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."

<table>
<thead>
<tr>
<th>Investigation #1</th>
<th>YES □</th>
<th>NO □</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigation #2</td>
<td>YES □</td>
<td>NO □</td>
</tr>
</tbody>
</table>

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?

<table>
<thead>
<tr>
<th>Investigation #1</th>
<th>YES □</th>
<th>NO □</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigation #2</td>
<td>YES □</td>
<td>NO □</td>
</tr>
</tbody>
</table>
If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

<table>
<thead>
<tr>
<th>IND #</th>
<th>YES □</th>
<th>NO □</th>
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<tr>
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<td>!</td>
<td>Explain:</td>
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</table>

Investigation #2

<table>
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<tr>
<th>IND #</th>
<th>YES □</th>
<th>NO □</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>!</td>
<td>Explain:</td>
</tr>
</tbody>
</table>

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?
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/

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Wiley Chambers
11/2/2006 10:43:47 PM

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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
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:

<table>
<thead>
<tr>
<th>Min</th>
<th>kg</th>
<th>mo.</th>
<th>yr.</th>
<th>Tanner Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max</td>
<td>kg</td>
<td>mo.</td>
<td>yr.</td>
<td>Tanner Stage</td>
</tr>
</tbody>
</table>

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:

<table>
<thead>
<tr>
<th>Min</th>
<th>kg</th>
<th>mo.</th>
<th>yr.</th>
<th>Tanner Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max</td>
<td>kg</td>
<td>mo.</td>
<td>yr.</td>
<td>Tanner Stage</td>
</tr>
</tbody>
</table>

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
10/26/2006 10:29:33 PM

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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

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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 - 25°C 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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/s/

Michael Puglisi
9/15/2006 12:00:01 PM

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NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-994

Trade Name: Travatan Z
Established Name: travoprost 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) X (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 X
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 X NO □

User Fee Status: Paid X 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 X NO ☐**
  If yes, explain: **There is remaining exclusivity for Alcon's original formulation of Travatan (NDA 21-257).**

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

- 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 X**
  If yes, explain:

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

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

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

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

- If an electronic NDA, does it follow the Guidance? **N/A X 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 X YES ☐ NO ☐**

- Is it an electronic CTD (eCTD)? **YES ☐ NO X**
  **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 X NO ☐**
Exclusivity requested? YES □ NO X

NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

Correctly worded Debarment Certification included with authorized signature? YES X 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 X 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 X NO □

PDUFA and Action Goal dates correct in COMIS? YES X 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 X
If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? Date(s) ___________________________ NO X
If yes, distribute minutes before filing meeting.

Project Management

Was electronic “Content of Labeling” submitted? YES X NO □ If no, request in 74-day letter.

All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES X NO □

Risk Management Plan consulted to ODS/IO? N/A X YES □ NO □

Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y X NO □

MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A X YES □ NO □
• If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A  X  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  X  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  X  NO  □

  • If a parenteral product, consulted to Microbiology Team (HFD-805)?
    YES  X  NO  □

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

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

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

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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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Thank you.

• 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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/s/
Michael Puglisi
9/12/2006 01:16:12 PM

Appears This Way
On Original
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

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

• 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 is _____ 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.
(11). It is stated that sterility testing of the first commercial batches will be performed initially and at or beyond shelf life. Sterility test for the first 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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/s/

Michael Puglisi
7/5/2006 08:39:32 AM

Appears This Way
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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. Travoprost 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 enrollee. 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):

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

*If international site, please insert column for country.

### Key to Classifications

- **NAI** = No deviation from regulations. Data acceptable.
- **VAI** = No Response Requested = Deviation(s) from regulations. Data acceptable.
- **VAI** = Response Requested = Deviation(s) form 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

Appears This Way
On Original
NDA 21-994

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,

(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/DAIOH 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

DESIGNED 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-ND A 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

☐ TYPE A OR B NDA REVIEW
☐ END OF PHASE II MEETING
☐ CONTROLLED STUDIES
☐ PROTOCOL REVIEW
☐ OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

☐ 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 Hunenber, 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.

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

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

**Chemistry Reviewer:** Suresh Pagay, Ph.D.  
**Pharmaceutical Assessment Lead:** Linda Ng, Ph.D.  
**Branch Chief:** 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.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Protocol #</th>
<th>Site (Name and Address)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data Audit</td>
<td>C-04-17</td>
<td>David L. Witra, M.D.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eye Research Foundation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1501 Superior Avenue, Suite 303</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Newport Beach, CA  92663</td>
</tr>
</tbody>
</table>

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
1/5/2006 03:21:18 PM

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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

Appears This Way
On Original
NDA 21-994

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
Beltville, MD 20705-1266

Appears This Way On Original
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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On Original
REQUEST FOR CONSULTATION

TO (Division/Organization):
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

NAME OF FIRM
Alcon, Inc.

DESIRED COMPLETION DATE
March 15, 2006

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL
☐ PROGRESS REPORT
☐ NEW CORRESPONDENCE
☐ DRUG ADVERTISING
☐ ADVERSE REACTION REPORT
☐ MANUFACTURING CHANGE/ADDITION
☐ MEETING PLANNED BY

☐ PRE-ND A MEETING
☐ END OF PHASE 2
☐ RESUBMISSION
☐ SAFETY/EFFICACY
☐ X TRADE NAME REVIEW
☐ CONTROL SUPPLEMENT

☐ RESPONSE TO DEFIciENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVISION
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMATIVE REVIEW
☐ OTHER (SPECIFY BELOW):

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

☐ TYPE A OR B NDA REVIEW
☐ END OF PHASE II MEETING
☐ CONTROLLED STUDIES
☐ PROTOCOL REVIEW
☐ OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

☐ CHEMISTRY REVIEW
☐ PHARMACOLOGY
☐ BIOPHARMACEUTICS
☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION
☐ BIOPHARMACEUTICS STUDIES
☐ PHASE IV STUDIES

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

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

/s/

-------------------

Michael Puglisi
12/15/2005 11:21:16 AM

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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

☐ NEW PROTOCOL
☐ PROGRESS REPORT
☐ NEW CORRESPONDENCE
☐ DRUG ADVERTISING
☐ ADVERSE REACTION REPORT
☐ MANUFACTURING CHANGE/ADDITION
☐ MEETING PLANNED BY

☐ PRE-ANDA MEETING
☐ END OF PHASE 2
☐ RESUBMISSION
☐ SAFETY/EFFICACY
☐ ORIGINAL NDA

☐ CONTROL SUPPLEMENT

☐ RESPONSE TO DEFICIENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVISION
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMATIVE REVIEW
☐ OTHER (SPECIFY BELOW):

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

☐ TYPE A OR B NDA REVIEW
☐ END OF PHASE II MEETING
☐ CONTROLLED STUDIES
☐ PROTOCOL REVIEW
☐ OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

☐ CHEMISTRY REVIEW
☐ PHARMACOLOGY
☐ BIOPHARMACEUTICS
☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION
☐ AVAILABILITY STUDIES
☐ PHASE IV STUDIES

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

☐ V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL
☐ PRECLINICAL

Comments:

David-

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).

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.

If you have any questions, please contact me at 301-796-0791. Thanks.
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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**

**Application Type:**
- (X) 505(b)(1)
- ( ) 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.)

**Listed drug(s) referred to in 505(b)(2) application (NDA #(#), Drug name(s)):**

(X) Confirmed and/or corrected

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<th>(X) Standard</th>
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| User Fee Goal Dates | September 21, 2006 |

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<td>( ) 21 CFR 314.510 (accelerated approval)</td>
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<td>( ) 21 CFR 314.520 (restricted distribution)</td>
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<td>( ) Fast Track</td>
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<td>( ) Rolling Review</td>
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<td>( ) CMA Pilot 1</td>
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<td>( ) CMA Pilot 2</td>
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<td>( ) Barrier-to-Innovation</td>
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<td>( ) Other (specify)</td>
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<td>OC clearance for approval</td>
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<td><strong>Debarment certification</strong>: verified that qualifying language (e.g., willingly, knowingly) was not used in certification &amp; certifications from foreign applicants are cosigned by US agent.</td>
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<td><strong>Patent</strong></td>
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<td>Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.</td>
<td></td>
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<tr>
<td>Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</td>
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<tr>
<td>[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</td>
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<tr>
<td>[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications, mark &quot;N/A&quot; and skip to the next box below (Exclusivity)).</td>
<td></td>
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<tr>
<td>[505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.</td>
<td></td>
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</table>

Answer the following questions for each paragraph IV certification:

1. Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?
   - (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).
   - If "Yes," skip to question (4) below. If "No," continue with question (2).

2. Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?
   - 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 (3).

3. Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?
(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)?

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?

(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.

☑ Yes, Application #
☑ No

Enclosed
### General Information

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<td>(X) AP ( ) TA ( ) AE ( ) NA</td>
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<td>- Previous actions (specify type and date for each action taken)</td>
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<td>- Status of advertising (approvals only)</td>
<td>(X) Materials requested in AP letter ( ) Reviewed for Subpart H</td>
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<td>(X) Yes ( ) Not applicable</td>
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<td>- Indicate what types (if any) of information dissemination are anticipated</td>
<td>(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter</td>
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<td>- Original applicant-proposed labeling</td>
<td>In Package – Submitted 11/18/05</td>
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<tr>
<td>- Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)</td>
<td>DDMAC- 7/14/06 DMETS – 4/20/06</td>
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<td>- Other relevant labeling (e.g., most recent 3 in class, class labeling)</td>
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<th>Labels (immediate container &amp; carton labels)</th>
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<td>- Reviews</td>
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<td>- Documentation of discussions and/or agreements relating to post-marketing commitments</td>
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<td>- Outgoing correspondence (i.e., letters, E-mails, faxes)</td>
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| Memoranda and Telecons                                                  | N/A |

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<td>- Pre-Approval Safety Conference (indicate date; approvals only)</td>
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<td>- 48-hour alert</td>
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<td>Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)</td>
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<td>Summary Application Review</td>
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<td>▶ Microbiology (efficacy) review(s) (indicate date for each review)</td>
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<td>▶ Safety Update review(s) (indicate date or location if incorporated in another review)</td>
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<td>▶ Risk Management Plan review(s) (indicate date/location if incorporated in another review)</td>
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<td>▶ Pediatric Page (separate page for each indication addressing status of all age groups)</td>
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<td>▶ Demographic Worksheet (NME approvals only)</td>
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<td>- Categorical Exclusion (indicate review date)</td>
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<td>- Review &amp; FONSI (indicate date of review)</td>
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<td>- Review &amp; Environmental Impact Statement (indicate date of each review)</td>
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<td>▶ Microbiology (validation of sterilization &amp; product sterility) review(s) (indicate date for each review)</td>
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<td>▶ CAC/ECAC report</td>
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/s/
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Michael Puglisi
9/12/2006 01:37:19 PM
CSO

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

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