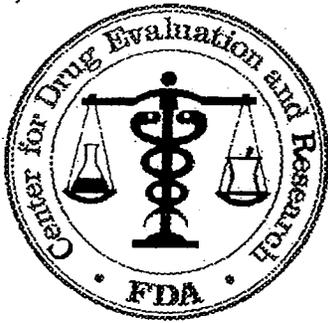


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-994

CHEMISTRY REVIEW(S)



Food & Drug Administration

Memorandum

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.

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/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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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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NDA 21-994 Travatan
Travoprost Ophthalmic Solution, 0.004%
Review #2



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C. CC Block.....	
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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.....65

IV. Appendix (Specifications for Drug Substance, Drug Product, Retest Date and Shelf life 72

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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:

Previous Documents

Document Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

11/18/05

Amendment

12/14/05

Amendment

7/25/06

Amendment

9/1/06

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Chemistry Review Data Sheet

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

Chemistry Review Data Sheet

12. STRENGTH/POTENCY: 0.004%

13. ROUTE OF ADMINISTRATION: Ophthalmic

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

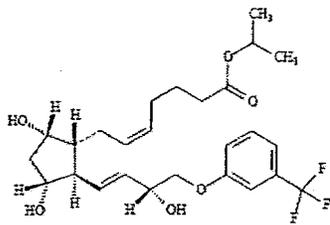
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

[1R-[1 α (Z),2 β (1E,3R*),3 α ,5 α]]-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: C₂₆H₃₅F₃O₆

• Relative Molecular Mass: 500.55



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



CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
						9/4/06	
						9/4/06	
						9/4/06	

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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-257	Different formulation of the same drug with preservative.

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



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	12/20/05	
Pharm/Tox	NA		
Biopharm	NA		
LNC	Establish name negotiated	7/25/06	Same name as for NDA 21-257 BAC formulation/ S.Pagay
Methods Validation			
OPDRA	Trade name negotiated	9/15/06	DMET/Clinical
EA	Categorical Exemption accepted	12/15/05	L.Ng
Microbiology	Satisfactory	9/8/06	R. Mello

19. COMMENTS: Review 2 covers review 1 plus **Amendment 9/1/06** : The samples from the _____ out of the _____ lots placed on stability studies and stored for _____ at _____% 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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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 F_{2α} 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

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~~ 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



Executive Summary Section

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 _____ a+ _____ 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

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/s/

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

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

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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 _____. 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 _____

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/s/

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

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

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NDA 21-994

TRAVATAN Z

Travoprost ophthalmic solution, 0.04%

Alcon Inc.

Shrikant N. Pagay

Anti-Infective and Ophthalmic Drug Products

CMC REVIEW # 1

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NDA 21-994 Travatan

Travoprost Ophthalmic Solution, 0.004%

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P DRUG PRODUCT [Name, Dosage form].....	15
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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.....59

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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:

Previous Documents

Document Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

11/18/05

Amendment

12/14/05

Amendment

7/25/06

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NDA 21-994 Travatan
Travoprost Ophthalmic Solution, 0.004%



Chemistry Review Data Sheet

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%**



CHEMISTRY REVIEW



Chemistry Review Data Sheet

12. STRENGTH/POTENCY: 0.004%

13. ROUTE OF ADMINISTRATION: Ophthalmic

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

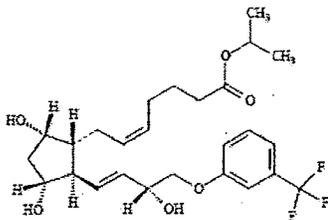
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

[1R-[1 α (Z),2 β (1E,3R*),3 α ,5 α]]-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: C₂₆H₃₅F₃O₆

• Relative Molecular Mass: 500.55



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NDA 21-994 Travatan
Travoprost Ophthalmic Solution, 0.004%

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS

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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-257	Formulation of the same drug with preservative.

18. STATUS:

**NDA 21-994 Travatan
Travoprost Ophthalmic Solution, 0.004%**



CHEMISTRY REVIEW



Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	12/20/05	
Pharm/Tox	NA		
Biopharm	NA		
LNC	Establish name negotiated		
Methods Validation			
OPDRA	Trade name negotiated	Pending	
EA	Categorical Exemption accepted	12/15/05	L.Ng
Microbiology	Pending		

19. COMMENTS: No Comments

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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 F₂ α 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 editate containing preservative formulation. The same drug substance is used in this NDA but free of benzalkonium/disodium editate.

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 complete _____, the

Executive Summary Section

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 _____ 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 editate containing formulation. Benzalkonium/disodium editate can produce deleterious effect upon prolonged use. Therefore, the proposed formulation is developed free of benzalkonium/disodium editate 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
ChemistryTeamLeader Name/Date: Norman Schmuff
Project Manager Name/Date: Michael Puglisi

C. CC Block

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/s/

Shrikant Pagay
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Norman Schmuff
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CHEMIST

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