CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 206276/S-001

Trade Name: PAZEO

Generic Name: olopatadine hydrochloride ophthalmic solution

Sponsor: Alcon Research, Ltd.

Approval Date: 11/27/2015

Indication: PAZEO is a mast cell stabilizer indicated for the treatment of ocular itching associated with allergic conjunctivitis.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 206276/S-001

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 206276/S-001

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206276/S-001

APPROVAL LETTER

Alcon Research, Ltd.
Attention: Teresa McElvaney, Technical (CMC) Regulatory Affairs, Fort Worth
6201 South Freeway, R3-50
Fort Worth, TX 76134-2099

Dear Ms. McElvaney:

Please refer to your Supplemental New Drug Application (sNDA) dated July 29, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Pazeo® (olopatadine hydrochloride) Ophthalmic Solution, 0.7%.

This "Prior Approval" supplemental new drug application provides for addition of an additional fill size (3.5 mL) for the drug product and changes to the package insert and carton label.

We have completed our review of this supplemental new drug application. This supplement is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Erin Andrews, Regulatory Business Process Manager, at (240) 402-8578.

Sincerely,

Dorota M. Matecka -S

Digitally signed by Dorota M. Matecka -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300123291, cn=Dorota M. Matecka -S
Date: 2015.11.27 15:02:19 -05'00'

(Signed on behalf of)
Balajee Shanmugam, Ph.D.
Acting Branch Chief, Branch III
Division of New Drug Product I
Office of New Drug Products
Center for Drug Evaluation and Research Branch

Enclosures:
Carton and Container Image
Prescriber Information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 206276/S-001

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PAZEO safely and effectively. See full prescribing information for PAZEO.

PAZEO (olopatadine hydrochloride ophthalmic solution) 0.7%
For topical ophthalmic administration.
Initial U.S. Approval: 1996

----------INDICATIONS AND USAGE----------

PAZEO * is a mast cell stabilizer indicated for the treatment of ocular itching associated with allergic conjunctivitis. (1).

----------DOSAGE AND ADMINISTRATION----------

The recommended dose is one drop in each affected eye once a day. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Ophthalmic solution: 7.76 mg of olopatadine hydrochloride in one mL of solution (0.7%) in a four mL bottle. (3)

----------CONTRAINDICATIONS----------

None.

----------WARNINGS AND PRECAUTIONS----------

Contamination of Tip and Solution. To prevent contaminating the dropper tip and solution, do not touch the eyelids or surrounding areas with the dropper tip of the bottle. (5.1)

----------ADVERSE REACTIONS----------

The most common adverse reactions (2-5%) were blurred vision, superficial punctate keratitis, dry eye, abnormal sensation in eye, and dysgeusia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Alcon Laboratories, Inc. at 1-800-757-9195 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 7/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

PAZEO • is indicated for the treatment of ocular itching associated with allergic conjunctivitis.

2 DOSAGE AND ADMINISTRATION

The recommended dosage of PAZEO is to instill one drop in each affected eye once a day.

3 DOSAGE FORMS AND STRENGTHS

Ophthalmic solution: 7.76 mg of olopatadine hydrochloride in one mL solution (0.7%) in a 4 mL bottle.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Contamination of Tip and Solution

As with any eye drop, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle to prevent contaminating the tip and solution. Keep bottle tightly closed when not in use.

5.2 Contact Lens Use

Patients should not wear a contact lens if their eye is red.

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate or well-controlled studies with PAZEO in pregnant women. Olopatadine caused maternal toxicity and embryofetal toxicity in rats at levels 1,080 to 14,400 times the maximum recommended human ophthalmic dose (MRHOD). There was no toxicity in rat offspring at exposures estimated to be 45 to 150 times that at MRHOD. Olopatadine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data
In a rabbit embryofetal study, rabbits treated orally at 400 mg/kg/day during organogenesis showed a decrease in live fetuses. This dose is 14,400 times the MRHOD, on a mg/m^2 basis.

An oral dose of 600 mg/kg/day olopatadine (10,800 times the MRHOD) was shown to be maternally toxic in rats, producing death and reduced maternal body weight gain. When administered to rats throughout organogenesis, olopatadine produced cleft palate at 60 mg/kg/day (1080 times the MRHOD) and decreased embryofetal viability and reduced fetal weight in rats at 600 mg/kg/day. When administered to rats during late gestation and throughout the lactation period, olopatadine produced decreased neonatal survival at 60 mg/kg/day and reduced body weight gain in offspring at 4 mg/kg/day. A dose of 2 mg/kg/day olopatadine produced no toxicity in rat offspring. An oral dose of 1 mg/kg olopatadine in rats resulted in a range of systemic plasma area under the curve (AUC) levels that were 45 to 150 times higher than the observed human exposure [9.7 ng·hr/mL] following administration of the recommended human ophthalmic dose.

8.3 Nursing Mothers
Olopatadine has been identified in the milk of nursing rats following oral administration. Oral administration of olopatadine doses at or above 4 mg/kg/day throughout the lactation period produced decreased body weight gain in rat offspring; a dose of 2 mg/kg/day olopatadine produced no toxicity. An oral dose of 1 mg/kg olopatadine in rats resulted in a range of systemic plasma area under the curve (AUC) levels that were 45 to 150 times higher than the observed human exposure [9.7 ng·hr/mL] following administration of the recommended human ophthalmic dose. 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 PAZEO is administered to a nursing mother.

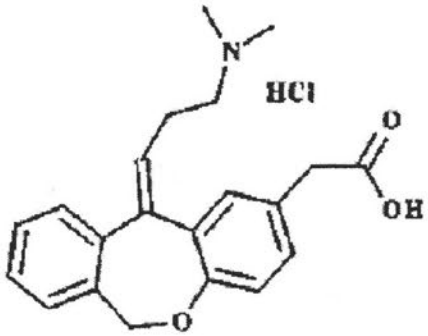
8.4 Pediatric Use
The safety and effectiveness of PAZEO have been established in pediatric patients two years of age and older. Use of PAZEO in these pediatric patients is supported by evidence from adequate and well-controlled studies of PAZEO in adults and an adequate and well controlled study evaluating the safety of PAZEO in pediatric and adult patients.

8.5 Geriatric Use
No overall differences in safety and effectiveness have been observed between elderly and younger patients.

11 DESCRIPTION
PAZEO is a sterile ophthalmic solution containing olopatadine, which is a mast cell stabilizer, for topical administration to the eyes. Olopatadine hydrochloride is a white, crystalline,

water-soluble powder with a molecular weight of 373.88 and a molecular formula of $C_{21}H_{23}NO_3 \cdot HCl$.

The chemical structure is presented below:



Chemical Name: 11-[(Z)-3(dimethylamino) propylidene]-6-11dihydrodibenz[b,e] oxepin-2-acetic acid, hydrochloride

Each mL of PAZEO solution contains an active ingredient [7.76 mg of olopatadine hydrochloride (7 mg olopatadine)] and the following inactive ingredients: povidone; hydroxypropyl-gamma-cyclodextrin; polyethylene glycol 400; hydroxypropyl methylcellulose; boric acid; mannitol; benzalkonium chloride 0.015% (preservative); hydrochloric acid/sodium hydroxide (to adjust pH); and purified water.

PAZEO solution has a pH of approximately 7.2 and an osmolality of approximately 300 mOsm/kg.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Olopatadine is a mast cell stabilizer and a histamine H_1 antagonist. Decreased chemotaxis and inhibition of eosinophil activation has also been demonstrated.

12.3 Pharmacokinetics

In healthy subjects, topical ocular dosing of 1 drop of PAZEO once daily for 7 days into both eyes resulted in mean ± SD (range) steady state plasma olopatadine C_{max} and AUC_{0-12} of 1.6 ± 0.9 ng/mL (0.6 to 4.5 ng/mL) and 9.7 ± 4.4 ng*h/mL (3.7 to 21.2 ng*h/mL), respectively. The olopatadine C_{max} and AUC_{0-12} after the first dose were similar to those measured on day 7 in these subjects, suggesting that there was no systemic accumulation of olopatadine after repeated topical ocular dosing with PAZEO. The median (range) time to achieve peak olopatadine concentrations (T_{max}) was 2.0 hours (0.25 to 4 hours). The mean ± SD (range) elimination half-life of olopatadine was 3.4 ± 1.2 hours (2 to 8 hours). N-oxide olopatadine (M3) was detected during the first 4 hours after bilateral topical ocular dosing of PAZEO in approximately half of the subjects and in less than 10% of the total plasma samples collected, at concentrations

not exceeding 0.121 ng/mL on day 1 and 0.174 ng/mL on day 7. None of the plasma samples from these subjects had mono-desmethyl olopatadine (M1) concentrations that were above the lower limit of quantitation (0.05 ng/mL) of the PK assay.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity
Olopatadine administered orally was not carcinogenic in mice and rats in doses up to 500 mg/kg/day and 200 mg/kg/day, respectively. Based on a 35 μL drop size and a 60 kg person, these doses are approximately 4,500 and 3,600 times the MRHOD, on a mg/m^2 basis.

Mutagenesis
No mutagenic potential was observed when olopatadine was tested in an in vitro bacterial reverse mutation (Ames) test, an in vitro mammalian chromosome aberration assay or an in vivo mouse micronucleus test.

Impairment of fertility
Olopatadine administered at an oral dose of 400 mg/kg/day (approximately 7,200 times the MRHOD) produced toxicity in male and female rats, and resulted in a decrease in the fertility index and reduced implantation rate. No effects on reproductive function were observed at 50 mg/kg/day (approximately 900 times the MRHOD).

14 CLINICAL STUDIES
The efficacy of PAZEO was established in two randomized, double-masked, placebo-controlled, conjunctival allergen challenge (CAC) clinical studies in patients with a history of allergic conjunctivitis (Studies 1 and 2).

In Study 1, patients were randomized to receive one of the following study treatments: PAZEO, PATADAY, or vehicle ophthalmic solutions. In Study 2, patients were randomized to receive one of the following study treatments: PAZEO, PATADAY, PATANOL, or vehicle ophthalmic solutions.

Patients were evaluated with an ocular itching severity score ranging from 0 (no itching) to 4 (incapacitating itch) at several time points after CAC administration. Table 1 displays the mean ocular itching severity scores after ocular administration of a specific antigen using the CAC model in Studies 1 and 2, respectively. A one unit difference compared to vehicle is considered a clinically meaningful change in the ocular itching severity score.

PAZEO demonstrated statistically significantly improved relief of ocular itching compared to vehicle at 30-34 minutes, 16 hours, and 24 hours after study treatment. PAZEO demonstrated statistically significantly improved relief of ocular itching compared to PATADAY at 24 hours after study treatment, but not at 30-34 minutes after study treatment.

Table 1. Itching Scores by Treatment Group and Treatment Difference* in Mean Itching

	Time Point	PAZEO (Olopatadine, 0.7%)	PATADAY (Olopatadine, 0.2%)		Vehicle	
Study 1		(N = 66)	(N = 68)		(N = 68)	
		Mean	Mean	Difference (95% CI)	Mean	Difference (95% CI)
Onset	3 mins	0.36	0.39	-0.02 (-0.31, 0.26)	1.90	-1.54 (-1.82, -1.25)
	5 mins	0.53	0.61	-0.08 (-0.39, 0.22)	2.06	-1.53 (-1.84, -1.22)
	7 mins	0.48	0.61	-0.13 (-0.44, 0.17)	1.97	-1.49 (-1.80, -1.18)
16h	3 mins	0.70	0.87	-0.17 (-0.44, 0.11)	2.20	-1.50 (-1.77, -1.23)
	5 mins	0.79	1.04	-0.24 (-0.55, 0.07)	2.27	-1.48 (-1.79, -1.16)
	7 mins	0.75	0.98	-0.23 (-0.54, 0.08)	2.13	-1.38 (-1.69, -1.07)
24h	3 mins	0.93	1.41	-0.48 (-0.76, -0.20)	2.54	-1.61 (-1.88, -1.33)
	5 mins	1.10	1.52	-0.42 (-0.72, -0.12)	2.62	-1.51 (-1.81, -1.21)
	7 mins	1.09	1.50	-0.41 (-0.72, -0.10)	2.50	-1.41 (-1.72, -1.11)
Study 2		(N = 98)	(N = 99)		(N = 49)	
Onset	3 mins	0.38	0.47	-0.09 (-0.28, 0.09)	1.91	-1.53 (-1.76, -1.30)
	5 mins	0.53	0.61	-0.08 (-0.29, 0.12)	1.99	-1.46 (-1.71, -1.22)
	7 mins	0.65	0.61	0.04 (-0.18, 0.26)	1.82	-1.17 (-1.45, -0.90)
24h	3 mins	1.01	1.33	-0.31 (-0.57, -0.06)	2.30	-1.29 (-1.60, -0.97)
	5 mins	1.22	1.48	-0.26 (-0.51, -0.01)	2.37	-1.15 (-1.46, -0.84)
	7 mins	1.25	1.41	-0.16 (-0.42, 0.11)	2.14	-0.89 (-1.22, -0.57)

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

16 HOW SUPPLIED/STORAGE AND HANDLING

PAZEO (olopatadine hydrochloride ophthalmic solution) 0.7% is supplied in a white, oval, low density polyethylene DROP-TAINER® dispenser with a natural low density polyethylene dispensing plug and a white polypropylene cap. Tamper evidence is provided with a shrink band around the closure and neck area of the package. PAZEO is supplied in a 4 mL bottle that contains olopatadine hydrochloride ophthalmic solution [7.76 mg of olopatadine hydrochloride in one mL of solution (0.7%)] in the following sizes:

2.5 mL in a 4 mL bottle	NDC 0065-4273-25
3.5 mL in a 4 mL bottle	NDC 0065-4273-32

Storage: Store at 2°C to 25°C (36°F to 77°F). Keep bottle tightly closed when not in use.

17 PATIENT COUNSELING INFORMATION

•Risk of Contamination: Advise patients to not touch dropper tip to eyelids or surrounding areas, as this may contaminate the dropper tip and ophthalmic solution.

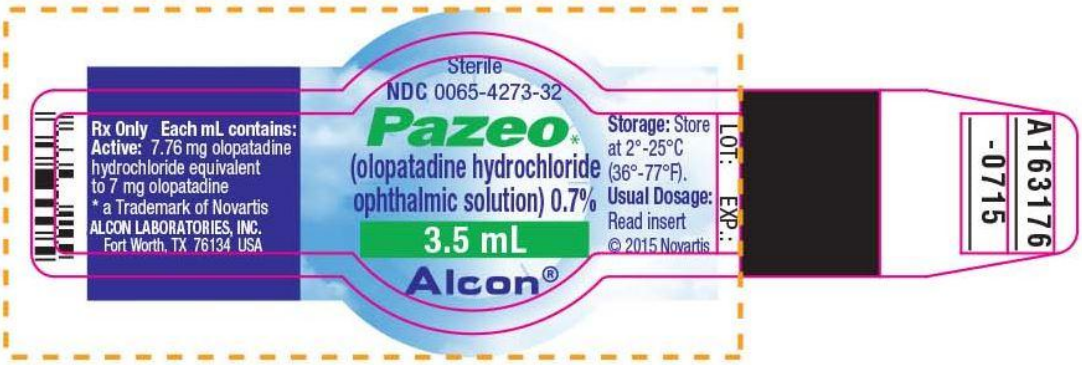
•Concomitant Use of Contact Lenses: Advise patients not to wear contact lenses if their eyes are red. Advise patients that PAZEO should not be used to treat contact lens-related irritation. Advise patients to remove contact lenses prior to instillation of PAZEO. The preservative in PAZEO solution, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted 5 minutes following administration of PAZEO.

Patents: 8,791,154

ALCON®

ALCON LABORATORIES, INC.
Fort Worth, Texas 76134 USA

(01)00300654273325



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 206276/S-001

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW #1	1. ORGANIZATION	2. NDA NUMBER	Original ☒
	ONDP	N 206276	RESUBMISSION ☐

3. NAME AND ADDRESS OF APPLICANT		4. SUPPLEMENT(S)	
		NUMBER(S)	TYPE
Company Name:	Alcon Research, Ltd.	S-001	PAS
Street Address:	6201 South Freeway, R3-50	5. DATE(S)	
City:	Fort Worth	Submit Date	July 29, 2015
State:	Texas	FDA Receipt Date	July 29, 2015
Zip Code:	76134-2099	Goal Date	November 29, 2015
Country:	USA	Chemist Receipt Date	July 31, 2015
		Amendments	None
		Date Completed	November 4, 2015

6. PROPRIETARY NAME	7. NAME OF THE DRUG
Pazeo	Olopatadine Hydrochloride Ophthalmic Solution, 0.77%

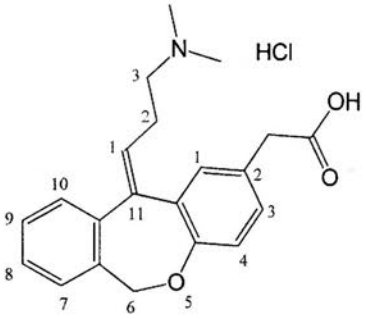
8. SUPPLEMENT PROVIDES FOR:

addition of an additional fill size (3.5 mL) for the drug product

9. INDICATION	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Treatment of ocular itching associated with allergic conjunctivitis	RX ☒ OTC ☐	
12. DOSAGE FORM	**13. POTENCY**	
Solution	0.77 %	

14. CHEMICAL NAME AND STRUCTURE

11-[(Z)-3(dimethylamino) propylidene]-6-11dihydrodibenz[b,e] oxepin-2-acetic acid, hydrochloride



Chemical Formula: $C_{21}H_{24}ClNO_3$
Molecular Weight: 373.87

15. RECORDS AND REPORTS

16. COMMENTS

In support of the proposed change, the applicant provided batch data, stability data and revised labeling. The applicant indicated that no changes to the manufacturing process (except fill volume), composition, specifications, analytical methods, container closure, or indication. The batch data and stability data were evaluated and no OOS data are reported. No major trends were observed in 13 week (3 months) stability data. The changes made to the carton container, container label, and PI to reflect the increased volume are acceptable from the CMC perspective. The labeling was also found to be acceptable from the DMEPA perspective (Review dated October 20, 2015 by Michelle Rutledge, PharmD).

EES Status: N. A.

17. CONCLUSION AND RECOMMENDATION

This submission is recommended for approval from the stand point of chemistry, manufacturing and controls.

18. REVIEWERS SIGNATURE	REVIEWER	BRANCH CHIEF
See appended electronic signature sheet	Anamitro Banerjee, Ph.D.	Balajee Shanmugam, Ph.D.

Review Notes

Pazeo was approved on January 30, 2015 for the treatment of ocular itching associated with allergic conjunctivitis.

Proposed changes

Additional fill trade size of 3.5 mL in 4 mL bottles.

Rationale: *Larger product fill size will provide patients with additional medication for an extended duration of use through the majority of allergy season and reduce the need for multiple refills. Additional amount will also allow for inadvertent wastage and enable patients to complete full course of therapy (up to 45 days of use).*

Summary

In support of the proposed change, the applicant provided:

1. Draft labeling text
2. Description and composition →*same as approved in original NDA. No changes proposed.*
3. Batch data
4. Stability data, summary and post approval stability protocol and commitment.

The applicant indicated that the packaging configuration (4 mL oval, white LDPE bottle, LDPE dispensing plug, white polypropylene closure, and (b) (4) tamper evidence feature) remains same as currently approved for the 2.5 mL fill.

The clinical division (Dr. William Boyd, via email) has indicated no concerns for the proposed change.

3.2.P.5.4 Batch Data

The applicant provided batch data for several batches of (b) (4) batches of the proposed 3.5 mL fill product. The batch data for the 3.5 mL fill batches are comparable to the currently approved 2.5 mL fill batches. No OOS result is reported. The batch data for 3.5 mL fill bathes are listed in the Table 3.2.P.5.4 below. The proposed 3.5 mL fill sizes do not have (b) (4) (b) (4)

Table 3.2.P.5.4 Batch Data Olopatadine HCl Solution 0.77% (3.5 mL/4 mL Trade Size)

	Manufacturing lot number	**250433F**	**250434F**	**250435F**
	Bulk Lot Number	246998F	247000F	246997F
	Fill Date	Feb 11, 2015	Feb 11, 2015	Feb 12, 2015
Test	**Acceptance Specifications**			
Olopatadine Assay	(b) (4) [redacted]	98, 98, 97	98, 98, 98	100, 100, 100
Olopatadine Identity (TLC)		Pass (Positive)	Pass (Positive)	Pass (Positive)
Olopatadine Identity (HPLC)		Pass (Positive)	Pass (Positive)	Pass (Positive)
Olopatadine Impurities				
(b) (4) [redacted]		0.0, 0.0, 0.0	0.0, 0.0, 0.0	0.0, 0.0, 0.0
		0.0, 0.0, 0.0	0.0, 0.0, 0.0	0.0, 0.0, 0.0
		0.0, 0.0, 0.0	0.0, 0.0, 0.0	0.0, 0.0, 0.0
		0.0, 0.0, 0.0	0.0, 0.0, 0.0	0.0, 0.0, 0.0
		0.0, 0.0, 0.0	0.0, 0.0, 0.0	0.0, 0.0, 0.0
		0.0, 0.0, 0.0	0.0, 0.0, 0.0	0.0, 0.0, 0.0
Total Impurities		0.0, 0.0, 0.0	0.0, 0.0, 0.0	0.0, 0.0, 0.0
Benzalkonium Chloride Assay		100, 100	99, 99	100, 101
Benzalkonium Chloride Identity		Conforms	Conforms	Conforms
pH		7.2	7.2	7.2
Osmolality (mOsm/kg)		316	313	316
Viscosity (mPa.s)		34	27	29
Appearance				
Color		Pale Yellow	Colorless	Colorless
Clarity		NMT EP I, Clear	NMT EP I, Clear	NMT EP I, Clear
Precipitate		None	None	None
Particulate Matter by HIAC				
(b) (4) [redacted]		3	5	1
		2	0	0
		1	0	0
Bacterial Endotoxins		<0.25	<0.25	<0.25
Sterility		Sterile	Sterile	Sterile

(b) (4) [redacted]

Fill Size / Bottle Size 3.5 mL/ 4 mL

Reviewer Evaluation ***Acceptable***

The batch data provided by the applicant for the proposed configuration is comparable to the currently approved 2.5 mL configuration. No OOS data is reported.

3.2.P.8 Stability Data

The applicant provided stability data for eight primary stability lots of 2.5 mL trade size, five primary stability lots of 0.5 mL sample size, and three primary stability lots of 3.5 mL trade size. Thirteen week (3 months) of stability data provided in this submission for the three lots of 3.5 mL trade size in 4 mL oval

LDPE bottles manufactured at the Alcon ASPEX, Fort Worth facility is evaluated here (Table 3.2.P.8). In the table, the data from accelerated storage conditions (40°C/<25%RH) is indicated in red font, intermediate condition (30°C/75%RH) is in black fonts and long term conditions (25°C/40%RH) are indicated in blue fonts. Any trends noted (or not observed) in the Table 3.2.P.8 is preliminary as only 3 data points are reported for each condition.

Table 3.2.P.8 Summary of Stability Data Olopatadine HCl Solution 0.77% (3.5 mL/4 mL Trade Size)

Test	Acceptance Specifications	250433F (Stability Lot 19059-01)	250434F (Stability Lot 19059-02)	250435F (Stability Lot 19059-03)
Olopatadine Assay	(b) (4)	101 (No change) *Range:* 100 – 101 (no trends) *Range:* 100 – 101 (no trends)	*Range:* 100 – 101 (no trends) *Range:* 99 – 100 (no trends) *Range:* 99 – 100 (no trends)	*Range:* 101 – 102 (no trends) *Range:* 101 – 102 (no trends) 101 No change
Olopatadine Impurities (% of active)				
(b) (4)		*Range:* 0 – <0.1 (no trends) Not observed Not observed Not observed under any conditions Not observed under any conditions None observed under any conditions None observed under any conditions	*Range:* 0 – <0.1 (no trends) Not observed Not observed Not observed under any conditions Not observed under any conditions None observed under any conditions None observed under any conditions	*Range:* 0 – <0.1 (no trends) Not observed Not observed Not observed under any conditions Not observed under any conditions None observed under any conditions None observed under any conditions
Benzalkonium Chloride Assay (% of Label)		*Range:* 95 – 104 (no trends) *Range:* 100 – 103 (no trends) *Range:* 96 – 102 (no trends)	*Range:* 95 – 104 (no trends) *Range:* 94 – 102 (no trends) *Range:* 93 – 101 (no trends)	*Range:* 97 – 103 (no trends) *Range:* 95 – 101 (no trends) *Range:* 96 – 101 (no trends)
Boric Acid Assay (% of Label)		*Range:* 102 – 106 (no trends) *Range:* 99 – 104 (no trends) *Range:* 96 – 102 (no trends)	*Range:* 96 – 104 (no trends) *Range:* 96 – 102 (no trends) *Range:* 96 – 107 (no trends)	*Range:* 99 – 105 (no trends) *Range:* 99 – 103 (no trends) *Range:* 99 – 105 (no trends)
pH		*Range:* 7.09 – 7.17 (no trends) *Range:* 7.11 – 7.18 (no trends) *Range:* 7.11 – 7.20 (no trends)	*Range:* 7.08 – 7.15 (no trends) *Range:* 7.09 – 7.15 (no trends) *Range:* 7.10 – 7.16 (no trends)	*Range:* 7.09 – 7.16 (no trends) *Range:* 7.13 – 7.17 (no trends) *Range:* 7.12 – 7.18 (no trends)
Osmolality (mOsm/kg)		*Range:* 309 – 315 (increase) *Range:* 309 – 318 (increase) *Range:* 308 – 310 (no trends)	*Range:* 307 – 315 (increase) *Range:* 307 – 311 (increase) *Range:* 302 – 307 (no trends)	*Range:* 310 – 322 (increase) *Range:* 310 – 316 (increase) *Range:* 310 – 315 (no trends)
Viscosity, Liquid (b) (4) (b) (4)		*Range:* 30.5 – 31.6 (no trends) *Range:* 30.3 – 33.2 (no trends) *Range:* 30.5 – 31.7 (no trends)	*Range:* 25.4 – 27.6 (no trends) *Range:* 25.4 – 26.6 (no trends) *Range:* 25.4 – 27.8 (no trends)	*Range:* 26.8 – 28.6 (no trends) *Range:* 26.7 – 28.1 (no trends) *Range:* 27.8 – 29.2 (no trends)
Color		Conforms for all conditions	Conforms for all conditions	Conforms for all conditions
Clarity		Conforms for all conditions	Conforms for all conditions	Conforms for all conditions
Precipitate		Conforms for all conditions	Conforms for all conditions	Conforms for all conditions
Particles/Particulates by Visual Observation		Conforms for all conditions	Conforms for all conditions	Conforms for all conditions
Package Condition		Satisfactory for all conditions	Satisfactory for all conditions	Satisfactory for all conditions
Average % Weight Change		– 2.1 @ 13 weeks – 0.2 @ 13 weeks – 0.4 @ 13 weeks	– 2.0 @ 13 weeks – 0.2 @ 13 weeks – 0.4 @ 13 weeks	– 2.1 @ 13 weeks – 0.2 @ 13 weeks – 0.4 @ 13 weeks
Bacterial Endotoxins Test		Not Tested	Not Tested	Not Tested
Preservative Efficacy Test		Not Tested	Not Tested	Not Tested
Sterility		Not Tested	Not Tested	Not Tested

Reviewer Evaluation ***Acceptable***

No OOS data is reported in the stability data. Minor trends are noticed in osmolality under accelerated and intermediate conditions.

Labeling

The applicant provided revised PI for the product. The only change reported is in the section 16 HOW SUPPLIED/STORAGE AND HANDLING as noted below:

16 HOW SUPPLIED/STORAGE AND HANDLING

PAZEO (olopatadine hydrochloride ophthalmic solution) 0.7% is supplied in a white, oval, low density polyethylene DROP-TAINER® dispenser with a natural low density polyethylene dispensing plug and a white polypropylene cap. Tamper evidence is provided with a shrink band around the closure and neck area of the package. PAZEO is supplied in a 4 mL bottle that contains ~~2.5 mL of~~ olopatadine hydrochloride ophthalmic solution [7.76 mg of olopatadine hydrochloride in one mL of solution (0.7%)] in the following sizes:

2.5 mL in a 4 mL bottle	NDC 0065-4273-25
3.5 mL in a 4 mL bottle	NDC 0065-4273-32~~NDC 0065-4273-25~~

Revised carton container and container labels are shown below:

(b) (4)

(b) (4)

Reviewer Evaluation ***Acceptable***

The revisions to the PI and the carton container and label are acceptable from the CMC perspective. The proposed labeling was found be acceptable from the DMEPA perspective (Michelle Rutledge, PharmD, Dated October 20, 2015).

Recommendation:

This submission is recommended for APPROVAL from the stand point of chemistry, manufacturing and controls.

Anamitro Banerjee -S
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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000423276, cn=Anamitro Banerjee -S
Date: 2015.11.04 12:31:06 -05'00'

Balajee Shanmugam -S
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Date: 2015.11.04 12:35:57 -05'00'

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 206276/S-001

OTHER REVIEW(S)

RBPM LABELING REVIEW
Review

Office of Pharmaceutical Quality

Application Number: NDA 206276/S-001

Name of Drug: Pazeo (olopatadine hydrochloride) Ophthalmic Solution 0.7%

Applicant: Alcon Research Ltd

Material Reviewed:

Material	Submit Date	Receipt Date	Compared to
Content of Labeling (SPL)	7/29/2015	7/29/2015	2/11/2015
Carton and Container Labels	7/29/2015	7/29/2015	2/11/2015

Background and Summary

NDA 206276/S-001 was submitted as a Prior Approval supplement and provides for an additional fill trade size of 3.5mL for the drug product. Container, carton, and PI were updated with the new fill volume size. The information supporting these changes was reviewed by Michelle Rutledge, Division of Medical Error Prevention and Analysis on October 22, 2015. The CMC changes were reviewed by Anamitro Banerjeee on November 4, 2015 and found to be acceptable.

Review

This comparison was done by visually comparing the July 29, 2015 carton and container labeling, and content of labeling to the last approved labeling on file (February 11, 2015).

The following are the assessments for each change identified:

Carton/Container Label:

1. Change #1 - For carton and immediate container, volume fill amount changed to 3.5mL (already approved fill volume is 2.5 mL).
   Comment: Acceptable. It indicates the new amount in the bottle.

2. Change #2 –Green bar background behind 3.5mL. Fill volume was moved up and center justified and that the green bar added making the fill volume more permanent.

Comment: Acceptable. It highlights the fill volume on the carton.

3. Change #3 - For carton and immediate container, new NDC number
   Comment: Acceptable. Identifying product number for new fill size.

4. Change #4 – For immediate container, location of word "sterile" changed. The word "sterile" was moved from the bottom of the label to the top of the label (above the NDC number).
   Comment: Acceptable. Made more prominent.

5. (b) (4)

Labeling:

1. Change #1 –New fill size. The fill volume was removed from the text in the "How Supplied/Storage and Handling" section and the phrase "in the following sizes:" was added and followed by the listing of the two available fill sizes.
   Comment: Acceptable. Clearly indicates the new fill size (3.5mL in 4mL bottle) in addition to the original fill size (2.5mL in 4mL) on two separate lines, aligned right and followed by corresponding NDC.

2. Change #2 – Addition of NDC# for new fill size.
   Comment: Acceptable. Clearly indicates the NDC (0065-4273-32) of the new fill size in addition to the NDC (0065-4273-25) of the original fill size on two separate lines immediately following the fill size.

3. Change #3 –Revision date of PI in footnote.
   Comment: Acceptable. Clearly indicates month and year the PI was revised.

4. Change #4 – Updated distribution year.
   Comment: Acceptable. Clearly indicates distribution year.

Recommendations

The changes to the content of labeling and the carton/container labels are acceptable.

Erin Andrews -A
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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Erin Andrews -A, 0.9.2342.19200300.100.1.1=2001366614
Date: 2015.11.25 13:45:02 -05'00'

LT Erin Andrews, Pharm.D, USPHS
Regulatory Business Process Manager
Office of Program and Regulatory Operations

Date: November 17, 2015

Office of Pharmaceutical Quality
CDER/FDA

Sonni Kim — Date
Branch Chief
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
CDER/FDA

Enclosures:

Carton Image
Label Image
Prescriber Information

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 206276/S-001

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206276/S-001

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

Alcon Research, Ltd.
Attention: Teresa McElvaney, Technical (CMC) Regulatory Affairs, Fort Worth
6201 South Freeway
Mail Stop: TC-45
Fort Worth, TX 76134-2099

Dear Ms. McElvaney:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 206276

SUPPLEMENT NUMBER: S-001

PRODUCT NAME: Pazeo® (Olopatadine Hydrochloride) Ophthalmic Solution

DATE OF SUBMISSION: July 29, 2015

DATE OF RECEIPT: July 29, 2015

This "Prior Approval" supplemental application provides for an additional fill size of 3.5mL

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 27, 2015, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be November 29, 2015.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have questions, call me, at 240-402-3815.

Sincerely,

Navdeep Bhandari -S

Digitally signed by Navdeep Bhandari -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001220182, cn=Navdeep Bhandari -S
Date: 2015.08.04 10:47:11 -04'00'

LT Navi Bhandari, Pharm.D, USPHS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
CDER/FDA

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Karen Townsend
Mail: DMEPA/OSE

FROM:
Navi Bhandari, Regulatory Project Manager, ONDQA, Tel 240-402-3815

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
8/3/2015		NDA 206276/S-001	CMC supplement (PAS)	7/29/2015

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Pazeo	PAS		10/29/2015

NAME OF FIRM: HERITAGE PHARMACEUTICALS INC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ **LABELING REVISION**
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please evaluate the revised labels. It is an electronic submission accessible through DARRTS.

Provides for the addition of an alternate fill size for 3.5mL.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☒ E-MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NAVDEEP BHANDARI
08/03/2015