

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-994

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 21-994

SUPPL #

HFD # 520

Trade Name Travatan Z

Generic Name Travoprost Ophthalmic Solution, 0.004%

Applicant Name Alcon, Inc.

Approval Date, If Known September 21, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

Study was designed to demonstrate bioequivalence to Travatan using a clinical endpoint, intraocular pressure (IOP).

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-257

Travatan (travoprost ophthalmic solution), 0.004%

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section:

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #1 !
! YES ! NO
! Explain: ! Explain:

Investigation #2 !
! YES ! NO
! Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Michael Puglisi
Title: Regulatory Project Manager
Date: September 12, 2006

Name of Office/Division Director signing form: Wiley A. Chambers, M.D.
Title: Deputy Director, Division of Anti-Infective and Ophthalmology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Wiley Chambers

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PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA #: 21-994

Stamp Date: November 21, 2005 Action Date: September 21, 2006

HFD- 520 Trade and generic names/dosage form: Travatan Z (travoprost ophthalmic solution) 0.004%

Applicant: Alcon, Inc.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: **For the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to other intraocular pressure lowering medications.**

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns**
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Michael Puglisi
Regulatory Project Manager

cc: NDA 21-275/S-013
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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/s/

Wiley Chambers
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**Division of Anti-Infective and
Ophthalmology Products**

Center for Drug Evaluation and Research, HFD-520
10903 New Hampshire Avenue, Building 22
Silver Spring, MD 20993

To: Angela Kothe, O.D., Ph.D.

From: Mike Puglisi/ Project Manager

Fax: 817-551-4630

Fax: 301-796-9881

Phone:

Phone: 301-796-0791

Pages: 3 (including cover page)

Date: September 15, 2006

Re: CMC Comments re: NDA 21-994

Urgent **For Review** **Please Comment** **Please Reply** **Please Recycle**

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● **Comments:**

Angela,

Attached please find the CMC reviewer's comments concerning Travatan Z (NDA 21-994). Please let me know if you have any questions about these comments. Thanks.

Mike

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Reviewer's Comments:

FDA Response to Issue 1:

Storage statement for the trade samples is not supported with appropriate stability data as to how long the product is stored at _____ after it is dispensed, e.g., storage for _____ months at _____ as the long term storage condition, then removed and stored for "In Use" time at room temperature e.g., _____ as appropriate.

Labeling with 2 different storage statements in order to differentiate the trade and professional samples can be confusing for a patient.

Also, confusing for shippers and pharmacies and for patients if the products with similar trade names, i.e., approved drug TRAVATAN (NDA 21-257) and TRAVATAN Z (this NDA) have different storage statements.

Please revise the expiration date for the trade samples to _____ with storage temperature from 2 to 25°C

FDA Response to Issue 2:

FDA concurs for the commitment to validate a test method for analysis of _____ in HCO-40 (raw material) and set limits and report in the first Annual Report after discussions with the Agency.

For _____ limit in the finished drug product, it is necessary to demonstrate through commercial scale stability batches that controlling the level of _____ in the raw material indeed controls the _____ level as well as the particulate matter with the proposed pH limits. The data provided in the 9/1/06 Amendment does not provide sufficient data for _____ to make any such conclusions. This information needs to be established before deleting such a test for _____ limit in the drug product.

FDA Response to Issue 3:

FDA concurs with the travoprost standard to the system suitability testing for the unrelated impurities which will include _____

FDA Comments on Label

Description Section

Components for sofZia are included as requested by FDA. That is adequate. "Preserved in the bottle with an ionic buffered system, sofZia". _____

How Supplied Section

The storage statements for the trade samples are not supported with the appropriate stability data, i.e., long term storage and "in use" storage and therefore should match with the same storage statement as the professional samples, i.e., 2 - 25C with _____ expiration date.

Container Labels

Three labels include for 2.5 and 5 mL Trade samples and 2.5 mL Professional samples. The label statements are acceptable with _____ expiration date.

Carton Labels

The three labels include for 2.5 and 5 mL Trade samples and 2.5 mL Professional samples. Include "sofZia" with the buffer components listed in the carton label similar to the description statement in the package insert. "Preserved in the bottle with an ionic buffered system, sofZia". This is now

All three (2 trade and one professional) storage statements are 2-25°C. That is acceptable. The expiration date is _____ for both professional and trade samples with the storage statements proposed on the carton.

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Michael Puglisi
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NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-994

Trade Name: **Travatan Z**
Established Name: **travaoprost ophthalmic solution**
Strengths: **0.004%**

Applicant: **Alcon. Inc.**

Date of Application: **November 18, 2005**
Date of Receipt: **November 21, 2005**

Date of Filing Meeting: **January 9, 2006**
Filing Date: **January 19, 2006**
User Fee Goal Date: **September 21, 2006**

Indication(s) requested: **for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication**

Type of Original NDA: (b)(1) (b)(2)
OR
Type of Supplement: (b)(1) (b)(2)

NOTE:

- (1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.*
- (2) *If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:*

Therapeutic Classification: S P
Resubmission after withdrawal? **no** Resubmission after refuse to file? **no**
Chemical Classification: (1,2,3 etc.) **5**
Other (orphan, OTC, etc.) **n/a**

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient*

population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO
If yes, explain: **There is remaining exclusivity for Alcon's original formulation of Travavtan (NDA 21-257).**

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO

- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all forms and certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A YES NO

- Is it an electronic CTD (eCTD)? YES NO
If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO

- Exclusivity requested? YES, _____ Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.
NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."
- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section)? Y NO
- PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: **IND 51,000**
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES NO
If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES NO
- Risk Management Plan consulted to ODS/IO? N/A YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES NO

If Rx-to-OTC Switch application: N/A

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

**PREPARED BY: MICHAEL PUGLISI
REGULATORY PROJECT MANAGER
CDER/OND/OAP/DAIOP**

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Michael Puglisi
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CSO

Michael Puglisi
9/12/2006 01:42:47 PM
CSO

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Division of Anti-Infective and Ophthalmology Products

Center for Drug Evaluation and Research, HFD-520
10903 New Hampshire Avenue, Building 22
Silver Spring, MD 20993

To: Angela Kothe, O.D., Ph.D.

From: Mike Puglisi/ Project Manager

Fax: 817-551-4630

Fax: 301-796-9881

Phone:

Phone: 301-796-0791

Pages: 2 (including cover page)

Date: September 12, 2006

Re: CMC Comments re: NDA 21-994

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● **Comments:**

Angela,

Attached please find the CMC reviewer's comments concerning Travatan Z (NDA 21-994). Please let me know if you have any questions about these comments. Thanks.

Mike

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Reviewer's Comments:

1. The ophthalmic solution should meet the particulate matter criteria. The updated stability data at _____ RH provided for 78 weeks support a _____ shelf life. The expiry dating can be extended in future Annual Reports based upon full shelf-life data obtained from the _____ commercial batches under the stability protocol. Please revise your proposed expiry period accordingly.
2. A test and acceptance criteria for _____ should be included in the HCO-40 specification and in the drug product specification.
3. For the impurities HPLC test, it is recommended to include a standard at the quantitation limit as part of system suitability testing to ensure detectability of impurities down to that level.

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 Draft Labeling

✓ Deliberative Process

Withheld Track Number: Administrative- 1

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**Division of Anti-Infective and
Ophthalmology Products**

Center for Drug Evaluation and Research, HFD-520
10903 New Hampshire Avenue, Building 22
Silver Spring, MD 20993

To: Angela Kothe, O.D., Ph.D.

From: Mike Puglisi/ Project Manager

Fax: 817-551-4630

Fax: 301-796-9881

Phone:

Phone: 301-796-0791

Pages: 3 (including cover page)

Date: July 5, 2006

Re: CMC Information Request re: NDA 21-994

Urgent **For Review** **Please Comment** **Please Reply** **Please Recycle**

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● **Comments:**

Angela,

Attached is a list of information being requested by the CMC reviewer for Travatan Z (NDA 21-994). Please respond in an amendment to the NDA. Please let me know if you have any questions about this request. Thanks.

Mike

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Reviewer's Comments:

- (1). Please provide stability data of travoprost stock solution for manufacturing the drug product to support that it is stable for 6 months.
- (2). It is not clear if the in-process chemical testing of travoprost bulk solution is performed on each batch since the same testing is performed on the finished drug product. Please clarify. Also, indicate if the in-process testing is performed _____.
- (3). No information is provided on the _____ of the drug product. Please indicate if a failed batch will be reprocessed.
- (4). The batch analysis data for unrelated impurities for all lots is _____. Since these impurities primarily arise from the container closure and the label, the in-process acceptance criteria should be tightened from the proposed _____ to _____.
- (5). Please provide in a table format, those impurities which clearly arise from the container/closure/label, from the ophthalmic solution and from both the container and the solution.
- (6). The proposed acceptance criteria for _____ and the total travoprost degradation products each is _____ in the finished drug product. These values are inconsistent in the presence of other known degradation products. The primary stability data show that the maximum value for _____ after storage for _____ weeks at _____ RH i _____, for both the 2.5 and 5.0 mL batches; also, after _____ weeks storage under long term storage condition _____ RH), the maximum degradation for _____ occurred is _____. Based on the data, specifications for _____ should be tightened.
- (7). The proposed acceptance criteria for AL-5848, _____ and _____ are not supported by the available stability data. Please tighten these impurities.
- (8). HPLC chromatogram for the travoprost assay and impurities in the finished drug product shows incomplete separation between the drug substance and _____. _____ is also controlled as a major related impurity in the drug substance. Please explain if complete separation can be achieved.
- (9). Although, the HPLC methods for travoprost and impurities _____ boric acid and zinc are the proposed NDA methods, if applicable, please provide the equivalent terminology of chromatographic column packings, phases and supports listed in the USP/NF <621>.
- (10). It is not clear if the extractable/leachable studies were conducted in the finished packaging container, i.e., container, label, ink and secondary packaging for light protection or in the primary container in contact with the solution without the secondary packaging. Please explain.

July 5, 2006

(11). It is stated that sterility testing of the first ~~3~~ commercial batches will be performed initially _____, and at or beyond shelf life. Sterility test for the first ~~3~~ commercial batches should be conducted annually to support the shelf life.

(12). Since a major impurity _____ is formed when exposed to light, consider a statement in the label to _____

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Michael Puglisi
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MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: May 11, 2006

TO: Michael Puglisi, Regulatory Project Manager
Martin Nevitt, M.D., Clinical Reviewer
Division of Anti-infective and Ophthalmology Products, HFD-520

THROUGH: Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

FROM: Dianne Tesch, Consumer Safety Officer

SUBJECT: Evaluation of Clinical Inspections

NDA: #21-994

NME: No

APPLICANT: Alcon

DRUG: Travatan® BAC-free

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment or prophylaxis of open angle glaucoma or ocular hypertension

CONSULTATION REQUEST DATE: January 4, 2006

DIVISION ACTION GOAL DATE: June 21, 2006

PDUFA DATE: September 21, 2006

I. BACKGROUND:

Glaucoma refers to a group of eye diseases characterized by an increase in the intraocular pressure (IOP) which causes pathological changes in the optic disc and defects in the field of vision. It affects one person in 200 over the age of 40. It is the leading cause of irreversible blindness in the United States. Glaucoma causes a progressive loss of retinal nerve fibers, resulting in vision loss. The various types of glaucoma are distinguished by the causative physiological defect.

In the normal eye, active secretion accounts for approximately 80% of the aqueous production. It is secreted by the non-pigmented ciliary epithelium. The remaining 20% of the aqueous production is passive via processes such as ultrafiltration and diffusion. These processes are dependent on the level of blood pressure in the ciliary capillaries, the plasma oncotic pressure and the level of intraocular pressure.

Aqueous outflow is primarily through the trabecular meshwork, a series of channels in the uveal and corneoscleral layers of the epithelium.

Normal intra-ocular pressure varies between 10 and 21 mm Hg. The rate of aqueous secretion, resistance in the outflow channels, and the level of episcleral venous pressure determine intra-ocular pressure. Intra-ocular pressure follows a diurnal pattern. It is higher in the morning than in the evening. Individuals with glaucoma have a greater diurnal variation than normal individuals. Blood pressure, pulse and respiration also affect IOP.

Primary open angle glaucoma (POAG) is a slowly progressive disease. It is usually bilateral, but progression can be asymmetric. The symptoms are insidious, and there is usually some degree of visual field loss before a diagnosis is made. In POAG, the primary abnormality is over-production of aqueous.

The diagnosis of glaucoma is made based on repeated elevations of IOP >21 mm Hg, changes in the appearance of the optic disc, and characteristic changes in the visual field. Generally, POAG is asymptomatic. Most diagnoses are made at the time of a routine ophthalmologic exam.

Treatment of glaucoma consists of both medical and surgical interventions. The treatments are designed to decrease the intra-ocular pressure by decreasing aqueous secretion, or increasing aqueous outflow. Travaprost is a selective full agonist for the FP-prostanoid receptor. FP agonists are known to lower intraocular pressure through both enhanced uveoscleral outflow and increased trabecular outflow facility. Studies comparing the corneal and tear film effects of ophthalmic solutions formulated with and without benzalconium chloride (BAC) have shown that tear film stability and corneal barrier function were better with the BAC-free solutions. This might be beneficial to people with dry eye syndrome.

Dr. Wirta's site was chosen for inspection for this NDA because he was the high enroller. He has 19 studies listed in the Clinical Investigator System (CIS) database. Dr. Wirta was last inspected in 2003. The inspection was classified NAI.

Summary Report of U.S. Inspection

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State*	Protocol #	Insp. Date	EIR Received Date	Final Classification
David L. Wirta	Newport Beach, CA	C-04-17	3/15-3/17/2006	5/8/06	NAI

*If international site, please insert column for country.

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

A. Protocol #C-04-17 "A Multicenter, Double-Masked, Study of the Safety and Efficacy of TRAVATAN® BAC-free Compared to TRAVATAN® in Patients with Open-Angle Glaucoma or Ocular Hypertension"

1. David L. Wirta, M.D., Newport Beach, CA (Site 2600): The data were acceptable.

- a. Forty-one subjects were screened; 40 subjects were randomized and 38 subjects completed the study. One subject terminated early due to an SAE of malignant melanoma. One subject moved away before study completion.

- b. There were no limitations to the inspection.
- c. An audit of 20 subjects' records was conducted. No Form FDA 483, Inspectional Observations, was issued at the end of inspection.
- d. There were no protocol violations or other regulatory deficiencies that would affect data integrity or reliability.

Dianne Tesch
Consumer Safety Officer

CONCURRENCE:

Supervisory comments

{See appended electronic signature page}

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II.
Division of Scientific Investigations

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/s/

Dianne Tesch
5/12/2006 08:48:58 AM
CSO

Leslie Ball
5/12/2006 11:09:43 AM
MEDICAL OFFICER

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-994

FILING COMMUNICATION

Alcon, Inc.
c/o Alcon Research, Ltd.
Attention: Angela C. Kothe, O.D., Ph.D.
Associate Director, Regulatory Affairs
Mail Code R7-18
6201 South Freeway
Fort Worth, Texas 76134-2099

Dear Dr. Kothe:

Please refer to your November 18, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Travatan BAC-free (travoprost ophthalmic solution) 0.004%.

We also refer to your submissions dated December 7, and 14, 2005, and January 10, 2006.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on January 20, 2006, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Michael Puglisi, Project Manager, at (301) 796-1400.

Sincerely,

{See appended electronic signature page}

Maureen P. Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective and
Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Maureen Dillon-Parker

2/3/2006 01:14:48 PM

NDA 21-994; Filing Communication

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REQUEST FOR CONSULTATION

TO (Division/Office):
Sheila Ryan
DHHS/FDA/CDER/OMP/DDMAC/HFD-042

FROM:
Mike Puglisi /Project Manager
DHHS/FDA/CDER/OND/ODE4/DAIOP HFD-520

DATE
January 13, 2006

IND NO.

NDA NO.
NDA 21-994

TYPE OF DOCUMENT
Original NDA

DATE OF DOCUMENT
November 18, 2005

NAME OF DRUG
**Travatan Z (travoprost
ophthalmic solution) 0.004%**

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG
prostaglandin

DESIRED COMPLETION DATE
April 13, 2006

NAME OF FIRM: **Alcon, 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 2
- RESUBMISSION
- SAFETY/EFFICACY

X ORIG. 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
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
- PROTOCOL-BIOPHARMACEUTICS
- IN-VIVO WAIVER REQUEST

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please provide a consultative review on the sponsor's proposed labeling for this NDA.

This is a paper NDA. I'll forward a copy of the proposed labeling along with this consult form via interoffice mail. An electronic version of the NDA can be found in the EDR.

This is the sponsor's proposed labeling. It does not reflect comment by HFD-520 reviewers.

If you have any questions, please contact me, Mike Puglisi, Project Manager at 301-796-0791. Thanks.

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)

Via: Interoffice Mail

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

Michael Puglisi
1/13/2006 10:00:32 AM

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NDA FILEABILITY CHECKLIST

NDA Number: 21-994

**Applicant: Alcon Inc, PO Box 62, Bosch 69, CH-6331 Hünenberg, Switzerland (US Agent:
Alcon Research, R7-18, 6201 South Freeway, Fort Worth, TX 76134**

Letter Date: 18-Nov-2005

Stamp Date: 21-Nov-2005

Drug Name: Travatan Z (travoprost ophthalmic solution) 0.004%

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	o		
2	Is the section indexed and paginated adequately?	o		
3	On its face, is the section legible?	o		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	o		Not adequate. IR sent Dec 8. Complete list received Dec 14.
5	Is a statement provided that all facilities are ready for GMP inspection?	o		Present in IR response of Dec 14
6	Has an environmental assessment report or categorical exclusion been provided?	o		Provided in 3.A.9
7	Does the section contain controls for the drug substance?	o		
8	Does the section contain controls for the drug product?	o		
9	Has stability data and analysis been provided to support the requested expiration date?	o		Approved drug substance. _____ of ✓ drug product batches each of 2 fill sizes provided.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			EOP2 meeting minutes in Vol 3. Reviewer will evaluate the applicant's comments for acceptability
11	Have draft container labels been provided?	o		
12	Has the draft package insert been provided?	o		
13	Has an investigational formulations section been provided?		o	None detected. This is a modified formulation from the approved product, Tavatan Ophthalmic Solution.
14	Is there a Methods Validation package?		o	Ready at firm and available to reviewer upon request. Validation data in vol. 3
15	Is a separate microbiological section included?	o		Micro reviewer is Robert Mello

If the NDA is not fileable from a manufacturing and controls perspective state why it is not.

Chemistry Reviewer:

Pharmaceutical Assessment Lead:

Branch Chief:

Suresh Pagay, Ph.D.

Linda Ng, Ph.D.

Norman Schmuff, Ph.D.

Prepared by: LNg 1/6/06

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/s/

Linda Ng
1/6/2006 04:09:32 PM
CHEMIST
Fileable from CMC

Norman Schmuff
1/6/2006 04:19:30 PM
CHEMIST

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DSI CONSULT: Request for Clinical Inspections

Date: January 4, 2006

To: Leslie K. Ball, M.D., Branch Chief
Good Clinical Practice Branch II, HFD-47

Through: Dianne Tesch, RNP, Consumer Safety Officer, Division of Scientific Investigations, HFD-45

From: Michael Puglisi, Regulatory Project Manager
Division of Anti-Infective and Ophthalmology Products, HFD-520

Subject: Request for Clinical Inspections
NDA 21-994
Alcon, Inc.
Travatan Z (travoprost ophthalmic solution) 0.004%

Protocol/Site Identification:

The following protocol/site has been identified for inspection based on patient enrollment (40 patients were studied at this site). We don't have any particular concerns about this site or any others involved in the studies for this NDA. Go forward with your inspection of this site only if your resources allow it.

Indication	Protocol #	Site (Name and Address)
Data Audit	C-04-17	David L. Witra, M.D. Eye Research Foundation 1501 Superior Avenue, Suite 303 Newport Beach, CA 92663

Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.

ADD THE FOLLOWING SECTION IF THERE ARE ANY FOREIGN SITES IN THE ABOVE LISTED SITES REQUESTED TO BE INSPECTED:

International Inspections:

We have requested inspections because (please check appropriate statements):

There are insufficient domestic data

- ___ Only foreign data are submitted to support an application
- ___ Domestic and foreign data show conflicting results pertinent to decision-making
- ___ There is a serious issue to resolve, e.g. suspicion of fraud, scientific misconduct, or significant human subject protection violations

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **June 21, 2006**. We intend to issue an action letter on this application by (action goal date) **September 21, 2006**.

Should you require any additional information, please contact Mike Puglisi, Regulatory Project Manager at (301) 796-0791.

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/s/

Michael Puglisi
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Initial Quality Assessment
Branch IV
Pre-Marketing Assessment Division II

OND Division: Division of Anti-Infective and Ophthalmology Products
NDA: 21,994
Applicant: Alcon Inc
Stamp Date: November 21, 2005
PDUFA Date:
Trademark: Travatan Z (to be determined)
Established Name: Latanoprost
Dosage Form: Ophthalmic solution
Route of Administration: Eye drops
Indication: For the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension

PAL: Linda Ng, Ph.D.

	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input type="checkbox"/>	<input checked="" type="checkbox"/>

Summary and Critical Issues:

Summary

In general, this NDA, 3S, is straightforward. The product is similar Travatan, NDA 21-257 except for the formulation. Benzalkonium chloride (BAC) was eliminated but others added to stabilize the product.

The facilities list of the two NDAs was compared. The list in this NDA does not appear to be comprehensive and thus an IR dated December 8, 2005 (Attachment 1) was sent. The response was inadequate and the applicant was informed to respond to the questions raised. The comprehensive list was received on December 14, 2005 and Robert Hummel, ONDQA will submit the EES request.

The drug substance manufacturing facility has been changed in NDA 21-257 as per supplements SCM-002 and SCM-007. The drug substance specification is acceptable.

A microbiology consult was submitted by the OND PM, Michael Puglisi and Robert Mello, microbiologist was assigned. Mr. Puglisi has submitted the trade name request to DMET on December 15, 2005 and will submit the labeling consult to DDMAC.

Critical issues for review

- It is suggested that comparison be made between this NDA and NDA 21-257. The applicant has dropped or replaced criteria for the drug product, e.g., any individual unspecified impurity should not be reported in ppm. Only leachables should be reported in ppm. Actual values, where appropriate, should be reported instead of meet requirement. The acceptance criteria should reflect actual values and the dosage form.
- ONDQA PM will request for EER according to the list of facilities from the applicant.

Comments for 74-Day Letter

None recommended.

D. Review, Comments and Recommendation:

(Summarize review including potential review issues and issues arising during the IND phases and at the pre-NDA meetings. Make a filing and a team review recommendation.)

Acceptable for filing. No team review is recommended. A single reviewer can review this NDA due to the fairly straightforward issues.

____ Linda Ng, Ph.D. _____
Pharmaceutical Assessment Lead

____ December 15, 2005 _____
Date

____ Norman Schmuff, Ph.D. _____
Branch Chief

Date

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Attachment 1

NDA 21-994

Travatan Bac-free (travoprost ophthalmic solution) 0.004%

CMC COMMENTS

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. Depending on the timing of your response, as per user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, provide the appropriate information. Your response should be submitted as an amendment to the submission and a copy via facsimile to the ONDQA project manager, Mr. Robert Hummel at 301-796-9850.

1. Please confirm/provide all facilities, including street address, contact name, phone and facsimile numbers, CFN/FEI numbers where available, for the following:
 - a. Manufacturing, and release and stability testing for the drug substance
 - b. Manufacturing, packaging, labeling, and release and stability testing for the drug product
2. Confirm that all facilities are ready for inspection.

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/s/

Linda Ng
12/16/2005 04:33:06 PM
CHEMIST

Norman Schmuff
12/19/2005 09:46:07 AM
CHEMIST

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-994

NDA ACKNOWLEDGMENT

Alcon, Inc.
c/o Alcon Research, Ltd.
Attention: Angela C. Kothe, O.D., Ph.D.
Associate Director, Regulatory Affairs
Mail Code R7-18
6201 South Freeway
Fort Worth, Texas 76134-2099

Dear Dr. Kothe:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Travatan Z (travoprost ophthalmic solution) 0.004%

Review Priority Classification: Standard (S)

Date of Application: November 18, 2005

Date of Receipt: November 21, 2005

Our Reference Number: NDA 21-994

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 January 20, 2006, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 21, 2006.

Please cite the NDA 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 and
Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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NDA 21-994

Page 2

If you have any questions, call Michael Puglisi, Project Manager, at (301) 796-1400.

Sincerely,

{See appended electronic signature page}

Maureen P. Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective and
Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Maureen Dillon-Parker
12/15/2005 03:17:00 PM
NDA 21-994 New NDA Ack Ltr

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REQUEST FOR CONSULTATION

TO (Division/Office):
**Associate Director, Medication Error Prevention
Office of Post Marketing Drug Risk Assessment, HFD-400
(Rm. 15B-03, PKLN Bldg.)**

FROM:
Mike Puglisi phone 301-796-0791
Project Manager
DHHS/FDA/CDER/ORM/DAIOP HFD-520

DATE
December 15, 2005

IND NO.

NDA NO.
21-994

TYPE OF DOCUMENT
Orig. NDA- Trade Name
Review

DATE OF DOCUMENT
November 18, 2005

NAME OF DRUG Travatan Z (travoprost
ophthalmic solution) 0.004%

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG
Prostaglandin

DESIRED COMPLETION DATE
March 15, 2006

NAME OF FIRM: Alcon, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE 2 | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | X TRADE NAME REVIEW | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

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
 BIOAVAILABILITY STUDIES
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
 PROTOCOL-BIOPHARMACEUTICS
 IN-VIVO WAIVER REQUEST

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS:

Please provide a trade name review for the name "Travatan Z" for NDA 21-994. This NDA is for a new preservative free formulation of Alcon's approved Travatan product (NDA 21-257). This NDA was submitted in paper and also electronically (on the EDR). I'll forward a paper copy of this consult form along with a copy of the first volume of the NDA (which includes labeling and hopefully everything else you need). I'm also including a couple other related IND amendments. Let me know if you need any additional information.

Alcon has actually proposed 3 trade names. Their first choice is Travatan Z. If you're willing to review more than one at a time, be my guest.

Although the sponsor has requested a Priority review, we disagree that it qualifies. So it will be a standard 10-month review clock unless something changes. The PDUFA goal date will be 9/21/06.

Thanks. -Mike

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)

Hand

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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Michael Puglisi
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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): David Hussong DHHS/FDA/CDER/OPS/ONDC/HFD-805		FROM: Mike Puglisi phone 301-796-0791 Project Manager DHHS/FDA/CDER/ORM/DAIOP HFD-520		
DATE November 30, 2005	IND NO.	NDA NO. 21-994	TYPE OF DOCUMENT Original NDA	DATE OF DOCUMENT November 18, 2005
NAME OF DRUG Travatan Z (travoprost ophthalmic solution) 0.004%	PRIORITY CONSIDERATION Standard review	CLASSIFICATION OF DRUG prostaglandin	DESIRED COMPLETION DATE tbd	
NAME OF FIRM: Alcon, Inc.				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE 2 <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY X ORIGINAL NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS:				
<p>David-</p> <p>Please provide a micro review for this original NDA. It should be a standard review with a PDUFA goal date of September 21, 2006. Our internal goal will be determined during the filing meeting (not yet scheduled).</p> <p>This is a paper only submission. I'll deliver the first volume of the submission with a hard copy of this consult form. The remaining volumes will be delivered to the assigned reviewer when that has been determined.</p> <p>If you have any questions, please contact me at 301-796-0791. Thanks.</p>				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) hand		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

Michael Puglisi
11/30/2005 10:25:09 AM

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NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information

NDA 21-994		
Drug: Travatan Z (travoprost ophthalmic solution), 0.004%	Applicant: Alcon Inc.	
RPM: Michael Puglisi	HFD-520	Phone # 301-796-0791
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p><i>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</i></p> <p>(X) Confirmed and/or corrected</p>	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):	
❖ Application Classifications:		
• Review priority	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
• Chem class (NDAs only)	Type 5, New Formulation	
• Other (e.g., orphan, OTC)	N/A	
User Fee Goal Dates	September 21, 2006	
❖ Special programs (indicate all that apply)		
	<input checked="" type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2	
❖ User Fee Information		
• User Fee	<input checked="" type="checkbox"/> Paid UF ID number – PD3006308	
• User Fee waiver	<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)	
• User Fee exception	<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)	
Application Integrity Policy (AIP)		
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)

- Exclusivity summary.
- Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)
- Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.

Enclosed

Yes, Application # _____
 No

General Information	
❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	None
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	In Package – Submitted 9/15/06
• Original applicant-proposed labeling	In Package – Submitted 11/18/05
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DDMAC- 7/14/06 DMETS – 4/20/06
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	In Package – Submitted 9/15/06
• Reviews	DDMAC- 7/14/06 DMETS – 4/20/06
❖ Post-marketing commitments	N/A
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	In Package
❖ Memoranda and Telecons	N/A
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
❖ Advisory Committee Meeting	N/A
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (<i>indicate date for each review</i>)	N/A
Clinical Information	
❖ Clinical review(s) (<i>indicate date for each review</i>)	May 24, 2006, Sept. 19, 2006
❖ Microbiology (efficacy) review(s) (<i>indicate date for each review</i>)	N/A
❖ Safety Update review(s) (<i>indicate date or location if incorporated in another review</i>)	In May 24, 2006, Clinical Review
❖ Risk Management Plan review(s) (<i>indicate date/location if incorporated in another rev</i>)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	In Package
❖ Demographic Worksheet (<i>NME approvals only</i>)	N/A
❖ Statistical review(s) (<i>indicate date for each review</i>)	N/A
❖ Biopharmaceutical review(s) (<i>indicate date for each review</i>)	June 28, 2006
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date for each review</i>)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	In Package – May 12, 2006
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (<i>indicate date for each review</i>)	August 29, 2006, September 18, 2006
❖ Environmental Assessment	
• Categorical Exclusion (<i>indicate review date</i>)	In 8/29/06, CMC Review
• Review & FONSI (<i>indicate date of review</i>)	N/A
• Review & Environmental Impact Statement (<i>indicate date of each review</i>)	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) (<i>indicate date for each review</i>)	September 8, 2006
❖ Facilities inspection (provide EER report)	Date completed: 12/20/05 (X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested (X) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	March 2, 2006
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	N/A
❖ CAC/ECAC report	N/A

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/s/

Michael Puglisi
9/12/2006 01:37:19 PM
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Michael Puglisi
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