CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 022212Orig1s015

Name: Durezol® (difluprednate) Emulsion

Sponsor: Alcon Pharmaceuticals, Ltd.

Approval Date: June 23, 2008

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA22212Orig1s015

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Reviews / Information Included in this Review

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Bioequivalence Review(s)	
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA22212Orig1s015

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022212/S-015, 022428/S-007, 050818/S-005, 200890/S-008, 203491/S-010, 204251/S-008, 204822/S-001 and 206276/S-002

APPROVAL LETTER

Alcon Pharmaceuticals, Ltd.
Attention: Kevin Nugent
Head of Change Assessment Regulatory Affairs
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Mr. Nugent:

Please refer to your Supplemental New Drug Applications (sNDAs), dated and received on December 16, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

NDA Number	Supplement Number	Product Name
NDA 022212	S-015	Durezol® (difluprednate) Emulsion
NDA 022428	S-007	Moxeza® moxifloxacin hydrochloride) Ophthalmic Solution
NDA 050818	S-005	Tobradex ST ® (tobramycin and dexamethasone) Ophthalmic Suspension
NDA 200890	S-008	Isopto Carpine ® (pilocarpine hydrochloride) Solution
NDA 203491	S-010	Ilevro ® (nepafenac) Suspension
NDA 204251	S-008	SIMBRINZA™ (brinzolamide/ brimonidine tartrate ophthalmic suspension)
NDA 204822	S-001	IZBA (travoprost ophthalmic solution)
NDA 206276	S-002	Pazeo (olopatadine hydrochloride ophthalmic solution)

These “Prior Approval” supplemental new drug applications provide for removal of the bacterial endotoxin test (BET) from the regulatory acceptance specification of these products.

We have completed our review of these supplemental new drug applications. These supplements are 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 Laya Keyvan, Regulatory Project Manager, at (240) 402-4598.

Sincerely,

David B. Lewis -S

Digitally signed by David B. Lewis -S
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Date: 2016.04.08 16:01:45 -04'00'

Hasmukh Patel, Ph.D.
Division Director (Acting)
Division of Post Marketing Activities I
Office of Lifecycle Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

David Lewis, Ph.D., OPQ/OLDP/DPMA1/BII, signing for Hasmukh Patel, Ph.D., DD/OPQ/OLDPMA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22212Orig1s015

CHEMISTRY REVIEWS

Chemistry Review: # 1	**1. Division:** DTOP	**2. NDA Number:** 22-212

3. Name and Address of Applicant:
Alcon Pharmaceuticals, Ltds.
6201 South Freeway
Fort Worth, TX 76134-2099

4. Supplement(s):
Number: S-015
Letter Date(s): December 16, 2015
Stamp Date: December 16, 2015
Due Date: April 16, 2016

5.Name of Drug:
DUREZOL®

6. Nonproprietary name:
Difluprednate ophthalmic emulsion, 0.05%

7. Supplement Provides for: removal of endotoxin test from Regulatory Acceptance Specification

8. Amendment(s):
None

9. Pharmacological Category:
Anti-Inflammatory

10. How Dispensed:
Rx

12. Dosage Form:
Emulsion

13. Potency(ies): 0.05%

11. Related Documents: This supplement is bundled with:

Alcon Pharmaceuticals, Ltd. applications

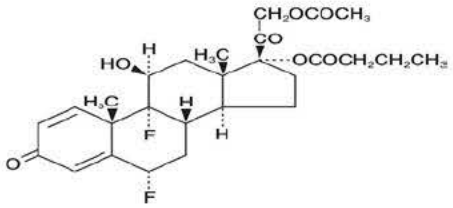
**MOXEZA®	NDA 22-428/S-007
TOBRADEX® ST	NDA50-818/S-005

Alcon Research, Ltd. Applications

*ILEVRO®	NDA 203-491/S-010
*ISOPTO® Carpine	NDA 200-890/S-008
*IZBA	NDA 204-890/S-001
*PAZEO	NDA 206-276/S-002
*SIMBRINZA®	NDA 204-251/S-008

* Filed as eCTD submission
** Filed as paper submission

14. Chemical Name and Structure: difluprednate; 6α,9-difluoro-11ß, 17, 21-trihydroxypregna-1,4-diene-3,20-dione 21-acetate 17-butyrate; *CAS-23674-86-4*: Molecular formula: $C_{13}H_{34}F_2O_7$; Formula weight:508.56.



15. Comments: The supplement is for requesting approval to remove the bacterial endotoxin test from the regulatory acceptance Specification of the products listed in this bundle. The applicant provided updated release and shelf-life specification sheets, in which endotoxin testing is removed. It is noted that the DUREZOL® product contains an (b) (4) preservative, sorbic acid. (b) (4)

This request was evaluated by the microbiology review team, OPS/NDMS/HFD-805, on April 15, 2016 and was recommended for approval by Dr. Bryan Riley, the microbiology reviewer, on the same date.

16. Conclusions and Recommendations: Based on the recommendation by the microbiology review, from the viewpoint of CMC this supplement is recommended for approval.

17. Name: **Libaniel Rodriguez, Ph.D., OPS/OLDP/DPMA1/BII**	**Signature:**	**Date:**
18. Concurrence: David Lewis, Ph.D., CMC lead/OPS/OLDP/DPMA1/BII signing for Hasmukh Patel, Ph.D., DD/OPS/OLDP/DMA1.	**Signature:**	**Date:**

Libaniel Rodriguez -S

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David B. Lewis -S

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22212Orig1s015

MICROBIOLOGY REVIEWS

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

DATE: 5 April 2016

TO: NDA 22212/S015 (lead for bundled supplement)

FROM: Bryan S. Riley, Ph.D.,
Branch Chief (acting)
OPQ/OPF/Division of Microbiology Assessment

THROUGH: Neal J. Sweeney, Ph.D.
Quality Assessment Lead (acting)
OPQ/OPF/Division of Microbiology Assessment

CC: Laya Keyvan
Regulatory Business Process Manager
OPQ/OPRO

SUBJECT: Product Quality Microbiology review of bundled supplements providing for the removal of the endotoxin specification from topical ophthalmic drug products.

Product Quality Microbiology Recommendation – This submission is recommended for approval from a product quality microbiology standpoint.

This supplement was submitted by Alcon Laboratories, Inc. to provide for the removal of the endotoxin specification of the following topical ophthalmic drug products.

M E M O R A N D U M

PRODUCT	NDA NUMBER	APPROVAL DATE
DUREZOL	022212	June 2008
ISOPTO CARPINE	200890	June 2010
IZBA	204822	May 2014
MOXEZA	022428	November 2010
ILEVRO	203491	October 2012
PAZEO	206276	January 2015
SIMBRINZA	204251	April 2013
TOBRADEX ST	050818	February 2009

To support the proposed removal of the endotoxin specification, the applicant cited USP Stimuli General Chapter Ophthalmic Ointments <771> (published 1 November 2015). The Chapter states that "…typically, endotoxin testing is not required for topically applied ophthalmic products…".

ADEQUATE

Reviewer Comment – The current CDER review practice is to not require endotoxin testing for topical ophthalmic drug products. Therefore, the proposed removal of the endotoxin specification for these products is acceptable.

END

Bryan S. Riley -S

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Neal J. Sweeney -S

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