CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-688 / S-001

Trade Name: Patanol

Generic Name: olopatadine

Sponsor: Alcon Laboratories

Approval Date: January 15, 1998
## Reviews / Information Included in this NDA Review.

<table>
<thead>
<tr>
<th>Review Type</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval Letter</td>
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<tr>
<td>Approvable Letter</td>
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<tr>
<td>Labeling</td>
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<tr>
<td>Summary Review</td>
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<tr>
<td>Officer/Employee List</td>
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<tr>
<td>Office Director Memo</td>
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<tr>
<td>Cross Discipline Team Leader Review</td>
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<tr>
<td>Medical Review(s)</td>
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<tr>
<td>Chemistry Review(s)</td>
<td>X</td>
</tr>
<tr>
<td>Environmental Assessment</td>
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<tr>
<td>Pharmacology Review(s)</td>
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<tr>
<td>Statistical Review(s)</td>
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<tr>
<td>Microbiology Review(s)</td>
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<tr>
<td>Clinical Pharmacology/Biopharmaceutics Review(s)</td>
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<tr>
<td>Risk Assessment and Risk Mitigation Review(s)</td>
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<tr>
<td>Proprietary Name Review(s)</td>
<td></td>
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<tr>
<td>Administrative/Correspondence Document(s)</td>
<td></td>
</tr>
</tbody>
</table>
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
20-688 / S-001

APPROVAL LETTER
Dear Ms. Caballa:

Please refer to your July 3, 1997, supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

<table>
<thead>
<tr>
<th>NDA Number</th>
<th>Supplement Number</th>
<th>Drug Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>19-270</td>
<td>S-019</td>
<td>BETOPTIC® (betaxolol HCl ophthalmic solution), 0.5% Ophthalmic Solution</td>
</tr>
<tr>
<td>19-387</td>
<td>S-006</td>
<td>PROFENAL® (suprofen ophthalmic solution), 1% Ophthalmic Solution</td>
</tr>
<tr>
<td>19-992</td>
<td>S-007</td>
<td>CILOXAN® (ciprofloxacin HCl ophthalmic solution), 0.3% Ophthalmic Solution</td>
</tr>
<tr>
<td>20-258</td>
<td>S-005</td>
<td>IOPIDINE® (apraclonidine HCl ophthalmic solution) 0.5% Ophthalmic Solution</td>
</tr>
<tr>
<td>20-688</td>
<td>S-001</td>
<td>PATANOL™ (olopatadine HCl ophthalmic solution) 0.1% Ophthalmic Solution</td>
</tr>
<tr>
<td>50-541</td>
<td>S-009</td>
<td>TOBREX® (tobramycin ophthalmic solution), 0.3% Ophthalmic Solution</td>
</tr>
</tbody>
</table>

We acknowledge receipt of your amendment dated January 8, 1998. These supplemental applications provide for an alternate manufacturing facility.

We have completed the reviews of these supplemental applications and they are approved effective as of the date of this letter.
These approvals affect only the changes specifically submitted in these supplemental applications. Other changes that may have been approved or are pending evaluation are not affected.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Lori Gorski, Project Manager, at (301) 827-2090.

Sincerely,

WAC 1/15/98
Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesics and Ophthalmic Drug Products, HFD-550
Office Of Drug Evaluation V
Center for Drug Evaluation and Research

cc: NDA 19-270
NDA 19-387
NDA 19-992
NDA 20-258
NDA 20-688
NDA 50-541
HFD-550/Div. Files
HFD-550/CSO/Gorski
HFD-550/DepDir/Chambers
HFD-550/Clin Rev/Holmes
HFD-550/Chem/Fenselau
HFD-805/Micro/Stinavage
HFD-550/Chem TL/Patel
HFD-92
DISTRICT OFFICE
HFD-830/DNDC III

n:gorski\alcon\19270s19.ap

APPROVAL
APPLICATION NUMBER:
20-688 / S-001

APPROVABLE LETTER
Alcon Laboratories
Attention: Susan H. Caballa
Associate Director, Regulatory Affairs
6201 South Freeway
Fort Worth, Texas 76134-2099

Dear Ms. Caballa:

Please refer to your July 3, 1997, supplemental new drug applications submitted under the Federal Food, Drug, and Cosmetic Act for:

<table>
<thead>
<tr>
<th>NDA Number</th>
<th>Supplement Number</th>
<th>Drug Name</th>
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<td>PROFENAL® (suprofen ophthalmic solution), 1% Ophthalmic Solution</td>
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<td>19-992</td>
<td>S-007</td>
<td>CILOXAN® (ciprofloxacine HCl ophthalmic solution), 0.3% Ophthalmic Solution</td>
</tr>
<tr>
<td>20-258</td>
<td>S-005</td>
<td>IOPIDINE® (apraclonidine HCl ophthalmic solution) 0.5% Ophthalmic Solution</td>
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<tr>
<td>20-688</td>
<td>S-001</td>
<td>PATANOL™ (olopatadine HCl ophthalmic solution) 0.1% Ophthalmic Solution</td>
</tr>
<tr>
<td>50-541</td>
<td>S-009</td>
<td>TOBREX® (tobramycin ophthalmic solution), 0.3% Ophthalmic Solution</td>
</tr>
</tbody>
</table>

These supplemental applications provide for an alternate manufacturing facility.
We have completed the review of these supplemental applications and they are approvable. Before these supplements may be approved, however, it will be necessary for you to provide the following information:

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to amend the supplemental applications, or follow one of the other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the applications.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division to discuss what further steps need to be taken before the applications may be approved.

These changes may not be implemented until you have been notified in writing that these supplemental applications are approved.

If you have any questions, please contact Lori Gorski, Project Manager, at (301) 827-2090.

Sincerely,

\[\text{WAC} \quad 1/7/98\]

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research
NDA 19-270/S-019
NDA 19-387/S-006
NDA 19-992/S-007
NDA 20-258/S-005
NDA 20-688/S-001
NDA 50-541/S-009
Page 3

cc:
NDA 19-270
NDA 19-387
NDA 19-992
NDA 20-258
NDA 20-688
NDA 50-541
HFD-550/Div. Files
HFD-550/CSO/Gorski
HFD-550/Acting SCSO/Koerner
HFD-550/DepDir/Chambers
HFD-550/Clin Rev/Holmes
HFD-550/Chem/Yaciw
HFD-550/Chem/Fenselau
HFD-160/Micro/Stinavage
HFD-550/Chem TL/ Patel
HFD-92
DISTRICT OFFICE
HFD-830/DNDC III

n:\gorski\alcon\19270s19.ae

APPROVABLE (AE)
<table>
<thead>
<tr>
<th>Chemistry Review</th>
<th>Review #1</th>
<th>1. Division HFD-550</th>
<th>2. NDA Number #20-688</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Name and Address of Applicant</td>
<td>4. Supplement Number Date</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcon Laboratories, Inc.</td>
<td>SCM-001 03-JUL-97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6201 South Freeway</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fort Worth, TX 76134</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Name of Drug</td>
<td>6. Nonproprietary Name</td>
<td></td>
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<tr>
<td>PATANOL 0.1%</td>
<td>Olopataidine Hydrochloride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Supplement Provides for:</td>
<td>8. Amendment(s)</td>
<td></td>
<td></td>
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<tr>
<td>Alternate manufacturing site</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Short-term prevention of itching of eye due to allergic conjunctivitis</td>
<td>Rx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Related Documents</td>
<td></td>
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<tr>
<td>NDA #19-387 (SCM-006)</td>
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<tr>
<td>NDA #19-992 (SCM-007)</td>
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<td></td>
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<tr>
<td>NDA #19-270 (SCM-019)</td>
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<tr>
<td>NDA #20-258 (SCM-005)</td>
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<tr>
<td>NDA #50-541 (SCM-009)</td>
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<tr>
<td>NDA #20-226 (SCM-008)</td>
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</tr>
<tr>
<td>12. Dosage Form</td>
<td>13. Potency(ies):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ophthalmic solution</td>
<td>Olopataidine hydrochloride 0.111%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(equivalent to 0.1% olopataidine base)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Chemical Name and Structure</td>
<td>see USAN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C₁₉H₂₄ClNO₃</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mol.Wt.: 373.88</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Z)-11-[3-(Dimethylamino)propylidene]-6,11-dihydrodibenzo[b,e]exepine-2-acetic acid hydrochloride</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLOPATIDINE HCl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name</td>
<td>Signature</td>
<td>Date</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>--------------</td>
<td>----------</td>
<td></td>
</tr>
<tr>
<td>Allan Fenselau</td>
<td>Allan Fenselau</td>
<td>12/19/97</td>
<td></td>
</tr>
<tr>
<td>Hasmukh B. Patel</td>
<td></td>
<td>12/22/97</td>
<td></td>
</tr>
</tbody>
</table>

cc: NDA #20-688  
HFD-550/Division File  
HFD-550/CSO/L.Gorski  
HFD-550/CHEM/A.Fenselau  
HFD-550/CHEM/TeamLdr/H.Patel  
HFD-550/MO/J.Bull  
HFD-550/SMO/W.Chambers  
Doc ID: n20688s.001
☐ Page(s) Withheld

☑ Trade Secret / Confidential

☐ Draft Labeling

☐ Deliberative Process
AMENDMENT TO CMC REVIEWS FOR

NDA 19-270/S-019 (BETOPTIC 0.5% Ophthalmic Solution)
NDA 19-387/S-006 (PROFENAL 1% Ophthalmic Solution)
NDA 19-992/S-007 (CILOXAN 0.3% Ophthalmic Solution)
NDA 20-258/S-005 (IOPIDINE 0.5% Ophthalmic Solution)
NDA 20-688/S-001 (PATANOL 0.1% Ophthalmic Solution)
NDA 50-541/S-009 (TOBREX 0.3% Ophthalmic Solution)

The original Microbiology Review [MR] of the supplement recommended approval on the basis of sterility assurance (see attached MR by P. Stinavage dated 23-OCT-97). However, in a Microbiology Review Amendment dated 19-NOV-97 (also attached) concern was expressed for the Qualitative terms used in the review, such as "..." were finally quantified. In the case of the present submission, the indicated both parameters substantially exceed the which have been approved for the present manufacturing site(s). Subsequent discussion between members of the Microbiology Review team and the sponsor permitted approval by the MR team (see attached Microbiology Review Amendment 2 dated 07-JAN-98). The sponsor has FAXED to the Microbiology Review team an agreement to which are presently approved for these products at their existing manufacturing site(s), and hard copy is to follow (see attached copy of an Alcon fax dated 05-JAN-98). The point emphasized by MR is that Agency inspection of the facility has revealed that the recorded The use of these Consequently, the recommendation is that this request to manufacture the six ophthalmic products at the alternative may be approved.

Allen Fenselau 1/7/98
Chemistry Reviewer HFD-550

Hasmukh B. Patel 1/7/98
Team Leader HFD-550

Chi-wan Chen 1/7/98
Director DNDIII HFD-830
AMENDMENT to REVIEW

PATANOL™ 0.1% Ophthalmic Solution

Alcon Laboratories, Inc.

MICROBIOLOGY REVIEW

The original Microbiology Review [MR] of the supplement recommended approval on the basis of sterility assurance (see attached MR by P. Stinavage dated 23-OCT-97). However, in a Microbiology Review Amendment dated 19-NOV-97 (also attached) concern was expressed for the Qualitative terms used in the review, such as 

which have finally been quantified. In the case of the present submission, the indicated substantially exceed the exceed the 

been approved for the present manufacturing site(s). Based on this information, the opinion of the Chemistry Review is that the issues raised from the Microbiology Review Amendment (dated 19-NOV-97) need to be fully resolved by official receipt of their agreement to the 

manufacturing site(s) and by receipt of the details of actions to be taken if the 

Consequently, the recommendation is that this request to manufacture PATANOL™ 0.1% Ophthalmic Solution at the alternative 

considered Approvable only.

Allen Fenselau
Chemistry Reviewer

Hasmukh B. Patel
Team Leader

Allan Fenselau 1/5/98
Date
HFD-550

Hasmukh B. Patel 1/5/98
Date
HFD-550
REVIEW FOR HFD-550
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW OF SUPPLEMENT
21 October 1997

A. 1. NDA 19-270/S-019     NDA 19-387/S-006
    NDA 19-992/S-007     NDA 20-258/S-005
    NDA 20-688/S-001     NDA 50-541/S-003

    APPLICANT: Alcon Laboratories, Inc.
                6201 South Freeway
                Fort Worth, TX  76134-2099

2. PRODUCT NAME: NDA 19-270:  Betoptic® (betaxolol HCl) 0.5%
                               Ophthalmic Solution
    NDA 19-387:  Profenal® (suprofen) 1%
                  Ophthalmic Solution
    NDA 19-992:  Ciloxan® (ciprofloxacin HCl)
                  0.3% Ophthalmic Solution
    NDA 20-258:  Iopidine® (apraclonidine HCl)
                  0.5% Ophthalmic Solution
    NDA 20-688:  Patanol® (olopatadine HCl)
                  0.1% Ophthalmic Solution
    NDA 50-541:  Tobrex® (tobramycin) 0.3%
                  Ophthalmic Solution

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
   The products are ophthalmic solutions for instillation into the eye.

4. METHODS OF STERILIZATION:
   The products are

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
   The products have a variety of indications for treatment of conditions
   affecting the eye.

B. 1. DATE OF INITIAL SUBMISSION:  3 July 1997

2. DATE OF AMENDMENT:  (none)

3. RELATED DOCUMENTS: Original NDA's 19-270, 19-387, 19-992, 20-
Alcon Labs, NDA 19-270/S-019 and Five Others, Microbiologist's Review of Supplement

258, 20-688, and 50-541

4. ASSIGNED FOR REVIEW: 28 July 1997

C. REMARKS: These submissions have been submitted as a bundled supplement to seek approval for an alternate manufacturing site

D. CONCLUSIONS: The applications are recommended for approval on the basis of sterility assurance.

Paul Stinavage, Ph.D.

cc: Original NDA 19-270                                    NDA 19-387
    NDA 19-992                                    NDA 20-258
    NDA 20-688                                    NDA 50-541
    HFD-550/D.A. Gunter
    HFD-805/Consult File/Stinavage

Drafted by: P. Stinavage, 21 October 1997
R/D initialed by P. Cooney