# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-770**

# CHEMISTRY REVIEW(S)

# NDA 21-770

# Brimonidine Purite® Ophthalmic Solution 0.1%

## Allergan, Inc.

**Libaniel Rodriguez, Ph.D.**
**Division of Anti-infective and Ophthalmology Products**

**HFD-520**

# Table of Contents

# Chemistry Review Data Sheet

1. NDA 21-770

2. REVIEW #: 2

3. REVIEW DATE: 29-JUL-2005

4. REVIEWER: Libaniel Rodriguez

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| IND 32-292 | 31-OCT-1988 |
| NDA 20-613 | 31-AUG-1995 |
| NDA 21-262 | 29-JUN-2000 |
| Original NDA 21-770 | 27-MAY-2004 |
| BC | 15-JUL-2004 |
| BC | 17-SEP-2004 |
| BC | 17-MAR-2005 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| AZ | 27-JUN-2005 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | Allergan, Inc |
| Address: | 2525 Dupont Drive<br>P.O. Box 19534<br>Irvine, CA 92623-9534 |
| Representative: | Lewis Gryziewicz |
| Telephone: | 714 246 4500 |

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Brimonidine Tartrate Ophthalmis Solution 0.1%
c) Code Name/# (ONDC only): AGN 190342
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Alpha 2 agonist

11. DOSAGE FORM: Ophthalmic Solution

12. STRENGTH/POTENCY: 0.1%

13. ROUTE OF ADMINISTRATION: Topical (one drop three times per day per eye)

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

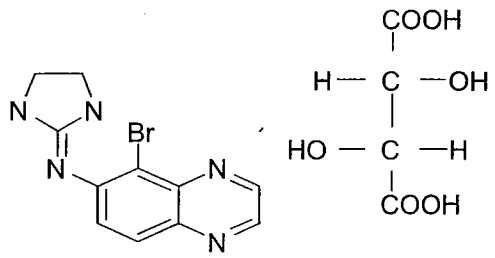
___X___Not a SPOTS product

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

Brimonidine tartrate, (1) 6-Quinoxaline, 5-bromo-*N*-(4,5-dihydro-1 *H*-imidazol-2-yl)-, [*S*-(R*R*)]-2-3-dihydroxybutanedioate (1:1)

(2) 5-Bromo-6-(2-imidazolin-2-ylamino)quinoxaline D-tartrate (1: 1)
$C_{11}H_{10}BrN_5 \bullet C_4H_6O_6$. MW 442.22. CAS Registry Number 79570-19-7.

**MOLECULAR STRUCTURE:**



Brimonidine Tartrate
(AGN 190342-LF)

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| [redacted] | III | [redacted] | [redacted] | 3 | Adequate | 11-JAN-1996 | No updates or changes since the first submission |
| | I | | | 2 | | | |
| | I | | | 2 | | | |

[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 |
|---|---|---|
| | | |
| | | |

18. STATUS:

**ONDC:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Biometrics | | | |
| EES | Withhold<br><br>Acceptable | 29-MAR-2005<br><br>12-JUL-2005 | Office of Compliance<br>R. Woods<br>S. Ferguson |
| Pharm/Tox | | | |
| Biopharm | | | |
| LNC | | | |
| Methods Validation | Non-compendial method, adequately validated by applicant. No need to send to FDA lab. for validation. | 28-MAR-2005 | Libaniel Rodriguez |
| DMETS | Proposed trade (ALPHAGAN [redacted] name not acceptable<br><br>Proposed ALPHAGAN P name sent for review | 04-FEB-2005 | Charles Hoppes |
| EA | Categorical Exclusion Acceptable | 27-MAY-2004 | Libaniel Rodriguez |
| Microbiology | Approvable<br>Approval | 02-March-2005<br>18-JUL-2005 | Stephen Langille<br>Stephen Langille |

# The Chemistry Review for NDA 21-770

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

From the CMC viewpoint, this 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)

Brimonidine Purite® ophthalmic solution 0.1% is a clear, greenish-yellow color, isotonic, sterile solution that contains 0.1% w/v brimonidine tartrate as the drug substance and Purite® [redacted] (0.005% w/v) as the preservative. The use of the Purite excipient contributes to the greenish–yellow color of the drug product. The excipients are: carboxymethylcellulose sodium (CMC), boric acid, sodium borate, sodium chloride, potassium chloride, calcium chloride, magnesium chloride and purified water. The product has a target pH of 7.7. All ingredients except for the drug substance and Purite® are either USP or NF grade. The proposed product contains the same ingredients as approved ALPHAGAN® P (NDA 21-262). No new ingredients have been added; only levels of the drug substance, borate buffer, salts, and product pH have been modified. The rationale for the pH modification is that at pH 7.7 (Alphagan P has a pH of 7.2), close to brimonidine tatrate's [redacted], a higher concentration of non-ionized brimonidine tartrate [redacted] for brimonidine tartrate in Alphagan P) is obtained. Allergan claims that the higher concentration of non-ionized drug substance increases corneal permeability and achieve similar efficacy with a lower concentration of drug substance.

The drug product is filled at [redacted] 5 mL/10 mL, 10 mL/10 mL and 15 mL/15/ mL multi-dose containers. The container-closure system consists of [redacted] low density polyethylene (LDPE) bottles [redacted] caps. This container/closure as well as the manufacturing procedure are the same as those approved for Alphagan® P.

The drug substance brimonidine tartrate is an off-white to pale yellow powder. It has a molecular formula of $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$ and a molecular weight of 442.24 as the

tartrate salt. It is soluble in both water [redacted] and in the product vehicle [redacted] at pH 7.7.

All the relevant information on the drug substance for this application was cross-referenced to the drug substance sections of approved Alphagan® (NDA 20-613) and Alphagan® P (NDA 21-262) drug products. The agency agreed to this cross-reference in the pre-NDA teleconference of October 20, 2003.

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

This drug product is indicated for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. It is to be administered one drop to each eye, three times per day for the life of the patient. Pre-clinical and clinical formulations are the same as that of the drug product.

The retest period for the drug substance brimonidine tartrate is [redacted] the shelf life for the drug product Brimonidine Purite Opthalmic Solution 0.1% is 18 months for all sizes.

**C. Basis for Approvability or Not-Approval Recommendation**

This application is recommended for approval. Issues resolved during this cycle included microbiology, tightening of acceptance criteria for impurities in the drug product and stability update (18 months). [redacted] bromonidine tartrate drug products, Alphagan (NDA 20-613) and Alphagan P (NDA 21-262). All inspection issues have been resolved satisfactorily (see attached OC report).

## III. Administrative

Executive Summary Section

**A. Reviewer's Signature**

Libaniel Rodriguez, Ph.D./Chemist/HFD-520/ 29-JUL-2005

**B. Endorsement Block**

Chemist/Libaniel Rodriguez, Ph.D./ 29-JUL-2005
ChemistryTeamLeader/Linda Ng, Ph.D./29-JUL-2005
ProjectManagerMichael Puglisi/29-JUL-2005

**C. CC Block**

Deputy Director HFD-520/Wiley Chambers/29-JUL-2005

# 9 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Chemistry-* 1

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

/s/

Libaniel Rodriguez
8/1/05 07:46:56 AM
CHEMIST
Review #2, APP

Linda Ng
8/1/05 02:35:56 PM
CHEMIST

# NDA 21-770

# Brimonidine Purite® Ophthalmic Solution 0.1%

## Allergan, Inc.

**Libaniel Rodriguez, Ph.D.**
**Division of Anti-inflamatory, Analgesic and Ophthalmic Drug Products**

**HFD-550**

# Table of Contents

# Chemistry Review Data Sheet

1. NDA 21-770

2. REVIEW #: 1

3. REVIEW DATE: 28-MAR-2005

4. REVIEWER: Libaniel Rodriguez

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| Previous Documents | Document Date |
|---|---|
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| NDA 20-613 | 31-AUG-1995 |
| NDA 21-262 | 29-JUN-2000 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Original NDA 21-770 | 27-MAY-2004 |
| BC | 15-JUL-2004 |
| BC | 17-SEP-2004 |
| BC | 17-MAR-2005 |

7. NAME & ADDRESS OF APPLICANT:

Name: Allergan, Inc

Chemistry Review Data Sheet

2525 Dupont Drive
Address: P.O. Box 19534
Irvine, CA 92623-9534

Representative: Lewis Gryziewicz

Telephone: 714 246 4500

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Brimonidine Tartrate Ophthalmis Solution 0.1%
c) Code Name/# (ONDC only): AGN 190342
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Alpha 2 agonist

11. DOSAGE FORM: Ophthalmic Solution

12. STRENGTH/POTENCY: 0.1%

13. ROUTE OF ADMINISTRATION: Topical (one drop three times per day per eye)

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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:

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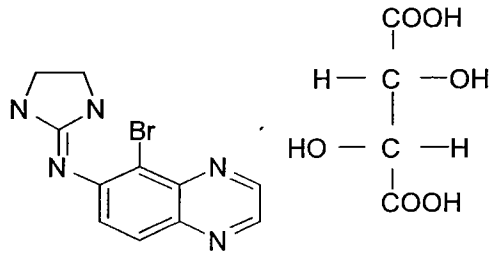
$C_{11}H_{10}BrN_5 \bullet C_4H_6O_6$. MW 442.22. CAS Registry Number 79570-19-7.

**MOLECULAR STRUCTURE:**



Brimonidine Tartrate
(AGN 190342-LF)

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| [redacted] | III | [redacted] | [redacted] | 3 | Adequate | 11-JAN-1996 | No updates or changes since the first submission |
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| | I | | | 2 | | | |

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| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
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| | | |
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| | | |
| | | |

## 18. STATUS:

**ONDC:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Biometrics | | | |
| EES | withhold | 29-MAR-2005 | Office of Compliance<br>R. Woods |
| Pharm/Tox | | | |
| Biopharm | | | |
| LNC | | | |
| Methods Validation | N/A | | |
| DMETS | Proposed trade name not acceptable | 04-FEB-2005 | Charles Hoppes |
| EA | Categorical Exclusion Acceptable | 27-MAY-2004 | Libaniel Rodriguez |
| Microbiology | Approvable | 02-March-2005 | Stephen Langille |

# The Chemistry Review for NDA 21-770

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

From the CMC viewpoint, this application is recommended as approvable, pending satisfactory resolution of microbiology and inspection issues.

### 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)

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This drug product is indicated for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. It is to be administered one drop to each eye, three times per day for the life of the patient. Pre-clinical and clinical formulations are the same as that of the drug product.

The retest period for the drug substance brimonidine tartrate is [redacted], the shelf life for the drug product Brimonidine Purite Opthalmic Solution 0.1% is 18 months for all sizes.

**C. Basis for Approvability or Not-Approval Recommendation**

This application is recommended as approvable because of unresolved microbiology issues. Issues resolved during this cycle included tightening of acceptance criteria for impurities in the drug product and stability update (18 months). [redacted] bromonidine tartrate drug products, Alphagan (NDA 20-613) and Alphagan P (NDA 21-262). Allergan's drug product manufacturing facility in [redacted] has been recommended for withhold on March 29, 2005 by the office of compliance (OC) (see OC report attached at the end of this review).

# III. Administrative

## A. Reviewer's Signature

Libaniel Rodriguez, Ph.D./Chemist/HFD-550/ 29-Mar-2005

## B. Endorsement Block

Chemist/Libaniel Rodriguez, Ph.D./ 29-Mar-2005
ChemistryTeamLeader/Linda Ng, Ph.D./29-Mar-2005
ProjectManagerMichael Puglisi/29-Mar-2005

## C. CC Block

Deputy Director HFD-550/Wiley Chambers/29-Mar-2005

# 40 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Chemistry-* 2

Chemistry Assessment Section

The following e-mail was sent on March 29, 2005 by the Office of Compliance to clarify the "acceptable" recommendation in the report below.

-----Original Message-----
**From:** [redacted]
**Sent:** Tuesday, March 29, 2005 12:25 PM
**To:** Na, Linda L [redacted]
**Cc:**
**Subject:** Withhold recommendation NDA 21-770

Hi Linda,

[redacted]

29-MAR-2005 FDA CDER EES

Page 1 of 2

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21770/000
Org Code : 550
Priority : 3S
Stamp Date : 01-JUN-2004
PDUFA Date : 01-APR-2005
Action Goal :
District Goal: 31-JAN-2005

Sponsor: ALLERGAN
2525 DUPONT DR
IRVINE, CA 926239534

Brand Name : BRIMONIDINE TARTRATE OPHTHALMIC SOL 0.1%

Estab. Name:

Generic Name: BRIMONIDINE TARTRATE OPHTHALMIC SOL 0.1%

Dosage Form: (SOLUTION)

Strength : 0.1%

| | | | |
|---|---|---|---|
| FDA Contacts: | M. PUGLISI | Project Manager | (HFD-550) 301-827-2090 |
| | L. RODRIGUEZ | Review Chemist | (HFD-830) 301-827-2069 |
| | L. NG | Team Leader | (HFD-830) 301-827-2511 |

---

Overall Recommendation: WITHHOLD on 29-MAR-2005by R. WOODS (HFD-322) 301-827-9011

WITHHOLD on 29-MAR-2005by S. FERGUSON(HFD-322) 301-827-9009

ACCEPTABLE on 29-MAR-2005by S. FERGUSON(HFD-322) 301-827-9009

---

Establishment : CFN : 1643525 FEI : 1643525

ALLERGAN INC

8301 MARS DR

WACO, TX 767126578

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : SNI OAI Status: OAI ALERT

Last Milestone: OC RECOMMENDATION

Milestone Date: 29-MAR-05

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

---

Establishment : CFN : 9610728 FEI : 3002806348

ALLERGAN PHARMACEUTICALS IRELAND [redacted]

CASTLEBAR ROAD

WESTPORT, , EI

DMF No: AADA:

Chemistry Assessment Section

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : SNI OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-JUN-04

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

---

Establishment : [redacted]

29-MAR-2005 FDA CDER EES

DMF No: AADA:

Responsibilities: [redacted]

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 21-JUN-04

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

---

Establishment : [redacted]

DMF No: AADA:

Responsibilities: [redacted]

# CHEMISTRY REVIEW TEMPLATE

## Chemistry Assessment Section

| | | | |
|---|---|---|---|
| Profile : | CSN | OAI Status: | NONE |
| Last Milestone: | OC RECOMMENDATION | | |
| Milestone Date: | 23-FEB-05 | | |
| Decision : | ACCEPTABLE | | |
| Reason : | DISTRICT RECOMMENDATION | | |

---

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

/s/

Libaniel Rodriguez
3/29/05 02:26:01 PM
CHEMIST
Review #1, Approvable

Linda Ng
3/29/05 02:54:33 PM
CHEMIST