CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-278

CHEMISTRY REVIEW(S)

CHEMISTRY REVIEW

NDA 22-278

MembraneBlue™
(trypan blue ophthalmic solution) 0.15%

Dutch Ophthalmic Research Center
International b.v.
(D.O.R.C International b.v.)

Lin Qi, Ph.D.
Division of Anti-Infective and Ophthalmology Product

Table of Contents

Chemistry Review Data Sheet 3

3,3'-[(3.3'-dimethyl-4,4'-biphenylene)bis(azo)]bis(5-amino-4-hydroxy-2,7-naphthalenedisulfonic acid) tetra sodium salts 5

The Executive Summary 7

I. Recommendations 7

A. Recommendation and Conclusion on Approvability 7

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 7

II. Summary of Chemistry Assessments 7

A. Description of the Drug Product(s) and Drug Substance(s) 7

B. Description of How the Drug Product is Intended to be Used 8

C. Basis for Approvability or Not-Approval Recommendation 8

III. Administrative 8

Reviewer's Signature 8

Chemistry Review Data Sheet

1. NDA 22-278

2. REVIEW #: 2

3. REVIEW DATE: Jan 6, 2009

4. REVIEWER: Lin Qi

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	Oct 1, 2007
Amendment	Dec 6, 2007
Amendment	Apr 14, 2008
Amendment	June 10, 2008

7. NAME & ADDRESS OF APPLICANT:

Name: D.O.R.C. International b.v.

Address: Scheijdelveweg 2
3214 VN Zuidland
The Neitherlands

Chemistry Review Data Sheet

Representative: Dutch Ophthalmic USA
One Little River Road, Kingston NH 03484
Telephone: 603-642-8486
Fax: 603-642-8465

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: MembraneBlue
b) Non-Proprietary Name (USAN): trypan blue ophthalmic solution
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 5
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: selectively staining epiretinal membranes during ophthalmic surgical vitrectomy procedures

11. DOSAGE FORM: ophthalmic solution 0.5 mL

12. STRENGTH/POTENCY: 0.15%

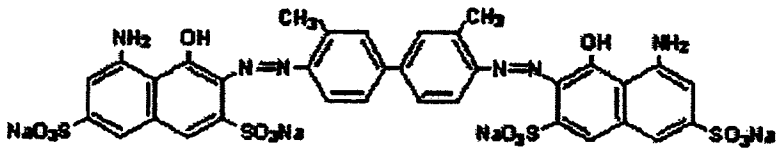
13. ROUTE OF ADMINISTRATION: intraocular injection

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) 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[1]	STATUS	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	Drug Substance	1	Adequate	03/06/2008	
[redacted]	III	BD Pharmaceutical Systems	BD [redacted]	4			
[redacted]	III	[redacted]	[redacted]	4			

b(4)

[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 application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-670	Trypan blue ophthalmic solution 0.06%, Approved

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	10/28/2008	Sharon Thoma
Pharm/Tox			
Biopharm			
LNC			
Methods Validation			
OPDRA			
EA			
Microbiology	Acceptable	8/5/2008	Stephen Langille

The Chemistry Review for NDA 22-278

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for approval based on product quality assessment.

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, the drug substance in MembraneBlue 0.15%, is ——— by ——— ——————— DMF ——— is authorized to be referenced for information regarding the ——— trypan blue. Reviews of DMF # ——— were completed and the DMF was noted adequate to support the current NDA. b(4)

The formulation of MembraneBlue 0.15% is similar to VisionBlue 0.06%, which was submitted by the same applicant and approved in June 2004. The only difference is an increased trypan blue concentration from 0.06% to 0.15% for MembraneBlue. Each mL of MembraneBlue 0.15% contains 1.5 mg trypan blue, 1.9 mg sodium mono-hydrogen orthophosphate ($Na_2HPO_4 \cdot 2H_2O$), 0.3 mg sodium di-hydrogen orthophosphate ($NaH_2PO_4 \cdot 2H_2O$), 8.2 mg sodium chloride (NaCl), and water for injection. The pH is 7.3 - 7.6. The osmolality is 257-314 mOsm/kg. MembraneBlue is filled in glass syringes to a volume of 0.5 mL.

The drug product is manufactured by a contract firm, ——————— located in ——————— The drug product is manufactured from ——————— ——— and a ——————— to obtain a 0.15% solution. The ——————— is supplied by ——— ——————— in ——————— b(4)

During drug product manufacturing process, the pH of the solution is verified and the solution is ——————— ——— . The prepared solution is then filled into a single-use Luer Lok 2.25 ml glass syringe (——— ml/syringe) and the syringe is closed with a tip cap and stopper. b(4)

The solution is [redacted] sterilized. The syringes are then placed into [redacted] pouches and the outside surface of the syringes is [redacted] sterilized. b(4)

A two year expiry dating period was proposed for this product when stored at 15-25°C (59-77°F) and protected from direct sunlight. Stability data was available on one batch of MembraneBlue 0.15% up to 3 months at long-term and accelerated conditions. Supporting stability data was available on three batches of VisionBlue 0.06% up to 26 months.

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

MembraneBlue is indicated for use as an aid in ophthalmic surgery by staining the epiretinal membranes during ophthalmic surgical vitrectomy procedures, facilitating removal of the tissue [redacted]. Staining the membranes will facilitate the surgical treatment and prevent incomplete peeling of the membrane. Trypan Blue is not absorbed in a viable cell, but traverses the membrane in a dead cell. Therefore only the membranes are stained in contrast to the retina. The excess of Trypan Blue is washed out of the eye using the common irrigation port and an additional aspirator. The stained membranes are removed from the eye, therefore the amount of Trypan Blue left in the patient after surgery is minimal. b(4)

The actual dosage of MembraneBlue is determined by the ophthalmic surgeon and will be in normal use between 0.3 and 0.5 mL.

C. Basis for Approvability or Not-Approval Recommendation

This application is recommended for approval because the remaining issues from review #1 were resolved:

- The microbiological processes and process controls were evaluated and recommended for approval in the product quality microbiological review by Dr. Stephen Langille dated Aug 5, 2008.
- The facilities were found acceptable in [redacted] as shown in the attached establishment evaluation report. b(4)

III. Administrative

Reviewer's Signature: {Signed and dated electronically in DFS}

Lin Qi, Ph.D.

Review Chemist — Date

Norman Schmuff, Ph.D.

Branch Chief — Date

2 Page(s) Withheld

√ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Lin Qi
1/7/2009 09:53:02 AM
CHEMIST

Norman Schmuff
1/7/2009 04:30:17 PM
CHEMIST

CHEMISTRY REVIEW

NDA 22-278

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(trypan blue ophthalmic solution) 0.15%

Dutch Ophthalmic Research Center
International b.v.
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Table of Contents

Table of Contents 2

Chemistry Review Data Sheet 3

The Executive Summary 7

I. Recommendations 7

A. Recommendation and Conclusion on Approvability 7

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 7

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A. Description of the Drug Product(s) and Drug Substance(s) 7

B. Description of How the Drug Product is Intended to be Used 8

C. Basis for Approvability or Not-Approval Recommendation 8

III. Administrative 9

A. Reviewer's Signature 9

B. Endorsement Block 9

C. CC Block 9

Chemistry Assessment 10

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data 10

S DRUG SUBSTANCE [Name, Manufacturer] 10

P DRUG PRODUCT [Name, Dosage form] 11

A APPENDICES 48

R REGIONAL INFORMATION 48

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 48

A. Labeling & Package Insert 48

B. Environmental Assessment Or Claim Of Categorical Exclusion 48

III. List Of Deficiencies To Be Communicated 48

Chemistry Review Data Sheet

1. NDA 22-278

2. REVIEW #: 1

3. REVIEW DATE: July 9, 2008

4. REVIEWER: Lin Qi

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	Oct 1, 2007
Amendment	Dec 6, 2007
Amendment	Apr 14, 2008
Amendment	June 10, 2008

7. NAME & ADDRESS OF APPLICANT:

Name: D.O.R.C. International b.v.

Address: Scheijdelveweg 2
3214 VN Zuidland
The Neitherlands

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Representative: Dutch Ophthalmic USA
One Little River Road, Kingston NH 03484
Telephone: 603-642-8486
Fax: 603-642-8465

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a) Proprietary Name: MembraneBlue
b) Non-Proprietary Name (USAN): trypan blue ophthalmic solution
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: selectively staining epiretinal membranes during ophthalmic surgical vitrectomy procedures

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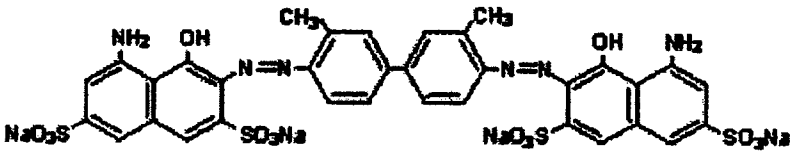

3,3'-[(3.3'-dimethyl-4,4'-biphenylene)bis(azo)]bis(5-amino-4-hydroxy-2,7-naphthalenedisulfonic acid) tetra sodium salts

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18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Pending		Sharon Thoma
Pharm/Tox			
Biopharm			
LNC			
Methods Validation			
OPDRA			
EA			
Microbiology	Pending		Stephen Langille

The Chemistry Review for NDA 22-278

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the perspective of quality review, this application is recommended as approvable pending satisfactory recommendations from establishment evaluation and microbiological review.

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, the drug substance in MembraneBlue 0.15%, is ——— by ——— ——————— DMF —— is authorized to be referenced for information regarding the ——— trypan blue. Reviews of DMF # —— were completed and the DMF was noted adequate to support the current NDA. b(4)

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syringe (——— ml/syringe) and the syringe is closed with a tip cap and stopper. The solution is ——— sterilized. The syringes are then placed into ——— pouches and the outside surface of the syringes is ——— sterilized. b(4)

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

MembraneBlue is indicated for use as an aid in ophthalmic surgery by staining the epiretinal membranes during ophthalmic surgical vitrectomy procedures, facilitating removal of the tissue ——— Staining the membranes will facilitate the surgical treatment and prevent incomplete peeling of the membrane. Trypan Blue is not absorbed in a viable cell, but traverses the membrane in a dead cell. Therefore only the membranes are stained in contrast to the retina. The excess of Trypan Blue is washed out of the eye using the common irrigation port and an additional aspirator. The stained membranes are removed from the eye, therefore the amount of Trypan Blue left in the patient after surgery is minimal. b(4)

The actual dosage of MembraneBlue is determined by the ophthalmic surgeon and will be in normal use between 0.3 and 0.5 mL.

C. Basis for Approvability or Not-Approval Recommendation

The formulation of MembraneBlue 0.15% is similar to VisionBlue 0.06%, which was submitted by the same applicant and approved in June 2004. The only difference is an increased trypan blue concentration from 0.06% to 0.15% for MembraneBlue. The drug product specification and container closure systems are same as those for VisionBlue. During the quality review process, the following missing information was provided upon request:

- Acceptance tests for the ———
- The study results of the drug product stability study performed according to the protocol ——— described in appendix Q. b(4)
- The study results of the "Extractable Study of Tipcap and Stopper of the BD — 2.25 ml syringe system (MembraneBlue) using HPLC" performed according to the protocol ——— described in appendix P.
- The analytical procedure and method validation for HPLC analysis for trypan blue content and for impurities
- A representative chromatogram
- Batch analysis data
- A sample of the packaged product

- A claim for categorical exclusion under 21 CFR 25.30-31 or an environmental assessment under 21 CFR 25.40.
- 6 months stability data on MembraneBlue 0.15% batch 33606
- Supporting stability results from VisionBlue 0.06%
- ———

b(4)

Analytical procedures and method validation results are acceptable. The manufacturing processes and process controls for MembraneBlue are similar to that for VisionBlue, and the only revised step, "mixing and ——— ", was validated using one batch of MembraneBlue. Complete validation results will be evaluated for establishment evaluation. The final establishment evaluation results are pending the applicant's satisfactory responses to the FDA-483. b(4)

The microbiological processes and process controls are evaluated in the product quality microbiological review by Dr. Stephen Langille.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

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_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Lin Qi
7/21/2008 10:17:30 AM
CHEMIST

Norman Schmuff
7/23/2008 10:19:59 AM
CHEMIST