CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-994

CHEMISTRY REVIEW(S)
Date: September 20, 2006

From: Linda Ng, Ph.D.
Pharmaceutical Assessment Lead for Ophthalmology

Through: Norman Schmuff, Ph.D.
Branch Chief, ONDQA Division II

Subject: NDA 21-994, Travatan Z (travoprost ophthalmic solution) 0.004%, Alcon Research Ltd.

To: The File

NDA 21-994, Travatan Z (travoprost ophthalmic solution) 0.004% is reviewed by Dr. Suresh Pagay, chemistry reviewer. He is on travel this week after completing chemistry review #2. Amendments were received after the DFS sign-off of his review. The PDUFA date is September 21, 2006.

This memo will complement Dr. Pagay’s review #2 to cover amendment N-000BL dated September 15 for updated labeling and N-000BC dated September 19, 2006 for response to the outstanding CMC issues.

NDA 21-994 N000BL met all the CMC comments on labeling mentioned in Dr. Pagay’s review. Acceptable.

NDA 21,994 N000BC provides confirmation of agreements made via a teleconference call of September 16, 2006 between Alcon and the Agency. They agreed to _______ expiry dating period for the physician sample and trade products with testing at _______. Products will have _______ expiry if test passes and _______ if test fails. They will develop test and acceptance criteria for _______ in the excipient polyoxyl 40 hydrogenated castor oil (HCO-40) specification and in the drug product specification. For the latter, they will discuss with the Agency and commit to submit a supplement. Acceptable.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Linda Ng
9/20/2006 03:00:28 PM
CHEMIST

Stephen Paul Miller
9/20/2006 03:12:25 PM
CHEMIST
Acting ONDQA Branch Chief

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On Original
NDA 21-994

TRAVATAN Z
Travoprost ophthalmic solution, 0.004%
Alcon Research Ltd.

Shrikant N. Pagay
Anti-Infective and Ophthalmic Drug Products
CMC REVIEW # 2

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On Original
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NDA 21-994 Travatan
Travoprost Ophthalmic Solution, 0.004%
Review #2
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

B. Environmental Assessment Or Claim Of Categorical Exclusion

III. List Of Deficiencies To Be Communicated

IV. Appendix (Specifications for Drug Substance, Drug Product, Retest Date and Shelf life)

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NDA 21-994 Travatan
Travoprost Ophthalmic Solution, 0.004%
Review #2
Chemistry Review Data Sheet

1. NDA 21-994

2. REVIEW #: 2

3. REVIEW DATE: Review 1:2/27/06 (Review 2: Date 8/28/06)

4. REVIEWER: Shrikant N. Pagay

5. PREVIOUS DOCUMENTS:

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NDA 21-994 Travatan
Travoprost Ophthalmic Solution, 0.004%
Review #2
7. NAME & ADDRESS OF APPLICANT:

Name: Alcon, Inc.
Alcon Research, Ltd.
Mail Code R7-18
Address: 6201 South Freeway
Fort Worth, TX 76134-2099
Representative: Angela Kothe

Telephone 817-551-4933

8. DRUG PRODUCT NAME/CODE/TYPE:

a). Proprietary Name: TRAVATAN® Z (travoprost ophthalmic solution, 0.004%) (Proposed)
b). Non-Proprietary Name (USAN): Travoprost (USAN, BAN, JAN)
c). Code Name/# (ONDC only):
   Company or Laboratory Code
   AL-6221 (Alcon)
   AL06221 (Alcon)
   CH-4074 (Dow)
   • Other Nonproprietary Name(s): NA
   • Chemical Abstracts Service (CAS) Registry Number
   157283-68-6

   Type/Submission Priority (ONDC only):
   • Chem. Type: 5
   • Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: Ophthalmic / Reduction of pressure in
glaucoma or ocular pressure.

11. DOSAGE FORM: Sterile Solution

NDA 21-994 Travatan
Travoprost Ophthalmic Solution, 0.004%
Review #2
12. STRENGTH/POTENCY: 0.004%

13. ROUTE OF ADMINISTRATION: Ophthalmic

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:

   [1R-[1α(Z),2β(1E,3R*)],3α,5α]-7-[3,5-Dihydroxy-2-[3-hydroxy-4-[3-
   (trifluoromethyl)phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid, 1-methylethylester

   (Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[(1E,3R)-3-hydroxy-4-[(α,α,α-trifluoro-m-isopropyltolyl)oxy]-1-butenyl]cyclopentyl]-5-heptenoate

   Molecular Formula: C_{26}H_{31}F_{3}O_{6}
   • Relative Molecular Mass: 500.55

   ![Chemical Structure](image)

NDA 21-994 Travatan
Travoprost Ophthalmic Solution, 0.004%
Review #2
17. RELATED/SUPPORTING DOCUMENTS:

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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:

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| NDA      | 21-257             | Different formulation of the same drug with preservative.

NDA 21-994 Travatan
Travoprost Ophthalmic Solution, 0.004%
Review #2
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19. COMMENTS: Review 2 covers review 1 plus Amendment 9/1/06: The samples from the lots placed on stability studies and stored for 50% RH showed particulates identified as the with Travatan Z samples (drug product) stored up to are free of particulates have low aqueous solubility. Since pH of the drug product was decreased from to 5.7. Review 2 covers the stability update and proposed changes in the acceptance criteria for pH of the drug product and label update. Also, setting shelf life, further revisions to package insert, label and setting impurity limits for

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NDA 21-994 Travatan
Travoprost Ophthalmic Solution, 0.004%
Review #2
The Chemistry Review for NDA 21-994

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend to approve this NDA from CMC perspective.

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

II. Summary of Chemistry Assessments

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

Drug Substance

Travoprost is in a class of compounds known as prostaglandin. Prostaglandins are naturally occurring and by synthesis from unsaturated 20-carbon fatty acids, primarily arachidonic acids. They are mediators of a diverse group of physiologic processes. Specifically, travoprost is a synthetic prostaglandin F₂α analogue. Travoprost, an isopropyl ester pro-drug, is hydrolyzed by esterases in the cornea to its biologically active free acid. The drug substance was approved earlier under NDA 21-257, Travatan, and benzalkonium/dsodium edetate containing preservative formulation. The same drug substance is used in this NDA but free of benzalkonium/dsodium edetate.

The drug substance is colorless yellow oil that is clear to slightly opalescent. It is practically insoluble in water and soluble in non-polar solvents, e.g., octanol, methanol. Travoprost is optically active and structurally well characterized. Although, synthesis is complex...
Drug Product

Travoprost Ophthalmic solution, 0.004% (Travatan BAC-free) is a sterile, preserved aqueous solution formulated for topical application. The inactive components include polyoxyl 40 hydrogenated castor oil (HCO-40), propylene glycol, boric acid, sorbitol, zinc chloride, sodium hydroxide, hydrochloric acid, and purified water. A level of HCO-40 was used in the formulation. HCO-40 concentration is the concentration of the drug substance. Although HCO-40 is a USP Monograph, As a result, Alcon tests the raw material HCO-40 with the more restrictive specifications from JP, USP and Eur Phar. The drug concentration is same as that approved for benzalkonium chloride containing drug product Travatan under NDA 21-257. The product is packaged in a natural polypropylene bottle with a polypropylene (PP) natural plug and a turquoise (PP) closure. The pH of the solution is approximately , the solution is sterile and isotonic. The major manufacturing steps are:

Sufficient information was provided to assess safety and set controls for leachables from the container closure and the label. The tests include assay and impurities for travoprost, assay for boric acid and zinc, and physical measurements, e.g., particulates, color, etc. The microbiological attributes include preservative effectiveness, sterility and container/closure integrity.

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

Travoprost free acid is a selective FP prostanoid receptor agonist which is believed to reduce intraocular pressure. Travoprost is used for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The ophthalmic solution is applied through a dropper.

C. Basis for Approvability or Not-Approval Recommendation

Travoprost was previously approved under NDA 21-257 in benzalkonium/disodium edetate containing formulation. Benzalkonium/disodium edetate can produce deleterious effect upon prolonged use. Therefore, the proposed formulation is developed free of benzalkonium/disodium edetate and having the same concentration of the drug substance and HCO-40 as in the approved formulation. The proposed formulation contains

Thus the proposed formulation is an improvement from safety consideration for long term use. The proposed manufacturing facilities have satisfactorily passed inspection by the Office of Compliance. Nine months stability data were provided to support shelf life. Alcon had updated the

NDA 21-994 Travatan
Travoprost Ophthalmic Solution, 0.004%
Review #2
stability data to  on 9/1/06. At the  time point, the samples stored at RH showed particulates identified as the lots manufactured and filled in both 2.5 mL and 5 mL bottles had particulate matter. Travatan Z samples stored up to RH are free of particulates. The samples stored at were free of particulates at and up to storage. have low aqueous solubility. Therefore, the proposed strategy is to decrease the pH of the solution below pH in order to eliminate particulates formed from The specification for pH of the drug product solution is tightened from in the planned commercial batches.

FDA made the risk assessment and set the shelf life as follows: Based on only lots had particulates while the lots were free of particulates after storage for months at RH and that the drug product is planned to be stored at at the distribution centers, a total of 14 month shelf life was approved

The approved shelf life is 14 months.

III. Administrative

A. Reviewer’s Signature

B. Endorsement Block

Chemist Name/Date: Shrikant N. Pagay
Chemistry Team Leader Name/Date: Norman Schmuff
Project Manager Name/Date: Michael Puglisi

C. CC Block

NDA 21-994 Travatan Travoprost Ophthalmic Solution, 0.004%
Review #2
62 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process
Shrikant Pagay
9/16/2006 04:33:24 PM
CHEMIST

Linda Ng
9/18/2006 08:30:49 AM
CHEMIST
Signing for Norman

Appears This Way
On Original
Food & Drug Administration

Memorandum

Date: September 12, 2006

From: Linda Ng, Ph.D.
Pharmaceutical Assessment Lead for Ophthalmology

Through: Elaine Morefield, Ph.D.
Director, ONDQA Division II

Subject: NDA 21-994, Travatan Z (travoprost ophthalmic solution) 0.004%, Alcon Research Ltd.

To: The File

Background

NDA 21-994, Travatan Z (travoprost ophthalmic solution) 0.004% is being reviewed by Dr. Suresh Pagay, chemistry reviewer. He is on travel and I, as the acting Branch Chief, am addressing issues to complement Dr. Pagay’s review #2. The PDUFA date is September 21, 2006.

Alcon Research Ltd submitted an amendment dated September 1, 2006 to support the proposed expiration dating period of the product stored at $RH. The data at $RH failed the particulate matter criteria in out of batches; and the data at $RH failed in out of the batches tested and failed the visible particles in of the . Data at the refrigerated condition at $RH met all criteria of the drug product specification for the batches.

Content

According to Alcon, the particulate is the insoluble . The formation is due to interaction between
Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Chemistry-2
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Linda Ng
9/12/2006 11:02:55 AM
CHEMIST
OND PM to convey comments to applicant

Blaine Morefield
9/13/2006 12:57:06 PM
CHEMIST

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On Original
NDA 21-994

TRAVATAN Z
Travoprost ophthalmic solution, 0.04%
Alcon Inc.

Shrikant N. Pagay
Anti-Infective and Ophthalmic Drug Products
CMC REVIEW # 1

Appears This Way
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NDA 21-994 Travatan
Travoprost Ophthalmic Solution, 0.004%
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NDA 21-994 Travatan
Travoprost Ophthalmic Solution, 0.004%
A. Labeling & Package Insert

B. Environmental Assessment Or Claim Of Categorical Exclusion

III. List Of Deficiencies To Be Communicated

Appear as this Way
On Original

NDA 21-994 Travatan
Travoprost Ophthalmic Solution, 0.004%
Chemistry Review Data Sheet

1. NDA 21-994

2. REVIEW #: 1

3. REVIEW DATE: 2/27/06

4. REVIEWER: Shrikant N. Pagay

5. PREVIOUS DOCUMENTS:

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NDA 21-994 Travatan
Travoprost Ophthalmic Solution, 0.004%
7. NAME & ADDRESS OF APPLICANT:

Name: Alcon, Inc.
Alcon Research, Ltd.
Mail Code R7-18
Address: 6201 South Freeway
Fort Worth, TX 76134-2099
Representative: Angela Kothe

Telephone 817-551-4933

8. DRUG PRODUCT NAME/CODE/TYPE:

a). Proprietary Name: TRAVATAN® Z (travoprost ophthalmic solution, 0.004%) (Proposed)
b). Non-Proprietary Name (USAN): Travoprost (USAN, BAN, JAN)
c). Code Name/# (ONDC only):
Company or Laboratory Code
AL-6221 (Alcon)
AL06221 (Alcon)
CH-4074 (Dow)
• Other Nonproprietary Name(s): NA
• Chemical Abstracts Service (CAS) Registry Number
157283-68-6

Type/Submission Priority (ONDC only):
• Chem. Type: 5
• Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: Ophthalmic / Reduction of pressure in glaucoma or ocular pressure.

11. DOSAGE FORM: Sterile Solution

NDA 21-994 Travatan
Travoprost Ophthalmic Solution, 0.004%
12. STRENGTH/POTENCY: 0.004%

13. ROUTE OF ADMINISTRATION: Ophthamlic

14. Rx/OTC DISPENSED: _X_Rx    _OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
   _____SPOTS product – Form Completed
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16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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   oxy]-1-butenyl]cyclopentyl]-5-heptenoate

   Molecular Formula: C_{28}H_{35}F_{5}O_{6}
   • Relative Molecular Mass: 500.55

   ![Chemical Structure](image-url)
17. RELATED/SUPPORTING DOCUMENTS:

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\(^1\) Action codes for DMF Table:
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\(^2\) Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

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18. STATUS:

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Travoprost Ophthalmic Solution, 0.004%
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<th>CONSULTS/CMC RELATED REVIEWS</th>
<th>RECOMMENDATION</th>
<th>DATE</th>
<th>REVIEWER</th>
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19. COMMENTS: No Comments
The Chemistry Review for NDA 21-994

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend to approve this NDA from CMC perspective pending satisfactory review of microbiology section by the OPS microbiologist, the trade name by the Division of Medication Errors and Technical Support and the establishment of the shelf life based on the observations in the samples stored for under long term storage condition.

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

II. Summary of Chemistry Assessments

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

Drug Substance

Travoprost is in a class of compounds known as prostaglandin. Prostaglandins are naturally occurring and by synthesis from unsaturated 20-carbon fatty acids, primarily arachidonic acids. They are mediators of a diverse group of physiologic processes. Specifically, travoprost is a synthetic prostaglandin F2α analogue. Travoprost, an isopropyl ester pro-drug, is hydrolyzed by esterases in the cornea to its biologically active free acid. The drug substance was approved earlier under NDA 21-257, Travatan, and benzalkonium/disodium edetate containing preservative formulation. The same drug substance is used in this NDA but free of benzalkonium/disodium edetate.

The drug substance is colorless yellow oil that is clear to slightly opalescent. It is practically insoluble in water and soluble in non-polar solvents, e.g., octanol, methanol. Travoprost is optically active and structurally well characterized. Although, synthesis is complex, the
Drug product

Travoprost Ophthalmic solution, 0.004% (Travatan BAC-free) is a sterile, preserved aqueous solution formulated for topical application. The inactive components include polyoxyl 40 hydrogenated castor oil (HCO-40), propylene glycol, boric acid, sorbitol, zinc chloride, sodium hydroxide, hydrochloric acid, and purified water. A concentration of HCO-40 was used in the formulation. HCO-40 concentration is the concentration of the drug substance. Although HCO-40 is a USP Monograph, as a result, Alcon tests the raw material HCO-40 with the more restrictive specifications from JP, USP and Eur Phar. The drug concentration is same as that approved for benzalkonium chloride containing drug product Travatan under NDA 21-257. The product is packaged in a natural polypropylene bottle with a polypropylene (PP) natural plug and a turquoise (PP) closure. The pH of the solution is approximately: the solution is sterile and the major manufacturing steps are... Sufficient information was provided to assess safety and set controls for leachables from the container closure and the label. The tests include assay and impurities for travoprost, assay for boric acid and zinc, and physical measurements, e.g., particulates, color, etc. The microbiological attributes include preservative effectiveness, sterility and container/closure integrity.

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

Travoprost free acid is a selective FP prostanoid receptor agonist which is believed to reduce intraocular pressure. Travoprost is used for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The ophthalmic solution is applied through a dropper.

C. Basis for Approvability or Not-Approval Recommendation

Travoprost was previously approved under NDA 21-257 in benzalkonium/disodium edilate containing formulation. Benzalkonium/disodium edilate can produce deleterious effect upon prolonged use. Therefore, the proposed formulation is developed free of benzalkonium/disodium edilate and having the same concentration of the drug substance and HCO-40 as in the approved formulation. The proposed formulation contains... The data is satisfactory for shelf life. The proposed manufacturing facilities have satisfactorily passed inspection by the Office of Compliance. Thus the proposed formulation is an improvement from safety consideration for long term use and satisfactory from the quality consideration.

NDA 21-994 Travatan
Travoprost Ophthalmic Solution, 0.004%
III. Administrative

A. Reviewer’s Signature

B. Endorsement Block

Chemist Name/Date: Shrikant N. Pagay
Chemistry Team Leader Name/Date: Norman Schmuff
Project Manager Name/Date: Michael Puglisi

C. CC Block

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NDA 21-994 Travatan
Travoprost Ophthalmic Solution, 0.004%
52 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

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

/s/
Shrikant Pagay
8/25/2006 08:59:24 AM
CHEMIST

Norman Schmuff
8/29/2006 10:40:05 AM
CHEMIST

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