

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-670**

**CHEMISTRY REVIEW(S)**

**CHEMISTRY REVIEW**

Chemistry Review Data Sheet

**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

## Chemistry Review Data Sheet

# 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:

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

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
None	

7. NAME & ADDRESS OF APPLICANT:

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

## CHEMISTRY REVIEW

### Chemistry Review Data Sheet

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: I  
• 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:  Rx  OTC

15. SPOTS (Special Products On-line Tracking System)

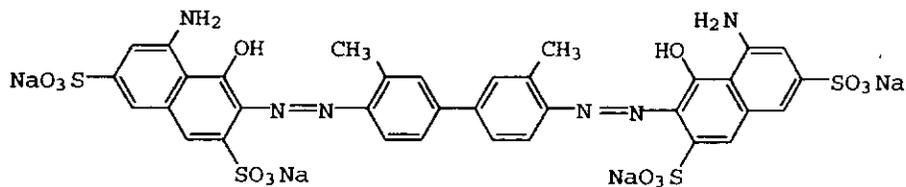
SPOTS product – Form Completed

Not a SPOTS product

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

# 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) tetrasodium salts

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

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
II	/	/	Trypan Blue,	1	Adequate	10/15/04	Only supports this NDA

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type I 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")

<sup>2</sup> 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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND		Not filed

### 18. STATUS:

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

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

APPEARS THIS WAY  
ON ORIGINAL

## CHEMISTRY REVIEW

### Executive Summary Section

# 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 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.

## CHEMISTRY REVIEW

### Executive Summary Section

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

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 Team Leader/LNg  
HFD-550/MED/WChambers

HFD-550/Chem Reviewer/YLu  
HFD-550/CSO/LGorski

**Withheld**

**6**

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/s/  
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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

**CHEMISTRY REVIEW**

Chemistry Review Data Sheet

**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

## Chemistry Review Data Sheet

### 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:

Previous Documents

Document Date

Original	24-Oct-2003
Amendment	29-Jan-2004
Amendment	08-Mar-2004
Approvable letter	27-Apr-2004
Amendment	05-Apr-2004
Amendment	11-Jun -2004
Amendment	13-Aug-2004
Amendment	14-Oct-2004
Amendment	19-Nov-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Amendment	24-Nov-2004
Amendment	30-Nov-2004
Amendment	08-Dec -2004(e-mail)
Amendment	13-Dec -2004(e-mail)

7. NAME & ADDRESS OF APPLICANT:

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

## CHEMISTRY REVIEW

### Chemistry Review Data Sheet

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: I  
• 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:  Rx  OTC

15. SPOTS (Special Products On-line Tracking System)

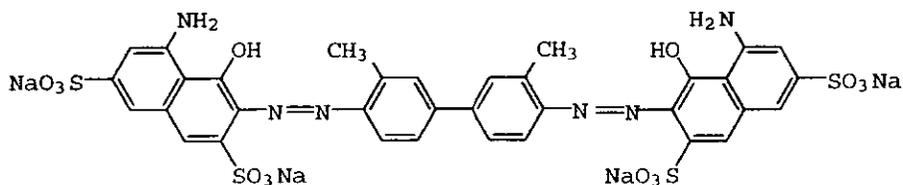
SPOTS product – Form Completed

Not a SPOTS product

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

# 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) tetrasodium salts

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

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
II	/	/	Trypan Blue,	1	Adequate	10/15/04	Only supports this NDA

<sup>1</sup> Action codes for DMF Table:

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Other codes indicate why the DMF was not reviewed, as follows:

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4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> 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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND		Not filed

### 18. STATUS:

**CHEMISTRY REVIEW**

## Chemistry Review Data Sheet

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

**APPEARS THIS WAY  
ON ORIGINAL**

## CHEMISTRY REVIEW

### Executive Summary Section

# 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 **approvable**.

#### 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.

## CHEMISTRY REVIEW

### Executive Summary Section

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, VisioBlue® can provides 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**

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

Linda Ng  
12/13/04 04:26:01 PM  
CHEMIST

**CHEMISTRY REVIEW**

Chemistry Review Data Sheet

**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

## Chemistry Review Data Sheet

# 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:

<u>Previous Documents</u>	<u>Document Date</u>
Original	24-Oct-2003
Amendment	29-Jan-2004
Amendment	08-Mar-2004
Approvable letter	27-Apr-2004

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	05-Apr-2004
Amendment	11-Jun -2004
Amendment	13-Aug-2004
Amendment	14-Oct-2004
Amendment	19-Nov-2004

7. NAME & ADDRESS OF APPLICANT:

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

## CHEMISTRY REVIEW

### Chemistry Review Data Sheet

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:  Rx  OTC

#### 15. SPOTS (Special Products On-line Tracking System)

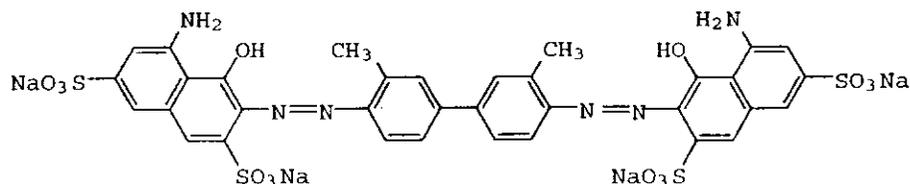
SPOTS product - Form Completed

Not a SPOTS product

## CHEMISTRY REVIEW

### Chemistry Review Data Sheet

**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

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

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DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
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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")

<sup>2</sup> 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:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND		Not filed

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

### 18. STATUS:

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

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 **approvable**.

#### 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 \_\_\_\_\_ 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 \_\_\_\_\_

## CHEMISTRY REVIEW

### Executive Summary Section

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, VisioBlue® can provides 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

**CHEMISTRY REVIEW**

Executive Summary Section

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

HFD-550/Chem Reviewer/YLu  
HFD-550/CSO/LGorski

**APPEARS THIS WAY  
ON ORIGINAL**

**Withheld**

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/s/

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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®  
(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**

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# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

# 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  
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One Litter River Road  
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# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

### 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: I  
• 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

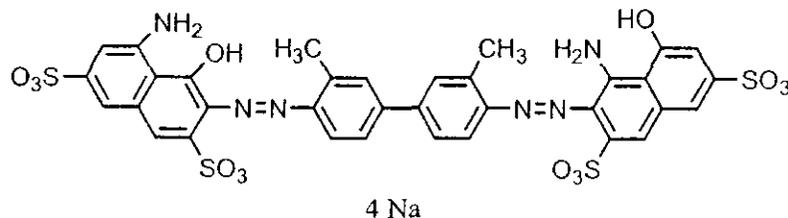
14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (Special Products On-line Tracking System)

SPOTS product – Form Completed

Not a SPOTS product

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



# 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:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
							None reference

<sup>1</sup> 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")

<sup>2</sup> 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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND		Not filed

### 18. STATUS:

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

**CHEMISTRY REVIEW**

Chemistry Review Data Sheet

EA	Claim for categorical exclusion was accepted		Yong-de Lu
Microbiology	Approvable	04/05/04	Paul Stinavage

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 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,

r. The prepared solution is

## CHEMISTRY REVIEW

### Executive Summary Section

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, VisioBlue® can provides contrast to aid visualization of the anterior lens capsule after it is injected into the anterior chamber of the eye.

VisionBlue® is packaged in \_\_\_\_\_ s 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.

**CHEMISTRY REVIEW**

Executive Summary Section

**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

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**Withheld**

**17**

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

**(b4)**

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/  
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Yong-De Lu  
4/16/04 03:36:39 PM  
CHEMIST

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