Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-257

REVIEW #: 1  DATE REVIEWED: 09-NOV-00

SUBMISSION TYPE  DOCUMENT DATE  CDER DATE  ASSIGNED DATE
Original pre-submission  05-MAY-00  11-MAY-00  XX-MAY-00
Original submission  06-JUN-00  07-JUN-00  XX-JUN-00
Amendment  04-AUG-00  07-AUG-00  17-AUG-00
Amendment  10-AUG-00  11-AUG-00  17-AUG-00
Amendment  12-SEP-00  13-SEP-00  25-SEP-00
Amendment  14-SEP-00  15-SEP-00  25-SEP-00
Amendment  15-SEP-00  18-SEP-00  25-SEP-00
Amendment  19-OCT-00  23-OCT-00  02-NOV-00
Amendment  24-OCT-00  25-OCT-00  XX-NOV-00
Amendment  06-NOV-00  XX-NOV-00  XX-NOV-00

NAME & ADDRESS OF APPLICANT:
Alcon Universal, Ltd.
6201 South Freeway
Fort Worth, TX  76134

DRUG PRODUCT NAME
Proprietary: Travatan
Established: Travoprost
Code Name/#: CAS-157283-68-6
Chem. Type/Ther. Class: IP

PHARMACOL. CATEGORY: Lowering of intraocular pressure
DOSAGE FORM: Solution
STRENGTHS: 0.004% and 0.0015%
ROUTE OF ADMINISTRATION: Topical/ocular (1 drop daily/eye)

DISPENSED:  _X_ Rx  _O_ OTC
SPECIAL PRODUCTS/SPOTS:  _Y_ Yes  _X_ No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

```
  H
 / \                        C_{25}H_{35}F_{3}O_{6}
 /   \                      M.W.: 500.56
 H   \                     Isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(1E,3R)-3-hydroxy-4-
\    \              [(α,α,α-trifluoro-m-tolyloxy]-1-butenyloxy)cyclopentyl]-5-heptenoate
```

TRAVOPROST

APPEARS THIS WAY ON ORIGINAL
SUPPORTING DOCUMENTS:

RELATED DOCUMENTS:
Chemistry Reviews of (Alcon Lab., Inc.)

CONSULT REVIEWS:
Review of Tradenames (CDER Labeling and Nomenclature Committee, Consult # 00-00XX)
Sterility Assurance Report (V. Pawar, HFD-160)

cc:
Orig. NDA 21-257
HFD-550/Division File
HFD-550/CSO/M.Puglisi
HFD-550/Chem/ A.Fenselau
HFD-550/TeamLdr./L.Ng
HFD-550/Pharm./Z.Chen
HFD-550/OM/L.Lim
HFD-830/Div.Dir.DNDCIII/C.-w.Chen

Allan Fenselau, Review Chemist, HFD-550
Linda Ng, Chemistry Team Leader, HFD-550

APPEARS THIS WAY ON ORIGINAL
Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs  
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-257

REVIEW # 2  
DATE REVIEWED: 28-FEB-01

<table>
<thead>
<tr>
<th>SUBMISSION TYPE</th>
<th>DOCUMENT DATE</th>
<th>CDER DATE</th>
<th>ASSIGNED DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original pre-submission</td>
<td>05-MAY-00</td>
<td>11-MAY-00</td>
<td>18-MAY-00</td>
</tr>
<tr>
<td>Original submission</td>
<td>06-JUL-00</td>
<td>07-JUL-00</td>
<td>20-JUL-00</td>
</tr>
<tr>
<td>Amendment, AZ</td>
<td>26-DEC-00</td>
<td>27-DEC-00</td>
<td>02-JAN-01</td>
</tr>
<tr>
<td>Amendment, BL</td>
<td>17-JAN-01</td>
<td>22-JAN-01</td>
<td>29-JAN-01</td>
</tr>
<tr>
<td>Amendment, BC</td>
<td>01-FEB-01</td>
<td>02-FEB-01</td>
<td>12-FEB-01</td>
</tr>
<tr>
<td>Amendment, BC</td>
<td>09-FEB-01</td>
<td>12-FEB-01</td>
<td>22-FEB-01</td>
</tr>
<tr>
<td>Amendment, BC</td>
<td>16-FEB-01</td>
<td>20-FEB-01</td>
<td>26-FEB-01</td>
</tr>
<tr>
<td>Amendment, BC</td>
<td>28-FEB-01</td>
<td>01-MAR-01</td>
<td>08-MAR-01</td>
</tr>
</tbody>
</table>

NAME & ADDRESS OF APPLICANT:  
Alcon Universal, Ltd.  
6201 South Freeway  
Fort Worth, TX 76134

DRUG PRODUCT NAME  
Proprietary: Travatan  
Established: Travoprost  
Code Name/#: CAS-157283-68-6  
Chem. Type/Ther. Class: IP

PHARMACOL. CATEGORY: Lowering of intraocular pressure

DOSAGE FORM: Solution

STRENGTHS: 0.004%

ROUTE OF ADMINISTRATION: Topical/ocular (1 drop daily/eye)

DISPENSED: X Rx ___ OTC

SPECIAL PRODUCTS/SPOTS: ___ Yes X No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

\[
\text{C}_{28}\text{H}_{35}\text{F}_{3}\text{O}_{6} \\
\text{M.W.: 500.56}
\]

TRAVOPROST

Isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(1E,3R)-3-hydroxy-4-
[(α,α,α-trifluoro-m-tolyl)oxy]-1-butenyl]cyclopentyl]-5-heptenoate
CONCLUSIONS & RECOMMENDATIONS: Based on a review of chemistry, manufacturing and control issues that pertain to the drug substance travoprost and its drug product travoprost ophthalmic solution, 0.004% (Travatan™), the application can be recommended for APPROVAL. The sponsor has committed to provide the analytical methods and their validation studies by 15-MAR-01 for all methods, except the one for __________. In this case, the method validation package will be submitted as an NDA supplement by 01-OCT-01.

cc:
Orig. NDA 21-257
HFD-550/Division File
HFD-550/CSO/M.Puglisi
HFD-550/Chem/ A.Fenselau
HFD-550/TeamLdr./L.Ng
HFD-550/Pharm./Z.Chen
HFD-550/MO/L.Lim
HFD-830/Div.Dir.DNDCIII/C.-w.Chen

Allan Fenselau, Review Chemist, HFD-550
Linda Ng, Chemistry Team Leader, HFD-550