CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-818

CHEMISTRY REVIEW(S)

NDA 50-818
Tobradex ST
(tobramycin and dexamethasone ophthalmic suspension)0.3%/0.05%
Review #2

Shrikant N. Pagay
CMC Review
ONDQA
Office of Pharmaceutical Sciences

NOTE
Review 2 covers the pending issues which include commitment to lower the endotoxin limit, OPS Microbiology review & recommendations, labeling and recommendations from the Office of Compliance for the manufacturing facilities. This review also covers changes made in processing xanthan gum to achieve reduction in endotoxin level and maintaining high viscosity of the solution. No changes were made in the Executive Summary from Review 1 except in Section IIC- Basis of Approvability.

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend to approve NDA 50-818 from CMC perspective. Previous endotoxin issues were adequately addressed as described in the quality microbiology review.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable:

There were no Phase IV commitment from CMC perspective.

II. Summary of Chemistry Assessment

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance
Dexamethasone: It is a class of corticosteroid drugs primarily used for its anti-inflammatory and anti-allergic activities. Clinically, it has been demonstrated that anti-inflammatory activity of corticosteroids correlates well with mineral corticoid activity, i.e., sodium retention activity, e.g., dexamethasone and betamethasone compared to other corticosteroids have highest anti-inflammatory activities and neither compound cause sodium retention in body fluids. Dexamethasone has been approved for oral, injectable and topical drug products. Dexamethasone and combination with tobramycin were previously approved in ophthalmic drug products (Tobradex). Dexamethasone solubility in water at 25°C is approximately 8-10 mg /100 mL (slightly soluble per USP). The concentration in the proposed drug product is 0.05%, i.e., 0.5 mg/mL as a suspension. Although, dexamethasone is available in several morphic forms, only one form exists in the drug product. The drug substance is ⌜ ⌟ before combining with other excipients during manufacturing the drug product. b(4)

Tobramycin: Tobramycin is an aminoglycoside antibiotic, exhibits bactericidal activity against a broad spectrum of bacteria. It inhibits bacterial protein synthesis. The drug substance is prepared by ⌜ ⌟ b(4)
Tobramycin is freely soluble in water (1 in 1.5 parts) and the pH of the aqueous solution is 9-11. Tobramycin in aqueous solution is stable at a controlled pH and temperature. Several

drug products of tobramycin solution have been approved as injectable and inhalation solution.

Drug Product

The drug product contains 0.3% tobramycin as a solution and 0.05% dexamethasone in aqueous suspension. Other components present in the formulation are benzalkonium chloride as preservative, editate disodium dihydrate as ——— xanthan gum as viscosity agent, propylene glycol, sodium sulfate and sodium chloride for : ——— and sodium hydroxide and hydrochloric acid for pH adjustment. Dexamethasone is ——— The applicant's similar product approved previously contains tobramycin 0.3% and 0.1% dexamethasone. However, the approved drug product contains hydroxyethylcellulose instead of xanthan gum. Also, the approved product does not contain propylene glycol but contains ——— of sodium sulfate than in the proposed formulation for ——— The manufacturing process for the proposed product use ——— techniques for product sterilization. ⌜ b(4)

⌟ The suspension was filled in 4 mL 8 mL and 10 mL bottles using ——— techniquegujjokos. The fill volume for ⌜ ⌟ ——— the trade presentation 2.5 mL, 5 mL and 10 mL. All packaging components were ——— The bottles and plugs were ⌜ ⌟ and closures ⌜ ⌟ The product is unstable when exposed to direct light; however, it is stable when placed in a cartoon.

B. Description of How the Drug Product is Intended to be Used

The drug product is indicated for the treatment of inflammation, swelling in the eye and infections associated with such conditions. The recommended dosing is instillation in the eye sac of one drop every 4-6 hours. The frequency and duration to use the product will depend upon improvement in clinical signs.

C. Basis for Approvability or Not-Approval Recommendation

Facilities are judged by Office of Compliance to be acceptable
Drug product is stable
Adequate in-process and finished drug product controls
Satisfactory resolution of all FDA comments
Review 2 information
Reduction in endotoxin limit
OPS Microbiology review & recommendations
Labeling
Status of manufacturing facilities since last approved on 2/11/08

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Shrikant N. Pagay
Chemistry Branch Chief Name /Date: Norman Schmuff
Project Manager Name/Date:

C. CC Block

10 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 1

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/s/

Shrikant Pagay
2/3/2009 03:46:26 PM
CHEMIST

Norman Schmuff
2/4/2009 03:16:02 PM
CHEMIST

NDA 50-818
Tobradex ST [Proposed]
(tobramycin and dexamethasone ophthalmic suspension)

Shrikant N. Pagay
CMC Review
ONDQA
Office of Pharmaceutical Sciences

Table of Contents

Chemistry Review Data Sheet

1. NDA 50-818

2. REVIEW #: 1

3. REVIEW DATE: 7th January 2008

4. REVIEWER: Shrikant N. Pagay

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	6/14/2007
Amendment	10/30/2007
Amendment	2/15/2008
Amendment	3/3/2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Alcon Inc.
Address:	P.O.Box 62 Bosch 69, CH-6331 Hunenberg, Switzerland
Representative:	Authorized Agent Listed blow:
Telephone:	
Name:	Alcon Research Ltd.

Chemistry Review Data Sheet

Address: 6201 South Freeway, Mail Code R7-18
Fore Worth, Texas 76134-2099

Representative: Brad Wooldridge
Associate Director, Regulatory Affairs

Telephone: 817-551-4052

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: TobraDex ST
Non-Proprietary Name (USAN): Tobramycin/Dexamethasone
a) Code Name/# (ONDC only): NA
b) Chem. Type/Submission Priority (ONDC only): NA

- Chem. Type: 3
- Submission Priority: S
-

9. LEGAL BASIS FOR SUBMISSION: 505(b) (2)

10. PHARMACOL. CATEGORY: Anti-infective/Anti-inflammatory Ophthalmic Suspension

11. DOSAGE FORM: Ophthalmic Suspension

12. STRENGTH/POTENCY: 0.3%/ Tobramycin/ 0.05% Dexamethasone

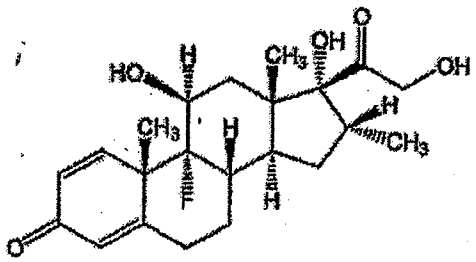
13. ROUTE OF ADMINISTRATION: Eye

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

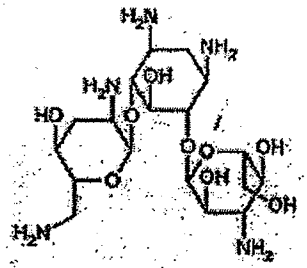
___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Dexamethasone

Molecular Formula: C22H29FO5
Relative Molecular Mass: 392.47



Tobramycin

Molecular Formula: $C_{18}H_{37}N_5O_9$

Relative Molecular Mass: 467.52

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
——	2			4, 1, For Vol. 9.1 Code -6	Adequate	11/21/05 A. Fenselau	For NDA 50-555/S25 and 50-616/S25
——	2			4, 1	Adequate	10/19/07	Reviewed C.Woodland
——	4			4	-	-	Approved for

b(4)

						NDA 50-592 Micro-concult
—	3		4,7	NA	2/24/03 for 2044	Manufacturing of plastic container
—	3		4,7	NA	--	Manufacturing of plastic container
—	3		4,7	Adequate	1/14/2005	Y.Lu
—	3		4,7	NA		

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: NA

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND		
TobraDex	NDA 50-592	Dexamethasone 0.1% and Tobramycin 0.3%

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	2/11/2008	CDER -Compliance
Pharm/Tox (container/closure)	Satisfactory	3/3/08	Amy Nostrandt
Biopharm	NA		
LNC	Acceptable		S.Pagay
Methods Validation	NA		
DMETS	Pending		
EA	Acceptable		
Microbiology	Pending		

19. COMMENTS:

Please note that all italicized portion of Chemistry Assessment Section are reviewer's notes. The remaining information (data, figures and some responses to deficiencies) are directly incorporated from the submission. Information provided in the Chemistry Review Data Sheet and the Executive Summary Sections are reviewer's comments.

The Chemistry Review for NDA 50-818

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend to approve NDA 50-818 from CMC perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable:

No Phase IV commitment from CMC perspective.

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Adequate in-process and finished drug product controls
Satisfactory resolution of all FDA comments
PENDING: proprietary name; OPS Microbiology review & recommendations

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Shrikant N. Pagay
Chemistry Branch Chief Name /Date: Norman Schmuff
Project Manager Name/Date:

C. CC Block

42 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry-2

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/s/

Shrikant Pagay
3/21/2008 01:43:45 PM
CHEMIST

Norman Schmuff
3/27/2008 06:46:22 AM
CHEMIST