

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-770

CHEMISTRY REVIEW(S)



CHEMISTRY REVIEW



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

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
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
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 [Brimonidine tartrate, Ash Stevens, Inc. and Torcan Chemicals, Ltd.]	10
P DRUG PRODUCT [Brimonidine Purite®, Ophthalmic Solution 0.1%]	10



CHEMISTRY REVIEW



Chemistry Review Data Sheet

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

IND 32-292
NDA 20-613
NDA 21-262
Original NDA 21-770
BC
BC
BC

Document Date

31-OCT-1988
31-AUG-1995
29-JUN-2000
27-MAY-2004
15-JUL-2004
17-SEP-2004
17-MAR-2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

AZ

Document Date

27-JUN-2005

7. NAME & ADDRESS OF APPLICANT:

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



CHEMISTRY REVIEW



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
- b) Non-Proprietary Name (USAN): Brimonidine Tartrate Ophthalmic 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: ☒ Rx ☐ OTC

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

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

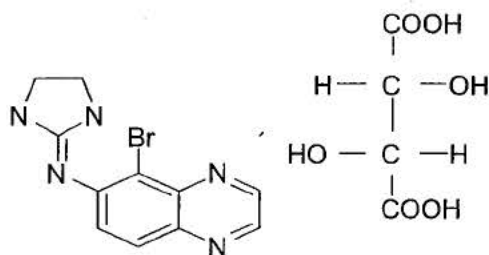
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR
FORMULA, MOLECULAR WEIGHT:

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)
C₁₁H₁₀BrN₅•C₄H₆O₆. MW 442.22. CAS Registry Number 79570-19-7.

MOLECULAR STRUCTURE:

Chemistry Review Data Sheet



Brimonidine Tartrate
(AGN 190342-LF)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
1	III	1	1	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



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Withhold	29-MAR-2005	Office of Compliance
	Acceptable	12-JUL-2005	R. Woods 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 name not acceptable Proposed ALPHAGAN P name sent for review	04-FEB-2005	Charles Hoppes
EA	Categorical Exclusion Acceptable	27-MAY-2004	Libaniel Rodriguez
Microbiology	Approvable Approval	02-March-2005 18-JUL-2005	Stephen Langille 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® (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 tartrate's pK_a , a higher concentration of non-ionized brimonidine tartrate, 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 5 mL/10 mL, 10 mL/10 mL and 15 mL/15 mL multi-dose containers. The container-closure system consists of low density polyethylene (LDPE) bottles 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



CHEMISTRY REVIEW



Executive Summary Section

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 Ophthalmic 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]

[REDACTED] brimonidine 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



CHEMISTRY REVIEW



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-inflammatory, Analgesic and
Ophthalmic Drug Products**

HFD-550



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
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.....	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].....	12
A APPENDICES	47
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	49
III. List Of Deficiencies To Be Communicated.....	49



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 21-770
2. REVIEW #: 1
3. REVIEW DATE: 28-MAR-2005
4. REVIEWER: Libaniel Rodriguez

5. PREVIOUS DOCUMENTS:

Previous Documents

IND 32-292
NDA 20-613
NDA 21-262

Document Date

31-OCT-1988
31-AUG-1995
29-JUN-2000

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original NDA 21-770
BC
BC
BC

Document Date

27-MAY-2004
15-JUL-2004
17-SEP-2004
17-MAR-2005

7. NAME & ADDRESS OF APPLICANT:

Name: Allergan, Inc



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Address: 2525 Dupont Drive
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 Ophthalmic 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: ☒ Rx ☐ OTC

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

☐ SPOTS product – Form Completed

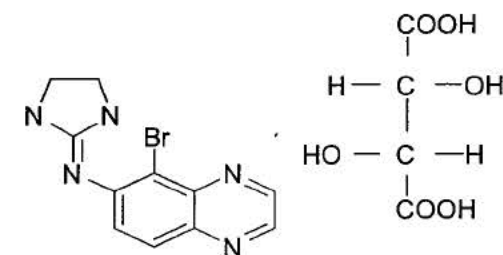
☒ Not a SPOTS product

Chemistry Review Data Sheet

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)
 $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$. 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
1	III			3	Adequate	11-JAN-1996	No updates or changes since the first submission
	I			2			
	I			2			

¹ Action codes for DMF Table:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

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	29-MAR-2005	Office of Compliance 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)

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[®] (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 tartrate's pK_a , a higher concentration of non-ionized brimonidine tartrate 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 5 mL/10 mL, 10 mL/10 mL and 15 mL/15 mL multi-dose containers. The container-closure system consists of low density polyethylene (LDPE) bottles caps. This container/closure as well as the manufacturing procedure are the same as those approved for Alphagan[®] P.

Executive Summary Section

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 () and in the product vehicle () 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 (), the shelf life for the drug product Brimonidine Purite Ophthalmic 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). ()

() brimonidine tartrate drug products, Alphagan (NDA 20-613) and Alphagan P (NDA 21-262). Allergan's drug product manufacturing facility in () 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).



CHEMISTRY REVIEW



Executive Summary Section

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 REVIEW TEMPLATE



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: No. Linda L
Cc: [REDACTED]
Subject: Withhold recommendation NDA 21-770

Hi Linda,

29-MAR-2005

FDA CDER EES

Page 1 of 2

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application	: NDA 21770/000	Sponsor:	ALLERGAN
Org Code	: 550		2525 DUPONT DR
Priority	: 3S		IRVINE, CA 926239534
Stamp Date	: 01-JUN-2004	Brand Name :	BRIMONIDINE TARTRATE OPHTHALMIC SOL 0.1%
PDUFA Date	: 01-APR-2005		
Action Goal	:	Estab. Name:	
District Goal:	31-JAN-2005	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
CASTLEBAR ROAD
WESTPORT, , EI

DMF No: AADA:



CHEMISTRY REVIEW TEMPLATE



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 : 

29-MAR-2005

FDA CDER EES

DMF No:

AADA:

Responsibilities: 

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 21-JUN-04

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : 

DMF No:

AADA:

Responsibilities: 



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