Pataday, with 37 SAEs.²³ The Applicant's initial submission did not provide safety information with analyses of AEs by Preferred Term. In response to a related IR requesting identification of SAEs where the olopatadine eye drop product was the primary suspect, the Applicant provided the following information. The table below shows which SOCs were most common.

Table 8: The Five Most Frequently Reported SAE SOCs for All Three Eye Drop Products (Applicant's Database)

Order	Patanol	Pataday	Pazeo
1	Eye disorders (N=54)	Eye disorders (N=9)	Eye disorders (N=7)
2	Skin and subcutaneous tissue disorders (N=18)	Nervous system disorders (N=6)	Injury, poisoning and procedural complications (N=3)
3	Nervous system disorders (N=14)	Gastrointestinal disorders (N=5)	Musculoskeletal and connective tissue disorders (N=3)
4	Immune system disorders (N=10)	General disorders and administration conditions (N=4)	Respiratory, thoracic and mediastinal disorders (N=3)
5	General disorders and administration conditions (N=9)	Infections and infestations (N=4)	Investigations (N=2)

Source data: Tables 1-3; 7-9; 13-15 [Source Data Tables Q4]

Source: Applicant submission of 9/16/2019, Clinical Information Amendment, pp. 4-5/10.

Reviewer Comment

The most common SOCs representing SAEs reported for Patanol included eye disorders (d/o), skin and subcutaneous d/o, nervous system d/o, immune system d/o, and general d/o and administration conditions. These findings are consistent with the known safety profile (e.g., eye d/o, swelling face, headache, hypersensitivity, drug ineffective) of Patanol. For Pataday, gastrointestinal d/o and infections and infestations were also included (diarrhea, nausea and

²³ Source: Applicant submission of 9/16/2019, 1.11.3 Clinical Information Amendment, p. 4/10.

orbital cellulitis, eye abscess, folliculitis). The actual number of reports are too low to accurately extrapolate any significant pattern.

The table below shows similar findings for non-serious AEs.

Table 9: The Five Most Frequently Reported Non-Serious AE SOC's for All Three Products (Applicant's Database)

Order	Patanol	Pataday	Pazeo
1	Eye disorders (N=1699)	Eye disorders (N=706)	Eye disorders (N=408)
2	General disorders and administration conditions (N=936)	General disorders and administration conditions (N=659)	General disorders and administration conditions (N=104)
3	Injury, poisoning and procedural complications (N=276)	Injury, poisoning and procedural complications (N=102)	Injury, poisoning and procedural complications (N=42)
4	Nervous system disorders (N=240)	Nervous system disorders (N=86)	Nervous system disorders (N=38)
5	Skin and subcutaneous tissue disorders (N=153)	Respiratory, thoracic and mediastinal disorders (N=60)	Product Issues (N=36)

Source data: Tables 4-6: 10-12: 16-18 [Source Data Tables O4]

Source: Applicant submission of 9/16/2019, Clinical Information Amendment, p. 5/10.

Reviewer Comment

The most common SOC's representing AEs reported for both Patanol and Pataday are consistent with the known safety profile of these eye drops. Examples of AEs reported under Injury, poisoning and procedural complications include "off-label use", "medication error" and "product use error". AEs under Respiratory, thoracic and mediastinal disorders included: "oropharyngeal pain", "cough", "rhinorrhea", and "throat irritation".

The table below shows the top PTs for Patanol from the Applicant's database.

Table 10: Patanol 0.1% Olopatadine Total SAEs With Preferred Term n≥3 (Applicant's Database)

All events	141
Eye disorders	54
Eye irritation	4
Eye pain	4
Eye pruritus	3
Eye swelling	3
Punctate keratitis	3
Ulcerative keratitis	3
Skin and subcutaneous tissue disorders	18
Swelling face	5
Nervous system disorders	14
Headache	3
Immune system disorders	10
Anaphylactic reaction	3
Hypersensitivity	3

Source: Applicant submission of 9/16/2019, Data Tables Q4 p. 4/175.

Reviewer Comment

These findings are consistent with identified risks on current prescription labeling. This reviewer notes that under sNDA 021545, Pataday, there were reports of blindness; based on review of the accompanying case report forms, the reports did not pose a safety concern. See the DNDP Clinical review under sNDA 021545 for more information.

In regard to post-market safety data specific to OTC use, the Applicant submitted the following information, providing the context that there is a very small number of units of OTC olopatadine eye drop solution products sold worldwide.

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Table 11: OTC Eye Drops, All AEs (Serious and Non-Serious) With Preferred Term n≥3 (Applicant's Database)

All events	57
Eye irritation	5
Accidental exposure to product by child	3
Eye pruritus	3
Ocular hyperaemia	3
Wrong product administered	3

Source: Applicant submission of 9/16/2019, Clinical Information Amendment, Data Tables Q4 p. 112/175

The Applicant further noted that “While there is a very small number of units of OTC olopatadine eye drop solution products sold worldwide, an analysis of most frequently reported AEs for OTC products by Preferred Term is not possible in the external databases since the OTC products share identical names as the Rx products, and the WHO database does not distinguish whether a primary suspect olopatadine eye drop solution is an Rx or OTC entity. OTC data from Alcon’s internal database was produced by tabulating those events that were reported from countries that have an OTC product.”

Novartis has information to indicate that Patanol was marketed as an OTC product in five countries (Italy, Myanmar, Namibia, South Africa, and Zimbabwe), and that Pataday was marketed as an OTC product in one country (Hong Kong).²⁴

Reviewer Comment

These findings are consistent with identified risks on current prescription labeling and are somewhat reassuring, although they represent a limited distribution, as they come from the OTC setting.

Applicant’s Postmarket Data related to Deaths

Reports of deaths from the Applicant’s pharmacovigilance database identified a total of 6 cases²⁵ that resulted in death; in 4 cases olopatadine was considered to be a primary suspect product. Narratives for these events were provided in Section 5.9 of the ISS.

A total of 6 deaths were reported in the post-marketing surveillance for olopatadine. One was related to use of Patanol (2 with Pataday, 2 with Patanase, 1 with Pazeo). Two of the deaths are

²⁴ Applicant’s submission of 4/15/2019, ISS, Module 5.3.5.3 p. 24/66.

²⁵ Applicant’s submission of 4/15/2019, ISS, Module 5.3.5.3 pp. 60-64/66.

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most likely unrelated to olopatadine use (a homicide and a car accident). One of the deaths is more readily explained by 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 polymedication. The remaining report of death (myocardial infarction) did not contain enough information to determine causality and is confounded by polymedication.

The “Patanol” death was in a 49-year old female whose medical history was not reported. She was on additional multiple medications including: Ritalin, Singulair, Lyrica, Dilaudid, Xyrem, Imitrex, Lidocaine patch and potassium chloride. Cause of death was not reported, it was not known if an autopsy was performed. The patient was on Patanol for “years”.

One of the deaths associated with “Pataday” listed “Patanol S Sol” in the report; this death was a homicide. The other death associated with “Pataday” was in an elderly male, age and medical history not reported. He was also using other eye drops: travoprost and brinzolamide [for presumptive glaucoma]. Unknown cause of death and unknown if autopsy was performed.

Reviewer Comment

The reports of “deaths” related to use olopatadine 0.1% do not provide sufficient detail to allow definitive conclusions, but the scenarios described do not change the known safety profile of the drug.

Additional Comments

This reviewer had concerns about reports attributed to a particular brand (“Patanol” v “Pataday”) which may not be accurate. With this in mind, this reviewer looked at the Applicant’s recently submitted Safety Reports for the olopatadine drug products²⁶.

(1) Reporting period 01 May 2018 – 30 April 2019

For “Patanol” there were 305 events and 128 cases.

Of those 305 events, 54 were serious unlisted (16 were eye disorders,). Four were serious listed (3 eye disorders and 1 drug ineffective). Non-serious unlisted events totaled 186 and listed were 61. Overall, eye d/o comprised 108 events in 61 cases, drug ineffective totaled 26 events in 26 cases; hypersensitivity 12 events in 12 cases and contraindicated product administered 11 events in 11 cases.

²⁶ Accessed in DARRTS, 10/10/2019.

That Safety Report listed “2 deaths” for “Patanol” but the narratives reference “Pataday”:

- *PHEH2019US016520 [Clinical Trial, non-HCP]: An 82-year-old female patient with an unspecified medical history enrolled in patient oriented program (POP20150553) received Pataday (route of administration, dose, and frequency were not reported) for an unknown indication. Concomitant medications were not reported. On an unspecified date post-initiation of Pataday, she died. Cause of death was not reported. It was unknown if an autopsy was performed.*

Applicant Comment: Death was the only event reported; no other associated adverse events were reported in the case. Considering the lack of information regarding relevant medical history, concomitant medication details, cause of death, therapy details, and autopsy details, causality for the event death is not assessable with olopatadine hydrochloride.

- *PHHY2019US065258 (Clinical Trial, non-HCP): A 91-year-old male patient with an unspecified medical history enrolled in a patient oriented program (POP20150553) received Pataday (route of administration, dose, and frequency were not reported) for an unknown indication. Co-suspect medication included Systane® (polyethylene glycol 400 in combination with propylene glycol). Concomitant medications were not reported. On an unspecified date post-initiation of Pataday, he died. Cause of death was not reported. It was unknown if an autopsy was performed.*

Applicant Comment: Death was the only event reported; no other associated adverse events were reported in the case. Due to lack of event details, antecedent conditions, medical history, treatment details with last dose latency, cause of death, and autopsy details if any, causality for the event death is not assessable with olopatadine hydrochloride and polyethylene glycol 400 in combination with propylene glycol.

This reviewer notes that the above reports for “death” found in the most recent Safety Report were not included in the Applicant’s ISS, however, the ISS submission pre-dated the submission of the Safety Report.

(2) Reporting Period 01 May 2017 – 30 April 2018

A total of 269 events and 138 cases related to “Patanol”. 26 events were serious unlisted [12 eye d/o, 4 nervous system d/o, 2 cerebrovascular accidents (CVA)]. Three events were serious listed [drug ineffective, hypersensitivity, keratitis]. Non-serious events comprised 152 unlisted and 88 listed. Overall, eye disorders represented 116 events and 67 cases, drug ineffective 42 events in 41 cases and hypersensitivity 15 events in 15 cases.

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This reviewer believes there are inherent drug brand confusion with olopatadine drug products in safety databases and reporting; that said, the findings are not of great concern and seem to be consistent with the known safety profile of olopatadine eye drop products.

The Applicant's 4-month safety update did not identify any new safety concerns.

FAERS²⁷

There was a total of 7,390 reports for all olopatadine products from 1997-2018; 3,787 (51.2%) from the U.S. There were 1,217 reports where olopatadine was considered the primary suspect; 137 were serious AEs, 1,080 non-serious AEs.

SOC classifications found most frequently in the overall group of adverse events include:

- General disorders and administration site conditions (11.7%),
- Nervous system disorders (8.7%), and
- Respiratory, thoracic and mediastinal disorders (7.9%).

For all olopatadine products, reports broken out by age showed:

- < 3 years:15
- 3-12 years:129
- >12-65 years: 2,933
- > 65 years:1,841
- Unknown: 2, 472

For all 7,390 reports, broken out by brand:

- Patanol: 1,924
- Pataday: 1,527
- Pazeo: 501
- Patanase: 821
- Unknown Olopatadine Brand: 2,719

Reviewer Comment

Additional analyses by age and by brand did not result in any significant findings, especially given that this represents all olopatadine products and there were a large number of reports where age and brand were unknown.

²⁷ Applicant's submission of 04/15/2019, ISS, Module 5.3.5.3, pp. 36-44/66.

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Of the 7,390 reports, there were 316 cases associated with the use of Patanol, 38 of which were serious. From the FAERS database, the 5 most frequently reported serious AE SOCs where use of olopatadine 0.1% was considered to be the primary suspect were: eye disorders (n=20), immune system disorders (n=20), nervous system disorders (n=15), general disorders and administration conditions (n=10); and skin and subcutaneous disorders (n=10).²⁸

Reviewer Comment

This information is consistent with findings from the Applicant's database and reflects known safety profile of the eye drops. However, this reviewer notes that the number of reports from FAERS, broken out by brand, for Pataday (approved in 2004) initially seems fairly high compared with Patanol which has been marketed since 1996 but the number of "unknown" brand is also very high. The Applicant's database had a much higher number of events (3,911) reported for Patanol. This reviewer notes that attribution to a specific brand of olopatadine drug product in these safety databases does not seem reliable.

The table below shows SAEs by Preferred Term where use of olopatadine 0.1% was considered to be the primary suspect.

²⁸ Applicant's submission of 9/16/2019, Clinical Information Amendment, p. 6/10.

Table 12: Patanol Cases With SAEs and Preferred Term n≥3 [1997-2018] (FAERS)

Total Number of CASES	38
Eye Irritation	4
Eye Pain	4
Headache	4
Hypersensitivity	4
Anaphylactic Reaction	3
Anaphylactoid Reaction	3
Eye Disorder	3
Ocular Hyperaemia	3
Pyrexia	3
Visual Impairment	3

Source: Applicant submission of 9/16/2019, Clinical Information Amendment, Data Tables Q4 p. 116/175.

In regard to reports of death, see below “Discussion of Reports of Postmarket Deaths for Olopatadine Products”.

Reviewer Comment

These FAERS findings do not alter the known safety profile for 0.1% olopatadine.

WHO

The Applicant searched the WHO database for olopatadine and found 3,427 cases with adverse events reported for all olopatadine products from 1997 to March 2019; 1,643 cases where olopatadine was reported as the primary suspect.²⁹ Olopatadine 0.1% represented 474 events; 119 were SAEs. In the WHO database, note that Olopat, Patanol/Patanol S and Opatanol all represent 0.1% olopatadine.

The table below shows the SAEs by PT for Patanol.

²⁹ Applicant submission of 4/15/2019, ISS, p. 47/66.

Table 13: Patanol SAEs With Preferred Term n≥3 (WHO)

Total Number of EVENTS	119
Alopecia areata	6
Contusion	5
Death	5
Eye pain	4
Muscle spasticity	4
Pain	4
Cerebrovascular accident	3
Eye disorder	3
Eye irritation	3
Head injury	3
Muscle rigidity	3
Visual impairment	3

Source: Applicant submission of 9/16/2019, Data Tables Q4 p. 156/175

In regard to reports of death, see below “Discussion of Reports of Postmarket Deaths for Olopatadine Products”.

In regard to reports of three CVA for Patanol from WHO, the Applicant submitted the following in response³⁰ to an IR:

“A review of the Applicant’s internal database and the FAERS database where Pataday was the primary suspect product confirmed that the 2 cases of cerebrovascular accident reported for Pataday are identical in both databases.” “Regarding the 3 cases of cerebrovascular accident reported for Patanol in the WHO database, case narratives were

³⁰ Applicant’s submission of 10/17/2019, Clinical Information Amendment, p. ¾.

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not available. Per the WHO database administrator, narrative information cannot be provided due to legal requirements on data protection (Regulation (EU) 2016/679, GDPR).” The Applicant provided narrative information for the two cases of CVA for Pataday identified in its database. One case occurred in an elderly male patient, medical history not provided but the patient was also using eye drops to treat glaucoma (presumably), outcome was not known. In the second case, “Pharmacy reports that a female patient administered Pataday (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.” Age, medical history and additional details not provided.

Reviewer Comment

Overall, adverse events reported by WHO were similar to FAERS, with the most common events related to eye disorders. An IR was sent 10/10/2019 to the Applicant to address discrepancies noted with the WHO database regarding reports for “Patanol” for “death” and for “cerebrovascular accidents”, separately. See below under “Discussion of Reports of Postmarket Deaths for Olopatadine Products” in regard to “death”. This reviewer notes that SAE reports for “cerebrovascular accidents” related to use of olopatadine eye drop products would be highly unlikely as there does not appear to be a plausible mechanism of action; the purpose of the IR was to explore likely discrepancies with the WHO database. Based on information the Applicant provided in the IR response to clarify apparent inconsistencies with brand attribution in the WHO database, this reviewer believes that any definitive association with “brand” to outcome is not reliable.

Also, in light of trying to verify information from the WHO database, this reviewer searched “Mercado” (represents FAERS data) for olopatadine products and nervous system disorders (cerebrovascular accident) and also “death” for the past year (to 10/10/2018) with zero results. This reviewer took a brief look at Safety Reports submitted since 2016; there were no narrative discussions of CVA events.

In a further attempt to clarify the value of WHO data in comparison with the Applicant’s data, this reviewer also looked briefly at narratives for Safety Reports since 2016; the 2016, 2017, and 2018 narratives do not mention alopecia. In 2016 there was 1 report of alopecia with a nasal spray and 1 with an “eye drop”; in 2017, there were 3 cumulative reports for alopecia, and report of alopecia areata – all with Patanol; 2018 there were no reports of alopecia. In 2019, narrative mentions 10 AEs/7 case reports in the Skin, subcutaneous tissue d/o SOC; 8 AEs were “serious unlisted” and alopecia areata and alopecia universalis are among the eight. No additional information was provided.

This reviewer then looked in Mercado (FAERS data) for reports of “alopecia” during the past year (to 10/16/2018); there were 3 expedited reports involving alopecia areata (one case also

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had a report for “alopecia universalis”) and Patanol; there were none with Pataday. One case involved a 5 year old girl who was actually taking Allelock tablets (not Patanaol), one case with a 34 yo female taking Patanol and an oral antihistamine where the case report stated that the reporting physician told the patient that use of antihistamines should be avoided as the patient had a family history of autoimmune disease (mother with Hashimoto’s thyroiditis and brother with Type 1 DM); and a third case in a 9 yo boy using Patanol who had pre-existing alopecia areata. This reviewer did a brief PubMed search with the terms “olopatadine” and “alopecia”; results showed one study³¹ which actually argued that, based on findings of a study using a rat model, “higher dose of olopatadine chloride clinically needs to inhibit chemotactic ability in the treatment of alopecia areata”; this study seems to suggest olopatadine may be used to treat alopecia areata. As there does not appear to be a plausible mechanism of action for olopatadine to cause alopecia, reports of alopecia related to its use do not pose safety concerns.

This reviewer believes that data from the WHO database has limited value for purposes of this review.

NPDS³²

The NPDS database search included years 512 exposures from 2000-2019. The NPDS is maintained by the American Association of Poison Control Centers and it serves as the data warehouse for the 55 poison control centers located in the U.S. The database was searched for the following terms: Olopatadine; Pataday; Patanol; Patanase; Pazeo; Opatanol; Olopat; Allelock. Each of the 512 events were also partitioned by age and date received by a poison control center. All data are presented irrespective of whether olopatadine was used with or without other substances. No deaths are mentioned.

The Applicant stated that the NPDS data that are currently available do not contain brand or duration of use information.³³

Reviewer Comment

This reviewer totaled the information provided by the Applicant in the ISS and found 549 reports.

Total reports by year:

- *2000-2004: 122*

³¹ T. Ito, et al; Antihistaminic drug olopatadine downmodulates T cell chemotaxis toward CXCL10 by reducing CXCR3 expression, F-actin polymerization and calcium influx in patients with alopecia areata; Letters to the Editor; *Journal of Dermatological Science*; 72 (2013) 61–77 69.

³² Applicant’s submission of 4/15/2019, ISS, pp.54- 55/66.

³³ Applicant’s submission of 9/16/2019, p.4/10.

Clinical Review

Elizabeth Donohoe, MD

sNDA 020688 Pataday Twice Daily Relief

- 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%) and dermal: 38 (7%).

By age: 13-69 yo: 237 (43%); ≤ 5yo: 117 (21%); 6-12 yo: 79 (14%); unknown: 73 (13%); and ≥ 70 yo: 43 (8%).

Children ≤ 5yo represent the second largest age group; this is not surprising given that NPDS is a poison control center.

Given the significant limitations with this database (including the inability to identify brand, varying years product may have entered market, and the unlikelihood that reports related to events seen with olopatadine drug products would be in a database for “poison control”), specific conclusions cannot be made in regard to these findings beyond a general impression that findings are consistent with the known safety profile of the drug product.

Discussion of Reports of Postmarket Deaths for Olopatadine Products³⁴

The Applicant submitted clarification regarding reports of deaths as the initial submission contained incomplete information.

In the Applicant’s pharmacovigilance database, there were a total of 6 cases that resulted in death, 4 of which where olopatadine was the primary suspect product. See above discussion regarding these 6 deaths. The number of deaths reported from differing external safety databases are FAERS: 5 Deaths; WHO data: 9 deaths. Five (5) deaths with differing attribution to brand compared to FAERS and an additional 4 deaths associated with use of Allelock—a tablet available in China and Japan—and thus not included in FAERS. The brand attribution for the 5 deaths between the FAERS and WHO is consistent for Pazeo (each database reporting 1 death) and Pataday (each database reporting 2 deaths). However, as shown in the following table, the WHO database reports two deaths attributable to “olopatadine” while FAERS codes them as Patanase (nasal spray approved in the U.S.). Thus, the differing attribution to brand between WHO and FAERS appears to be the result of WHO coding the cases as “olopatadine” and FAERS coding them as “Patanase.”

³⁴ Applicant’s submission of 9/16/2019, Clinical Information Amendment, pp.2-3/10.

In response³⁵ to an additional IR to clarify inconsistencies noted with WHO data, the Applicant submitted the following:

“There was an error when data was transcribed from the “175 page Data Tables Q4” into the “accompanying 10-page narrative” document. Following the identified error, an additional review was done of the raw data provided from the WHO database. Upon this review, it was identified there were 6 deaths associated with Patanol. The seriousness was blank on 1 “Report ID” and was listed as “yes” for the other 5 “Report IDs”. Therefore, in our original summary the blank “Report ID” was not counted. We conservatively considered the other 5 “Report IDs” of death as 5 separate patients even though the data could be interpreted as coming from 1 patient.”

Table 14: Death Total Reported With Use of Olopatadine Products (WHO, FAERS Databases)

DEATHS		
Drug	WHO	FAERS
Olopatadine	2	0
Pazeo	1	1
Pataday	2	2
Patanol	6	0
Patanase	0	2

Source: Applicant’s submission of 10/17/2019, Clinical Information Amendment, p.3/4.

Reviewer Comment

This reviewer noted inconsistencies with the data submitted for WHO database; subsequent information submitted by the Applicant suggest that the reports of “death” for 5 of the 6 reports are likely the same case. In FAERS, there were no deaths were associated with use of 0.1% olopatadine eye drops. This reviewer believes that information from the WHO database has limited value, especially in respect to brand attribution for olopatadine products. Reports of “death” do not raise safety concerns.

Summary of Postmarket Data from Databases

Postmarket database searches of products with olopatadine 0.1% provided valuable information though had limitations. Multiple IRs were sent to the Applicant to clarify information. Eye-related events accounted for most of all adverse events reported in the Applicant and FAERS databases. Data collected from the WHO database were somewhat similar but of less value. Information from NPDS did not provide additional insight into the known safety profile of Patanol as the risk of abuse or misuse of these products is unlikely.

³⁵ Applicant’s submission of 10/17/2019, Clinical Information Amendment, p.2/4

Reviewer comment

The adverse events reported in the searched databases are consistent with the known safety profile of olopatadine and no new trends or patterns were identified. Most AEs for both Patanol and Pataday involve eye disorders. In general, the reported AEs were similar to AEs listed in Rx labeling [e.g., hyperemia, foreign body sensation, keratitis, symptoms related to underlying condition]. Where reported, most AEs are for the 12 – 64 years and > 65 groups; this pattern is consistent with higher volume of use in these age groups relative to the other groups.

Literature³⁶

The Applicant conducted a PubMed search for published literature supporting the safety olopatadine. Previously, relevant publications containing important, new safety information published from May 1, 2015 through April 30, 2018 were retrieved from two scientific databases, Medline and Embase. No significant safety findings related to olopatadine were retrieved from published peer-reviewed scientific literature or made available as unpublished manuscripts during that reporting interval. In March of 2019, a literature search was conducted to update the search period to include relevant publications containing important, new safety information published from January 1, 2018 through March of 2019. Literature was retrieved from two scientific databases, PubMed/Medline and Google Scholar. The search criteria were inclusive of both ophthalmic and nasal applications, pregnancy outcomes (including termination) with no adverse outcomes, use in pediatric populations, compassionate supply, named patient use, lack of efficacy, asymptomatic overdose, abuse or misuse, medication error where no AEs occurred, or “near misses” and important non-clinical safety results. The search criteria were limited to human, primary research. Search terms included: olopatadine; olopatadine hydrochloride; Patanol; Pataday; Opatanol; Pazeo; Patanase.

From the period of January 1, 2019 through March of 2019, four studies were identified that described treatment-emergent adverse events (TEAEs). Two studies involved ophthalmic use of olopatadine to treat allergic conjunctivitis. Publication-reported treatment emergent side effects with use of olopatadine 0.1% included oropharyngeal discomfort (6.1%), headache 7%, and burning sensation of eyes 3%. See Table 15 in Appendix, Section 13.1 References/ Applicant Submitted Literature for Safety.

The Applicant’s 4-month safety update did not identify any new safety concerns in published literature.

Reviewer comment

³⁶ Applicant submission of 4/15/2019; ISS, p. 56/66.

Literature provided does not alter the known safety profile of 0.1% olopatadine eye drops. This reviewer conducted a PubMed search³⁷ using the terms “olopatadine” “eye drops” and “safety”; 29 articles were identified, none relevant to this discussion of postmarket safety as most involved clinical trials, efficacy and allergic conjunctivitis. Additional searches for “olopatadine” and “cerebrovascular event” and “stroke” yielded no results; search using “death” also yielded no results. An example of an article³⁸ identified here involved “an evaluation of 126 subjects (age range, 3-17) that revealed no clinically relevant treatment-related changes in visual acuity, intraocular pressure, slit-lamp assessments, fundus examinations, or cardiovascular parameters. All adverse events reported were mild or moderate” and concluded that “olopatadine 0.2% administered once-daily for 6 weeks is safe and well tolerated in children and adolescent patients.”

4 Month Safety Update³⁹

The Applicant submitted its 4 month safety update (4 MSU) which covered January 1, 2019 to October 31, 2019. Under its database, the Applicant notes that there was only one AE report for OTC olopatadine; it was under PT “product use issue”. The Applicant also included data from FAERS and WHO databases as well as an updated literature search. The literature search identified three studies, all of which reported similar TEAEs as previously described. This review already addresses findings from the Applicant’s Safety Update (data through April 30, 2019); the 4 MSU included findings consistent with previous safety data in regard to commonly reported SOCs and PTs. The 4 MSU does not change the known safety profile of the drug.

8.2.2. Expectations on Safety in the Postmarket Setting

The safety of olopatadine 0.1% eye drop products is generally well known. No new safety concerns are expected with use of the Applicant’s product in the OTC setting.

8.2.3. Additional Safety Issues From Other Disciplines

Not applicable.

8.3. Integrated Assessment of Safety

There were no new clinical studies conducted to support this review. This safety review involved analyses of postmarketing data only. Overall, there are few serious adverse events

³⁷ Accessed 10/10/2019.

³⁸ Lichtenstein, SJ et al; Safety and tolerability of olopatadine 0.2% in children and adolescents. *J Ocul Pharmacol Ther.* 2007 Aug;23(4):366-71.

³⁹ Sponsor submission of 11/20/2019

reported in the post-market setting for olopatadine 0.1% eye drops since approval in the U.S. in 1996.

Reviewer comment

AEs identified in clinical trials experience, as noted in the prescription labeling (largely related to eye disorders, symptoms related to the underlying disorder, and hypersensitivity) are similar to those identified through postmarket safety databases, especially the Applicant's database and FAERS. The most common SOC representing SAEs reported for Patanol included eye disorders (d/o), skin and subcutaneous d/o, nervous system d/o, immune system d/o, and general d/o and administration conditions. These findings are consistent with the known safety profile (e.g., eye d/o, swelling face, headache, hypersensitivity, drug ineffective) of Patanol. For Pataday, gastrointestinal d/o and infections and infestations were also included (diarrhea, nausea and orbital cellulitis, eye abscess, folliculitis). The actual number of reports are too low to accurately extrapolate any significant pattern. Initial concerns regarding the potential need for language to address pregnancy and/or lactation warnings were not supported upon further investigation. The "standard" warnings included in the OTC Drug Facts Label for anti-histamine eye drop products appear to sufficiently address the minimal safety concerns with proposed OTC consumer use of the olopatadine eye drop products.

9. Advisory Committee Meeting and Other External Consultations

Not applicable.

10. Labeling Recommendations

10.1. Nonprescription Drug Labeling

The proposed product label is comparable to similar OTC ophthalmic antihistamines. Of note, DNDP asked colleagues in DTOP to make recommendations regarding a few labeling issues including the following:

- "Wait at least 5 minutes between each product" should be standard OTC language for eye drops.
- "Patients should be advised not to wear a contact lens if their eye is red" should be included on all OTC olopatadine products.
- In regard to pregnancy or breastfeeding statements: "Patanol OTC applications be labeled in the same way as the OTC ophthalmic antihistamines."



Reviewer comment

No additional comments regarding the Drug Facts Label. However, the IDS reviewer is considering an Information Request to the Applicant about changing the Principle Display Panel (PDP) to allow consumers to more readily distinguish packaging for olopatadine 0.1% from that of 0.2%.

⁴⁰ Source: Applicant's submission SDN 408 on 6/20/2019, Module 1.14.1.3

11. Risk Evaluation and Mitigation Strategies

Not applicable for an OTC product.

12. Postmarketing Requirements and Commitments

Not applicable for an OTC product.

13. Appendices

13.1. References/ Applicant Submitted Literature for Safety

Table 15: Literature References to the Safety of Olopatadine Submitted by the Applicant

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. <i>Ocul Immunol Inflamm.</i> 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.	<ul style="list-style-type: none"> 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. <i>J Ophthalmic Vis Res.</i> 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.	<ul style="list-style-type: none"> 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: Integrated Summary of Safety, Mod 5.3.5.3, p. 57/66 Section 5.8.1. Table 27 Summary of Literature Relevant to the Safety of Olopatadine (January 2019 – March 2019), modified to include only articles with use of olopatadine 0.1% eye drops

13.2. Financial Disclosure

Not applicable.

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021545s022

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum: February 7, 2020

Requesting Office or Division: Division of Nonprescription Drug Products (DNDP)

Application Type and Number: NDA 020688/S-032
NDA 021545/S-022

Product Name and Strength: Pataday Twice Daily Relief (olopatadine) ophthalmic solution, 0.1%
Pataday Once Daily Relief (olopatadine) ophthalmic solution, 0.2%

Applicant/Sponsor Name: Alcon Research, LLC

OSE RCM #: 2019-923-1

DMEPA Safety Evaluator: Grace P. Jones, PharmD, BCPS

DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on January 22, 2020 for Pataday Twice Daily Relief (NDA 020688/S-032) and Pataday Once Daily Relief (NDA 021545/S-022). The Division of Nonprescription Drug Products (DNDP) requested that we review the revised container labels and carton labeling for Pataday Twice Daily Relief (NDA 020688/S-032) and Pataday Once Daily Relief (NDA 021545/S-022) (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^a Jones G. Label and Labeling Review for Pataday Twice Daily Relief (NDA 020688/S-032) and Pataday Once Daily Relief (NDA 021545/S-022). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JAN 07. RCM No.: 2019-923.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JANUARY 22, 2020

Container labels

NDA 020688/S-032



NDA 021545/S-022



Carton labeling

NDA 020688/S-032



(b) (4)



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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)

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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 FINDING 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 "Eye Itch Relief" 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, (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	<p>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.</p> <p>Children under 2 years of age: Consult a doctor</p>	<p>Adults and children 2 years of age and older: Put 1 drop in the affected eye(s) once daily, no more than once per day</p> <p>Children under 2 years of age: Consult a doctor</p>	<p>Adults and children 2 years of age and older: Put 1 drop in the affected eye(s) once daily, no more than once per day</p> <p>Children under 2 years of age: Consult a doctor</p>
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



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^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEMORANDUM

DEPARTMENT OF HEALTH AND
HUMAN SERVICES PUBLIC HEALTH
SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND
RESEARCH

FROM: Gettie Audain, DHSc, MPH, RN, Senior Regulatory Health Project Manager
Division of Pediatric and Maternal Health (DPMH)

THROUGH: George Greeley, MS, Lead Consumer Safety Officer
Division of Pediatric and Maternal Health (DPMH)

Jung Lee, RPh, Senior Regulatory Project Manager
Daniel Brum, PharmD, Chief, Project Management Staff
Jody Green, MD, Medical Officer Team Lead
Dorothy Chang, MD, Medical Officer
Division of Nonprescription Drug Products (DNDP)

IND: sNDA 20688/S-32
sNDA 21545/S-22

DRUG: **Patanol**[®] (olopatadine hydrochloride ophthalmic solution, 0.1%)
Pataday[™] (olopatadine hydrochloride ophthalmic solution, 0.2%)

SPONSOR: Alcon Research, LLC

Proposed Indications: Temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair and dander.

DNDP submitted a consult request to DPMH on May 30, 2019, to discuss PREA regulatory issues regarding the proposed full Rx-to-OTC of sNDA 20688/S-32, Patanol (olopatadine hydrochloride ophthalmic solution, 0.1%) and sNDA 21545/S-22, Pataday (olopatadine hydrochloride ophthalmic solution, 0.2%). Alcon Research, LLC is requesting full prescription to over-the-counter (Rx-to-OTC) switch for Patanol[®] and Pataday[™]. DNDP would like to know if this full switch would be considered a new indication, thus triggering PREA. Patanol 0.1% was approved as a prescription drug under NDA 20688 on December 15, 1996 for the treatment of signs and symptoms associated with allergic conjunctivitis. An

sNDA 20688/S-32Patanol (olopatadine hydrochloride ophthalmic solution, 0.1%)

sNDA 21545/S-22Pataday (olopatadine hydrochloride ophthalmic solution, 0.2%)

efficacy supplement was approved on March 20, 2000 for the expansion of the indication to the treatment of allergic conjunctivitis. The recommended dose is one drop in the affected eye(s) twice daily, every 6 to 8 hours, no more than twice per day. Pataday 0.2% was approved as a prescription drug under NDA 21545 on December 22, 2004 for the treatment of ocular itching associated with allergic conjunctivitis. The recommended dose is one drop in each affected eye once a day. The Sponsor proposes to market Patanol 0.1% under the proposed trade name *Pataday Regular Strength* and Pataday 0.2% under the proposed trade name *Pataday Extra Strength* if the supplements are approved for OTC marketing.

DPMH Response

Based on the approved indications, both products are indicated for the treatment of symptoms associated with allergic conjunctivitis which include redness and itching. In the proposed over-the-counter indication, there are no additional symptoms added as both Pataday and Patanol treat redness and itching associated with allergic conjunctivitis. Therefore, there is no change to the indication and the proposed indication would not trigger PREA. Note that the change in the number of times the product is dosed per day does not change the total amount of the drug that the patient will intake per day and therefore, there is no change to the dosing regimen. The dosage form and route of administration remain the same. Furthermore, the intended use of the product remains the same for the treatment of allergic conjunctivitis.

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021545s022

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)

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Date of This Review:	July 9, 2019
Application Type and Number:	NDA 020688/S-032
Product Name and Strength:	Pataday Twice Daily Relief (olopatadine) ophthalmic solution, 0.1%
Product Type:	Single Ingredient Product
Rx or OTC:	Over-the-counter (OTC)
Applicant/Sponsor Name:	Alcon Research, LLC (Alcon)
Panorama #:	2019-30833213
DMEPA Safety Evaluator:	Grace P. Jones, PharmD, BCPS
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS
DMEPA Deputy Director:	Danielle Harris, PharmD, BCPS

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1 INTRODUCTION

This review evaluates the proposed proprietary name, Pataday Twice 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

Patanol (olopatadine) ophthalmic solution, 0.1%, was originally approved on December 18, 1996 under NDA 020688 and is still currently marketed by Novartis Pharmaceuticals Corp (Novartis) as a prescription product. Generic versions of olopatadine ophthalmic solution, 0.1%, are also available through multiple manufacturers and distributors. Novartis has granted Alcon the rights for the full Rx-to-OTC switch of Patanol.^a Thus, Alcon submitted the name, Pataday Twice Daily Relief, for review on April 15, 2019, for the proposed full Rx-to-OTC switch of Patanol, under NDA 020688/Supplement-032.

Novartis also holds the applications for Pataday (olopatadine) ophthalmic solution, 0.2%, Pazeo (olopatadine) ophthalmic solution, 0.7%, and Patanase (olopatadine HCl) nasal spray, 0.665mg/spray (see Table 1 for complete line of Novartis's olopatadine products).

Table 1. Novartis Olopatadine Product Line (Source: Drugs@FDA)

Product Name	Strength	Dosage Form	Route	Application	Approval Date
Patanol	0.1%	Ophthalmic solution	Ophthalmic	NDA 020688	12/18/1996
Pataday	0.2%	Ophthalmic solution	Ophthalmic	NDA 021545	12/22/2004
Patanase	665 mcg	Nasal spray	Intranasal	NDA 021861	4/15/2005
Pazeo	0.7%	Ophthalmic solution	Ophthalmic	NDA 206276	1/30/2015

Additionally, Novartis has granted Alcon the rights for full Rx-to-OTC switch for Pataday (olopatadine) ophthalmic solution, 0.2%, under NDA 021545. Alcon is concurrently requesting review of the proposed proprietary name, Pataday Once Daily Relief, for olopatadine ophthalmic solution, 0.2%, under NDA 021545/Supplement-022; the proposed proprietary name, Pataday Once Daily Relief, is being reviewed under a separate cover.

1.2 PRODUCT INFORMATION

The following product information is provided in the proprietary name submission received on April 15, 2019.^b

- Intended Pronunciation: Pat-Ah-Day

^a Source: Cover Letter for NDA 020688/Supplement-032, available at: <\\cdsesub1\evsprod\nda020688\0018\m1\us\cover.pdf>

^b The name submission refers to the carton and container labeling for product information, which the updated container labels and carton labeling was submitted on June 20, 2019.

- Active Ingredient: olopatadine
- Indication of Use: Temporarily relieves itchy and red eyes due to pollen, ragweed, grass, animal hair and dander.^b
- Route of Administration: ophthalmic
- Dosage Form: ophthalmic solution
- Strength: 0.1%
- 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
- How Supplied: 5 mL bottle
- Storage: store between 4°-25°C (39°-77°F)

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name, Pataday Twice Daily Relief.

2.1 MISBRANDING ASSESSMENT & INITIAL COMMENTS

At the initial phase of the review, in response to our initial OSE, May 7, 2019 email, the Division of Nonprescription Drug Products (DNBP) and the Division of Transplant and Ophthalmology Products (DTOP) provided the following preliminary comments related to the proposed proprietary name, Pataday Twice Daily Relief (in conjunction with preliminary comments for the concurrently proposed proprietary name, Pataday Once Daily Relief):

- Consumers switching from Rx Pataday (0.2%) to the proposed OTC Pataday Twice Daily Relief (0.1%) may not realize that the OTC product (0.1%) is not the same as the Rx product (0.2%) because they share the same “Pataday” name.
- The suffix “-aday” in the root name Pataday implies once daily, which may appear confusing in the proposed proprietary name Pataday Twice Daily Relief because both “a day” and “twice daily” are together in the product name.
- The proposed names Pataday Once Daily Relief and Pataday Once Daily Relief imply the duration of efficacy or the frequency of administration.
- The Rx names, Patanol and Pataday, should remain for marketing the proposed OTC products due to potential confusion with the product’s dosing.
- Either strength (0.1% or the 0.2%) can be dosed once or twice daily to provide relief of itchiness and redness. The redness relief would wear off after 8 hours, but a repeat dosing would not result in any safety concerns.
- The safety margin of olopatadine is such that 2 or 3 of these products could be administered at the same time or sequentially without altering safety or efficacy.

We met internally with DNDP and DTOP to discuss these comments and learned that if confusion occurs between the 2 proposed OTC olopatadine ophthalmic products (i.e., 0.1% and 0.2% strengths), there would be minimal public health safety concern and no harm to consumers. Thus, DNDP and DTOP concluded that the proposed proprietary name, Pataday Twice Daily Relief, does not misbrand the proposed product. DMEPA agrees with DNDP and DTOP's misbranding assessment.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the proposed proprietary name, Pataday Twice Daily Relief.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proposed proprietary name^c.

2.2.2 Components of the Proposed Proprietary Name

Alcon indicated in their submission that the proposed proprietary name, Pataday Twice 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, Twice Daily Relief. We further discuss the modifiers, Twice Daily Relief, in Section 2.2.5.

2.2.3 FDA Name Simulation Studies

Ninety-five practitioners participated in DMEPA's prescription studies for Pataday Twice 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. Appendix B contains the results from the verbal and written prescription studies.

2.2.4 Medication Error Data Selection of Cases

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.

^c USAN stem search conducted on June 26, 2019.

Table 2. FAERS Search Strategy	
Search Date	June 3, 2019
Drug Name	Pataday [product name] *Pataday* [product verbatim]
Event (MedDRA Terms)	DMEPA Official PNR Name Confusion Search Terms Event List Event Preferred Term (PT): Medication Error
Date Limits	June 1, 2009 to June 1, 2019

Each report was reviewed for relevancy and duplication. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the case outcome and error root causes when provided by the reporter.

The search yielded 2 cases, which were not included in the final analysis for the following reasons: product quality issue and wrong drug dispensed unrelated to the proprietary name, Pataday.

2.2.5 Evaluation of the Proposed Modifiers, Twice Daily Relief

The root name, Pataday, appears first in the proposed proprietary name followed by the modifiers, Twice Daily Relief. Alcon indicates in its request for proprietary name review submission that the modifiers Twice Daily Relief, are used to connote the differences in dosing administration between the olopatadine 0.1% and olopatadine 0.2% products. In the proposed product, the modifiers, Twice Daily Relief, refers to the product's dosing. The proposed Drug Facts Label (DFL) *Directions* section states, "Put 1 drop in affected eye(s) twice daily", and the proposed product should not be used more than twice per day according to the *Directions*.

While we did not identify any application OTC products that incorporate the modifier "Twice 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 "Twice Daily". However, from a medication error perspective, we do not anticipate the combination of the words "Twice Daily Relief" to introduce any risk of confusion because the product is dosed twice daily and will provide relief of the symptoms when used twice daily.

Additionally, we learned from discussion with the review team that there is no risk of clinical harm if confusion were to occur between the olopatadine ophthalmic products. The safety margin for olopatadine is wide such that multiple olopatadine products can be administered at the same time with no safety concerns. Per the review team, even if consumers were to take this product incorrectly, dose it more frequently, or use more than one olopatadine product at a time, there is no safety concern. Therefore, for these reasons, we do not object to the use of the modifiers, Twice Daily Relief, and the proposed proprietary name in totality is acceptable.

2.2.6 Communication of DMEPA's Analysis at Midpoint of Review

DMEPA communicated our findings to the Division of Nonprescription Drug Products (DNNDP) via e-mail on July 9, 2019.

3 CONCLUSION

The proposed proprietary name, Pataday Twice 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 Twice Daily Relief, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your submission, received on April 15, 2019 and June 20, 2019, are altered prior to approval of the marketing application, the name must be resubmitted for review.

APPENDICES

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 Twice Daily Relief Study (Conducted on May 3, 2019)

Handwritten Medication Order/Prescription	Verbal Prescription
<p>Medication Order:</p> <p><i>Pataday Twice Daily Relief 1 drop</i> <hr/> <i>in affected eye(s) BID</i></p>	<p>Pataday Twice Daily Relief</p> <p>Instill 1 drop in affected eye twice daily</p> <p>Dispense 1 bottle</p>
<p>Outpatient Prescription:</p> <p><i>Pataday Twice Daily Relief</i> <i>1 drop in affected eye(s)</i> <i>BID #1 bottle</i></p>	

FDA Prescription Simulation Responses (Aggregate Report)

219 People Received Study

95 People Responded

Study Name: Pataday Twice Daily Relief

Total	23	17	55	
INTERPRETATION	OUTPATIENT	VOICE	INPATIENT	TOTAL
PADAY	0	0	1	1
PADIDAY	0	1	0	1
PATADARYL	0	0	1	1
PATADARZ	0	0	1	1
PATADAY	10	1	42	53
PATADAY TWICE DAILY RELIEF	0	0	1	1
PATADAY TWICE DAILY RELEASE	0	2	0	2
PATADAY TWICE DAILY RELIEF	12	7	6	25
PATADAY TWISE DAILY RELIEF	1	0	0	1
PATADAYTWICE DAILY RELIEF	0	0	1	1
PATADAZ	0	0	1	1
PATADAZ TWICE DAILY RELIEF	0	0	1	1
PATIDAY TWICE DAILY RELIEF	0	1	0	1
PATTIDAY TWICE DAILY RELIEF	0	1	0	1
TAFADAY TWICE DAILY RELIEF	0	2	0	2
TAFFIDAY	0	1	0	1
TATADAY TWICE DAILY RELIEF	0	1	0	1

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/s/

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