CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-670

CHEMISTRY REVIEW(S)
NDA 21-670

Vision Blue®
(trypsin blue ophthalmic solution) 0.06%

Dutch Ophthalmic Research Center,
International
(D.O.R.C International B.V.)

Yong-de Lu, Ph.D.

Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products

HFD-550
Chemistry Review Data Sheet

1. NDA  21-670

2. REVIEW #:  4

3. REVIEW DATE: 15-Dec-2004

4. REVIEWER:  Yong-de Lu, Ph.D.

5. PREVIOUS DOCUMENTS:

<table>
<thead>
<tr>
<th>Previous Documents</th>
<th>Document Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original</td>
<td>24-Oct-2003</td>
</tr>
<tr>
<td>Amendment</td>
<td>29-Jan-2004</td>
</tr>
<tr>
<td>Amendment</td>
<td>08-Mar-2004</td>
</tr>
<tr>
<td>Approvable letter</td>
<td>27-Apr-2004</td>
</tr>
<tr>
<td>Amendment</td>
<td>05-Apr-2004</td>
</tr>
<tr>
<td>Amendment</td>
<td>11-Jun-2004</td>
</tr>
<tr>
<td>Amendment</td>
<td>13-Aug-2004</td>
</tr>
<tr>
<td>Amendment</td>
<td>14-Oct-2004</td>
</tr>
<tr>
<td>Amendment</td>
<td>19-Nov-2004</td>
</tr>
<tr>
<td>Amendment</td>
<td>24-Nov-2004</td>
</tr>
<tr>
<td>Amendment</td>
<td>30-Nov-2004</td>
</tr>
<tr>
<td>Amendment</td>
<td>09-Dec-2004</td>
</tr>
<tr>
<td>Amendment</td>
<td>13-Dec-2004(e-mail)</td>
</tr>
</tbody>
</table>

6. SUBMISSION(S) BEING REVIEWED:

<table>
<thead>
<tr>
<th>Submission(s) Reviewed</th>
<th>Document Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

7. NAME & ADDRESS OF APPLICANT:

| Name: Dutch Ophthalmic Research Center, (D.O.R.C. International B.V.) |
|-----------------------------|------------------------------------------------|

International
Address: Scheijdelveweg 2
            3214 VN Zuidland
            The Netherlands
Representative: Fran Carleton, Operation Manager
               Dutch Ophthalmic USA
               One Litter River Road
               P. O. Box 968
               Kingston, NH 03848
               Tel: (603) 642-8468
               Fax: (603) 642-8465

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Vision Blue®
   b) Non-Proprietary Name (USAN): N/A
   c) Code Name/#: N/A
   d) Chem. Type/Submission Priority:
      • Chem. Type: 1
      • Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Tissue staining agent

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 0.06%,

13. ROUTE OF ADMINISTRATION: Injectable, Ophthalmic, 0.1 to 0.3 mL (6 to 18 µg) per injection

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (Special Products On-line Tracking System)
   ______SPOTS product – Form Completed
   ___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
3,3'-{(3,3'-dimethyl-4,4'-biphenylene)bis(azo))bis(5-amino-4-hydroxy-2,7-naphthalenedisulfonic acid) tetrassodium salts

C₃₄H₂₄N₆Na₄O₁₄S₄   MW: 960.82, [72-57-1]

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

<table>
<thead>
<tr>
<th>DMF #</th>
<th>TYPE</th>
<th>HOLDER</th>
<th>ITEM REFERENCED</th>
<th>CODE</th>
<th>STATUS</th>
<th>DATE REVIEW COMPLETED</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td></td>
<td></td>
<td>Trypan Blue,</td>
<td>1</td>
<td>Adequate</td>
<td>10/15/04</td>
<td>Only supports this NDA</td>
</tr>
</tbody>
</table>

1 Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

2 Adequate, Inadequate, or N/A (There is enough data in the NDA application, therefore the DMF did not need to be reviewed)

B. Other Documents:

<table>
<thead>
<tr>
<th>DOCUMENT</th>
<th>APPLICATION NUMBER</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND</td>
<td></td>
<td>Not filed</td>
</tr>
</tbody>
</table>

18. STATUS:
### CHEMISTRY REVIEW

Chemistry Review Data Sheet

<table>
<thead>
<tr>
<th>CONSULTS/ CMC RELATED REVIEWS</th>
<th>RECOMMENDATION</th>
<th>DATE</th>
<th>REVIEWER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biometrics</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EES</td>
<td>3 accepted</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 pending (drug product)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharm/Tox</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LNC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methods Validation</td>
<td>Will be Sent to DPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPDRA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EA</td>
<td>Claim for categorical exclusion was accepted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microbiology</td>
<td>Approval</td>
<td>10/01/04</td>
<td>Stephen E. Langille</td>
</tr>
</tbody>
</table>
The Chemistry Review for NDA 21-670

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint the application is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Trypan blue is a dye that was first used to visualize the capsulorhexis in eyes in 1997. In 1999 VisionBlue™ obtained CE approval as a medical device IIIa in Europe. Currently VisionBlue™ has been marketed in 30 countries.

was identified as the manufacturer of the drug substance and the documented DMF was filed to support this NDA. The cGMP inspection for facility has been completed by the Office of Compliance with an acceptable recommendation. The review of DMF was completed and found adequate to support the NDA.

The drug product is manufactured from trypan blue which is formulated with sodium chloride to obtain a solution of concentration of 0.06%. As part of the preparation, . The prepared solution is then filled into 2.25 ml syringe (0.5 ml/syringe) and the syringe is closed with a tip cap and stopper. The syringes are placed into film/paper pouches and

The drug product is manufactured by a contract firm located in The inspection is completed and acceptable by Office of Compliance.
Stability data of the drug product packed in syringes are not available at the time of submission, but evaluation of the stability data of the drug product packed in vials showed no significant change after storage under long-term conditions, indicating the dye solution was stable. An expiry period was proposed by the applicant.

B. Description of How the Drug Product is Intended to be Used

VisionBlue®, a tissue staining agent, is a sterile solution of trypan blue, 0.06%. VisionBlue® is intended for use as an aid in ophthalmic surgery on the front eye segment during cataract extraction. Specifically, VisioBlue® can provide contrast to aid visualization of the anterior lens capsule after it is injected into the anterior chamber of the eye.

VisionBlue® is packaged in 2.25 mL glass syringes that contain 0.5 mL fill of 0.06% solution for single dose use only.

The product should be stored at room temperature, protected from light.

C. Basis for Approvability or Not-Approval Recommendation

The cGMP inspection for the testing facility is accepted by Office of Compliance based on file review.

III. Administrative

A. Reviewer's Signature

Signed electronically in DFS

B. Endorsement Block

Signed electronically by Chemistry Team Leader in DFS

C. cc Block

Original NDA 21-670
HFD-550/Chem Reviewer/YLu
HFD-550/Chem Team Leader/LNg
HFD-550/MED/WChambers

HFD-550/CSO/LGorski
Withheld

6

page(s) of trade secret
and/or confidential commercial information

(b4)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Yong-De Lu
12/15/04 02:11:10 PM
CHEMIST

CMC review #4, approval

Linda Ng
12/15/04 02:16:22 PM
CHEMIST
NDA 21-670

Vision Blue®
(trypan blue ophthalmic solution) 0.06%

Dutch Ophthalmic Research Center,
International
(D.O.R.C International B.V.)

Yong-de Lu, Ph.D.

Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products

HFD-550
Chemistry Review Data Sheet

1. NDA 21-670

2. REVIEW #: 3

3. REVIEW DATE: 13-Dec-2004

4. REVIEWER: Yong-de Lu, Ph.D.

5. PREVIOUS DOCUMENTS:

<table>
<thead>
<tr>
<th>Previous Documents</th>
<th>Document Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original</td>
<td>24-Oct-2003</td>
</tr>
<tr>
<td>Amendment</td>
<td>29-Jan-2004</td>
</tr>
<tr>
<td>Amendment</td>
<td>08-Mar-2004</td>
</tr>
<tr>
<td>Approvable letter</td>
<td>27-Apr-2004</td>
</tr>
<tr>
<td>Amendment</td>
<td>05-Apr-2004</td>
</tr>
<tr>
<td>Amendment</td>
<td>11-Jun-2004</td>
</tr>
<tr>
<td>Amendment</td>
<td>13-Aug-2004</td>
</tr>
<tr>
<td>Amendment</td>
<td>14-Oct-2004</td>
</tr>
<tr>
<td>Amendment</td>
<td>19-Nov-2004</td>
</tr>
</tbody>
</table>

6. SUBMISSION(S) BEING REVIEWED:

<table>
<thead>
<tr>
<th>Submission(s) Reviewed</th>
<th>Document Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amendment</td>
<td>24-Nov-2004</td>
</tr>
<tr>
<td>Amendment</td>
<td>30-Nov-2004</td>
</tr>
<tr>
<td>Amendment</td>
<td>08-Dec-2004(e-mail)</td>
</tr>
<tr>
<td>Amendment</td>
<td>13-Dec-2004(e-mail)</td>
</tr>
</tbody>
</table>

7. NAME & ADDRESS OF APPLICANT:

Name: Dutch Ophthalmic Research Center,
International
(D.O.R.C. International B.V.)
8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Vision Blue®
   b) Non-Proprietary Name (USAN): N/A
   c) Code Name/#: N/A
   d) Chem. Type/Submission Priority:
      - Chem. Type: 1
      - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Tissue staining agent

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 0.06%,

13. ROUTE OF ADMINISTRATION: Injectable, Ophthalmic, 0.1 to 0.3 mL (6 to 18 µg) per injection

14. Rx/OTC DISPENSED: X Rx ___ OTC

15. SPOTS (Special Products On-line Tracking System)
   _____ SPOTS product – Form Completed
   ___ X ___ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
3,3’-[(3,3’-dimethyl-4,4’-biphenylene)bis(azo)]bis(5-amino-4-hydroxy-2,7-naphthalenedisulfonic acid) tetrasodium salts

C₃₄H₂₄N₆Na₄O₁₄S₄  MW: 960.82, [72-57-1]

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

<table>
<thead>
<tr>
<th>DMF #</th>
<th>TYPE</th>
<th>HOLDER</th>
<th>ITEM REFERENCED</th>
<th>CODE¹</th>
<th>STATUS²</th>
<th>DATE REVIEW COMPLETED</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>/</td>
<td>/</td>
<td>Trypan Blue.</td>
<td>1</td>
<td>Adequate</td>
<td>10/15/04</td>
<td>Only supports this NDA</td>
</tr>
</tbody>
</table>

¹ Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under “Comments”)

² Adequate, Inadequate, or N/A (There is enough data in the NDA application, therefore the DMF did not need to be reviewed)

B. Other Documents:

<table>
<thead>
<tr>
<th>DOCUMENT</th>
<th>APPLICATION NUMBER</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND</td>
<td></td>
<td>Not filed</td>
</tr>
</tbody>
</table>

18. STATUS:
<table>
<thead>
<tr>
<th>CONSULTS/CMC RELATED REVIEWS</th>
<th>RECOMMENDATION</th>
<th>DATE</th>
<th>REVIEWER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biometrics</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EES</td>
<td>3 accepted</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 pending (drug product)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharm/Tox</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LNC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methods Validation</td>
<td>Will be Sent to DPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPDRA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EA</td>
<td>Claim for categorical exclusion was accepted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microbiology</td>
<td>Approval</td>
<td>10/01/04</td>
<td>Stephen E. Langille</td>
</tr>
</tbody>
</table>
The Chemistry Review for NDA 21-670

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint the application is recommended for approachable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Trypan blue is a dye that was first used to visualize the capsulorhexis in eyes in 1997. In 1999 VisionBlue™ obtained CE approval as a medical device IIa in Europe. Currently VisionBlue™ has been marketed in 30 countries.

was identified as the manufacturer of the drug substance and the documented DMF was filed to support this NDA. The cGMP inspection for facility has been completed by the Office of Compliance with an acceptable recommendation. The review of DMF was completed and found adequate to support the NDA.

The drug product is manufactured from trypan blue which is formulated with sodium chloride to obtain a solution of concentration of 0.06%. As part of the preparation, The prepared solution is then filled into 2.25 ml syringe (0.5 ml/syringe) and the syringe is closed with a tip cap and stopper. The syringes are placed into film/paper pouches and

The drug product is manufactured by a contract firm located in The inspection is completed and acceptable by Office of Compliance.
Stability data of the drug product packed in syringes are not available at the time of submission, but evaluation of the stability data of the drug product packed in vials showed no significant change after storage under long-term conditions, indicating the dye solution was stable. A expiry period was proposed by the applicant.

B. Description of How the Drug Product is Intended to be Used

VisionBlue®, a tissue staining agent, is a sterile, solution of trypan blue, 0.06%. VisionBlue® is intended for use as an aid in ophthalmic surgery on the front eye segment during cataract extraction. Specifically, VisionBlue® can provide contrast to aid visualization of the anterior lens capsule after it is injected into the anterior chamber of the eye.

VisionBlue® is packaged in 2.25 mL glass syringes that contain 0.5 mL fill of 0.06% solution for single dose use only.

The product should be stored at room temperature, protected from light.

C. Basis for Approvability or Not-Approval Recommendation

Although study data for the 2.25 ml syringe system and the stability data for the drug product packed in the syringes were submitted and evaluated as adequate, as well as the specification for drug product has been finalized and supported by the release data and stability data. The cGMP inspection of one testing facility, is still pending. That is the only basis for the approvable recommendation.

III. Administrative

A. Reviewer’s Signature

Signed electronically in DFS

B. Endorsement Block

Signed electronically by Chemistry Team Leader in DFS

C. cc Block

Original NDA 21-670
HFD-550/Chem Team Leader/LNg
HFD-550/MED/WChambers
HFD-550/Chem Reviewer/YLu
HFD-550/CSO/LGorski
Withheld

14

page(s) of trade secret
and/or confidential commercial information

(b4)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Yong-De Lu
12/13/04 04:22:17 PM
CHEMIST
CMC #3 review

Linda Ng
12/13/04 04:26:01 PM
CHEMIST
NDA 21-670

Vision Blue®
(trypsin blue ophthalmic solution) 0.06%

Dutch Ophthalmic Research Center,
International
(D.O.R.C International B.V.)

Yong-de Lu, Ph.D.
Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products
HFD-550
Chemistry Review Data Sheet

1. NDA 21-670

2. REVIEW #: 2

3. REVIEW DATE: 01-Dec-2004

4. REVIEWER: Yong-de Lu, Ph.D.

5. PREVIOUS DOCUMENTS:

<table>
<thead>
<tr>
<th>Previous Documents</th>
<th>Document Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original</td>
<td>24-Oct-2003</td>
</tr>
<tr>
<td>Amendment</td>
<td>29-Jan-2004</td>
</tr>
<tr>
<td>Amendment</td>
<td>08-Mar-2004</td>
</tr>
<tr>
<td>Approvable letter</td>
<td>27-Apr-2004</td>
</tr>
</tbody>
</table>

6. SUBMISSION(S) BEING REVIEWED:

<table>
<thead>
<tr>
<th>Submission(s) Reviewed</th>
<th>Document Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amendment</td>
<td>05-Apr-2004</td>
</tr>
<tr>
<td>Amendment</td>
<td>11-Jun-2004</td>
</tr>
<tr>
<td>Amendment</td>
<td>13-Aug-2004</td>
</tr>
<tr>
<td>Amendment</td>
<td>14-Oct-2004</td>
</tr>
<tr>
<td>Amendment</td>
<td>19-Nov-2004</td>
</tr>
</tbody>
</table>

7. NAME & ADDRESS OF APPLICANT:

Name: Dutch Ophthalmic Research Center, International
(D.O.R.C. International B.V.)
8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Vision Blue®
b) Non-Proprietary Name (USAN): N/A
c) Code Name/#: N/A
d) Chem. Type/Submission Priority:
   • Chem. Type: 1
   • Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Tissue staining agent

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 0.06%.

13. ROUTE OF ADMINISTRATION: Injectable, Ophthalmic, 0.1 to 0.3 mL (6 to 18 μg) per injection

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (Special Products On-line Tracking System)
   _______SPOTS product – Form Completed
   ___X___ Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

\[
\begin{align*}
\text{NaO}_3\text{S} & \quad \text{NH}_2 \\
\text{SO}_3\text{Na} & \quad \text{CH}_3 \\
\text{H}_2\text{N} & \quad \text{N} = \text{N} \\
\text{C}_3\text{H}_4\text{N}_6\text{Na}_4\text{O}_{14}\text{S}_4 & \quad \text{SO}_3\text{Na}
\end{align*}
\]

3,3'\-[(3,3'-dimethyl-4,4'-biphenylene)bis(azo)]bis(5-amino-4-hydroxy-2,7-
naphthalenedisulfonic acid) tetrasodium salts

\[\text{C}_3\text{H}_4\text{N}_6\text{Na}_4\text{O}_{14}\text{S}_4 \quad \text{MW: 960.82, [72-57-1]}\]

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

<table>
<thead>
<tr>
<th>DMF #</th>
<th>TYPE</th>
<th>HOLDER</th>
<th>ITEM REFERENCED</th>
<th>CODE</th>
<th>STATUS</th>
<th>DATE REVIEW COMPLETED</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td></td>
<td></td>
<td>Trypan Blue,</td>
<td>1</td>
<td>Adequate</td>
<td>10/15/04</td>
<td>Only supports this NDA</td>
</tr>
</tbody>
</table>
### CHEMISTRY REVIEW
Chemistry Review Data Sheet

18. STATUS:

<table>
<thead>
<tr>
<th>CONSULTS/CMC RELATED REVIEWS</th>
<th>RECOMMENDATION</th>
<th>DATE</th>
<th>REVIEWER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biometrics</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EES</td>
<td>3 accepted</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 pending (drug product)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharm/Tox</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LNC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methods Validation</td>
<td>Will be Sent to DPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPDRA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EA</td>
<td>Claim for categorical exclusion was accepted</td>
<td>10/01/04</td>
<td>Stephen E. Langille</td>
</tr>
<tr>
<td>Microbiology</td>
<td>Approval</td>
<td>10/01/04</td>
<td>Stephen E. Langille</td>
</tr>
</tbody>
</table>

APPEARS THIS WAY ON ORIGINAL
The Chemistry Review for NDA 21-670

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the data submitted to this NDA are insufficient to support the approval action. Therefore, the application is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Trypan blue is a dye that was first used to visualize the capsulorhexis in eyes in 1997. In 1999 VisionBlue™ obtained CE approval as a medical device IIa in Europe. Currently VisionBlue™ has been marketed in 30 countries.

Initially the applicant did not provide appropriate CMC information for the drug substance trypan blue. No DMF was filed for the drug substance trypan blue. Later the applicant was identified as the manufacturer of the drug substance and the documented DMF was filed to support this NDA. The cGMP inspection for the facility has been completed by the Office of Compliance with an acceptable recommendation. The review of DMF was completed and found adequate to support the NDA.

The drug product is manufactured from trypan blue which is formulated with sodium chloride to obtain a solution of concentration of 0.06%. As part of the preparation, the prepared solution is then filled into 2.25 ml syringe (0.5 ml/syringe) and the syringe is closed with a tip cap and stopper. The syringes are placed into film/paper pouches and...
The drug product is manufactured by a contract firm located in. The inspection is completed and acceptable by Office of Compliance.

Stability data of the drug product packed in syringes are not available at the time of submission, but evaluation of the stability data of the drug product packed in vials showed no significant change after storage under long-term conditions, indicating the molecular form of the dye solution was stable. A expiry period was proposed by the applicant.

B. Description of How the Drug Product is Intended to be Used

VisionBlue®, a tissue staining agent, is a sterile solution of trypan blue, 0.06%. VisionBlue® is intended for use as an aid in ophthalmic surgery on the front eye segment during cataract extraction. Specifically, VisionBlue® can provide contrast to aid visualization of the anterior lens capsule after it is injected into the anterior chamber of the eye.

VisionBlue® is packaged in 2.25 mL glass syringes that contain 0.5 mL fill of 0.06% solution for single dose use only.

The product should be stored at room temperature, protected from light.

C. Basis for Approvability or Not-Approval Recommendation

The deficiencies on the quality control information for the drug product is the basis of the approvability for this NDA. For example, study data for the 2.25 ml syringe system and the stability data for the drug product packed in the syringes are still not available. Even more, the specification for drug product has not been finalized and supported by the release data and stability data. In addition, the cGMP inspection of one testing facility, is still pending.

III. Administrative

A. Reviewer's Signature

Signed electronically in DFS

B. Endorsement Block

Signed electronically by Chemistry Team Leader in DFS

C. cc Block
Withheld

27

page(s) of trade secret and/or confidential commercial information

(b4)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Yong-De Lu
12/1/04 04:47:45 PM
CHEMIST
CMC second cycle review, approvable.

Linda Ng
12/1/04 05:09:29 PM
CHEMIST
No action needed by PM
NDA 21-670

Vision Blue®
(trypsin blue ophthalmic solution) 0.06%

Dutch Ophthalmic Research Center,
International
(D.O.R.C International B.V.)

Yong-de Lu, Ph.D.

Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products

HFD-550
# Table of Contents

Chemistry Review Data Sheet Page 03

Executive Summary

I. Recommendations 07

II. Summary of Chemistry Assessments 07

III. Administrative 09

Chemistry Assessment

I. Drug Substance
   1. Description and Characterization 10
   2. Manufacturer 11
   3. Synthesis / Method of Manufacture 11
   4. Process control 12
   5. Reference Standard 12
   6. Specification / Analytical Methods 13
   7. Container / Closure System 15
   8. Stability 15

II. Drug Product
   1. Components/Composition 16
   2. Specifications & Methods for Drug Product Ingredients 16
   3. Manufacturer 17
   4. Methods of Manufacturing & Packaging 17
   5. Specification & Methods 18
   6. Container/Closure System 18
   7. Microbiology 20
   8. Drug product Stability 20

III. Investigational Formulation 23

IV. Environmental Assessment 23

V. Method Validation 23

VI. Labeling 23

VII. Establishment Inspection 24

VIII. Draft Deficiency Letter 24
Chemistry Review Data Sheet

1. NDA 21-670
2. REVIEW #: 1
3. REVIEW DATE: 06-Apr-2004
4. REVIEWER: Yong-de Lu, Ph.D.
5. PREVIOUS DOCUMENTS:

   Previous Documents                      Document Date
   N/A

6. SUBMISSION(S) BEING REVIEWED:

   Submission(s) Reviewed                   Document Date
   Original                                 24-Oct-2003
   Amendment                                29-Jan-2004
   Amendment                                08-Mar-2004

7. NAME & ADDRESS OF APPLICANT:

   Name: Dutch Ophthalmic Research Center,
   International (D.O.R.C. International B.V.)
   Address: Scheijdelveweg 2
             3214 VN Zuidland
             The Netherlands
   Representative: Fran Carleton, Operation Manager
                 Dutch Ophthalmic USA
                 One Litter River Road
                 P. O. Box 968
                 Kingston, NH 03848
                 Tel: (603) 642-8468
                 Fax: (603) 642-8465
8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Vision Blue®
   b) Non-Proprietary Name (USAN): N/A
   c) Code Name/#: N/A
   d) Chem. Type/Submission Priority:
      • Chem. Type: 1
      • Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: A tissue staining agent

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 0.06%,

13. ROUTE OF ADMINISTRATION: Injectable, Ophthalmic, 0.1 to 0.3 mL (6 to 18 µg) per injection

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (Special Products On-line Tracking System)
   __ ___ SPOTS product – Form Completed
   _X_ Not a SPOTS product

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

\[
\text{O}_3\text{S} \quad \text{H}_3\text{C} \quad \text{CH}_3 \quad \text{H}_2\text{N} \quad \text{O}_3\text{S} \\
\text{N=N} \quad \text{N=N} \quad \text{N=N} \quad \text{N=N} \quad \text{N=N} \\
\text{OH} \quad \text{H}_3\text{C} \quad \text{CH}_3 \quad \text{H}_2\text{N} \quad \text{O}_3\text{S} \\
\text{SO}_3 \quad \text{SO}_3 \quad \text{SO}_3 \quad \text{SO}_3 \quad \text{SO}_3 \\
\text{4 Na}
\]
CHEMISTRY REVIEW

Chemistry Review Data Sheet

3,3'-(3,3'-dimethyl-4,4'-biphenylene)bis(azo)]bis(5-amino-4-hydroxy-2,7-
naphthalenedisulfonic acid) tetra sodium salts

C_{34}H_{24}N_6Na_4O_{14}S_4   MW: 960.82, [72-57-1]

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

<table>
<thead>
<tr>
<th>DMF #</th>
<th>TYPE</th>
<th>HOLDER</th>
<th>ITEM REFERENCED</th>
<th>CODE¹</th>
<th>STATUS²</th>
<th>DATE REVIEW COMPLETED</th>
<th>COMMENTS</th>
</tr>
</thead>
</table>

¹ Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under “Comments”)

² Adequate, Inadequate, or N/A (There is enough data in the NDA application, therefore the DMF did not need to be reviewed)

B. Other Documents:

<table>
<thead>
<tr>
<th>DOCUMENT</th>
<th>APPLICATION NUMBER</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND</td>
<td></td>
<td>Not filed</td>
</tr>
</tbody>
</table>

18. STATUS:

<table>
<thead>
<tr>
<th>CONSULTS/CMC RELATED REVIEWS</th>
<th>RECOMMENDATION</th>
<th>DATE</th>
<th>REVIEWER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biometrics</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EES</td>
<td>1 withhold (drug substance)</td>
<td>1 pending (drug product)</td>
<td></td>
</tr>
<tr>
<td>Pharm/Tox</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LNC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methods Validation</td>
<td>Will be Sent to DPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPDRA</td>
<td>Consult sent</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 5 -
<table>
<thead>
<tr>
<th>EA</th>
<th>Claim for categorical exclusion was accepted</th>
<th>Yong-de Lu</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbiology</td>
<td>Approvable</td>
<td>04/05/04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paul Stinavage</td>
</tr>
</tbody>
</table>
The Chemistry Review for NDA 21-670

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the data submitted to this NDA are not adequate to support approval. Therefore, the application is recommended for an approvable action.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Trypan blue is a dye that was first used to visualize the capsulorhexis in eyes in 1997. In 1999 VisionBlue™ obtained CE approval as a medical device IIa in Europe. Currently VisionBlue™ has been marketed in 30 countries.

The applicant did not provide appropriate CMC information for trypan blue drug substance. No DMF was filed for trypan blue. Applicant cited one page copy of trypan blue from Merck Index and indicated the purity of trypan blue is determined by — The manufacturing site of trypan blue — was identified by Office of Compliance as a Laboratory Chemicals and Apparatus Supplier not involved in any manufacturing activity. Therefore, the cGMP inspection has been withheld. Currently, the applicant claimed that — is the manufacturer of trypan blue, but that claim is denied by —. It seems that applicant purchased trypan blue drug substance from —. Recently — disclosed that the original manufacturer of vision blue is —. The verification of the this site is in process.

The drug product is manufactured from trypan blue — which is formulated with sodium chloride to obtain a concentration of 0.06%. As part of the preparation, —. The prepared solution is
then filled into _ and the _ is closed with a stopper and cap (seal). The sealed _ are placed into film/paper pouches and _ 

The drug product is manufactured by a contract firm _ located in _. The inspection is pending.

Primary stability data of _ is evaluated under a simulated accelerated conditions. _ analysis showed no significant change after _ storage, indicating the molecular form of the dye solution was stable. A _ expiry period was proposed by the applicant. The primary stability study is not acceptable, because the simulated accelerated conditions need clarification and the _ method is not a stability-indicating method.

B. Description of How the Drug Product is Intended to be Used

VisionBlue®, a tissue staining agent, is a sterile _ solution of trypan blue, 0.06%. VisionBlue® is intended for use as an aid in ophthalmic surgery on the front eye segment during cataract extraction. Specifically, VisionBlue® can provide contrast to aid visualization of the anterior lens capsule after it is injected into the anterior chamber of the eye.

VisionBlue® is packaged in _ packages that contain 0.5 mL fill of 0.06% solution. _ are for single use only.

Currently, the applicant intends to replace the _ with _. syringes.

The product should be stored at room temperature, protected from _ light.

C. Basis for Approvability or Not-Approval Recommendation

The lack of manufacturing and quality control information for the drug substance, trypan blue is the basis for approvability of this NDA. Particularly, the original manufacturing site of the drug substance has not been finally identified so far. Therefore, cGMP inspection for the drug substance was withheld by Office of Compliance.

No written responses to the Agency's comments on the drug product, VisionBlue™, have been received since a facsimile communication to the applicant on 12/08/2003.

A Microbiology consult review recommended an approvable action on 04/05/04.
III. Administrative

A. Reviewer’s Signature

Signed electronically in DFS

B. Endorsement Block

Signed electronically by Chemistry Team Leader in DFS

C. cc Block

Original NDA 21-670
HFD-550/Chem Team Leader/LNg
HFD-550/MED/WChambers

HFD-550/Chem Reviewer/YLu
HFD-550/CSO/NHallenon
Withheld

17

page(s) of trade secret
and/or confidential commercial information

(b4)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Yong-De Lu
4/16/04 03:36:39 PM
CHEMIST

Linda Ng
4/16/04 04:34:57 PM
CHEMIST