

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-764

CHEMISTRY REVIEW(S)

NDA 21-764

Brimonidine Tartrate Ophthalmic Solution, 0.15%

Alcon, Inc.

Linda Ng, 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	8
I. Recommendations	8
A. Recommendation and Conclusion on Approvability	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	8
II. Summary of Chemistry Assessments	8
A. Description of the Drug Product(s) and Drug Substance(s)	8
B. Description of How the Drug Product is Intended to be Used	9
C. Basis for Approvability or Not-Approval Recommendation	9
III. Administrative	9
A. Reviewer's Signature	9
B. Endorsement Block	9
C. CC Block	9
Chemistry Assessment	10
I. Review Of Outstanding Deficiencies	Error! Bookmark not defined.
A ATTACHMENTS: Drug Product Specifications	13

Appears This Way
On Original



Chemistry Review Data Sheet

1. NDA 21-764
2. REVIEW #: 2
3. REVIEW DATE: 23-Feb-2005
4. REVIEWER: Linda Ng, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original IND 64,330	27-Nov-2002
Original NDA	27-Apr-2004
Amendment	11-May-2004
Amendment	03-Jan-2005
Amendment	20-Jan-2005

6. SUBMISSION(S) BEING REVIEWED:

<u>Previous Documents</u>	<u>Document Date</u>
Amendment	15-Oct-2004
Amendment	01-Feb-2005
Amendment	03-Feb-2005
Amendment	08-Feb-2005
Amendment	22-Feb-2005
Amendment	23-Feb-2005



CHEMISTRY REVIEW



Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Alcon, Inc.
P.O. Box 62
Address: Bosch 69
CH-6331, Hunenberg
Switzerland
Alcon Research, Ltd.
Representative: 6201 South Freeway
Fort worth, Texas 76134-2099
Telephone: 817-551-4877
Facsimile: 817-551-4630

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN): Brimonidine Tartrate
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Filed under 505 (b)(2) of the Federal Food, Drug and Cosmetic Act: Allergan's ALPHAGAN P (brimonidine tartrate ophthalmic solution) 0.15%

10. PHARMACOL. CATEGORY: Alpha-2 adrenergic agonist

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 0.15% (one drop in the affected eye(s) three-times-daily, approximately 8 hours apart)

13. ROUTE OF ADMINISTRATION: Ophthalmic

14. Rx/OTC DISPENSED: Rx OTC



CHEMISTRY REVIEW



Chemistry Review Data Sheet

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

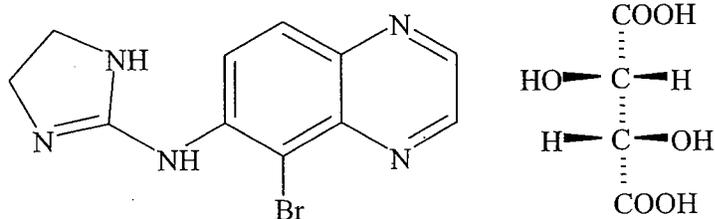
_____ SPOTS product – Form Completed

X Not a SPOTS product

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

CHEMICAL NAME: 5-Bromo-6-(2-imidazolidinylideneamino) quinoxaline
L-tartrate

STRUCTURAL FORMULA:



MOLECULAR FORMULA: $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$

MOLECULAR WEIGHT: 442.23

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
1				7			See chemistry review section P.2.4
							See chemistry review section P.2.4
2				8			See chemistry review section P.2.4



CHEMISTRY REVIEW



Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
							See chemistry review section P.2.4
							See chemistry review section P.2.4
							See microbiology review
							See microbiology review
							See chemistry review section P.2.4

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	21-262	ALPHAGAN P referenced through Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act
ANDA	76-254	Referenced for the manufacturing process of brimonidine tartrate used in Brimonidine Tartrate Ophthalmic Solution, 0.2%



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	10/22/04	S. FERGUSON(HFD-322)
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	See Section R3 (p. 60)		
OPDRA			
EA	Categorical Exclusion claimed		
Microbiology	Approval recommended	8/26/04	Bryan S. Riley, Ph.D.

Appears This Way
On Original



The Chemistry Review for NDA 21-764

The Executive Summary

I. Recommendations

- A. Recommendation and Conclusion on Approvability:** From the chemistry, manufacturing, and controls perspective, this NDA is approval.
- B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable:** See Agreements dated XXX submitted by Alcon Inc.

II. Summary of Chemistry Assessments

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

Drug substance, brimonidine tartrate, is a relative selective alpha-2 adrenergic agonist for ophthalmic use. The concentration of the substance, 0.15%, was chosen to be quantitatively identical to that of ALPHAGAN P. Brimonidine tartrate 1.5 mg/mL equals to brimonidine free base 1.0 mg/mL. The physical and chemical characterization of brimonidine tartrate drug substance has been performed and referred to Alcon's ANDA 76-254 for Brimonidine Tartrate Ophthalmic Solution, 0.2%.

Drug substance, brimonidine tartrate is manufactured by _____ The manufacturing process, process controls, process validation, manufacturing process development, the characterization of the drug substance, controls of the drug substance, and analytical procedures for the drug substance referred to Alcon's ANDA 76-254 for Brimonidine Tartrate Ophthalmic Solution, 0.2%.

Brimonidine Tartrate Ophthalmic Solution, 0.15% is developed as a product that is pharmaceutically and therapeutically equivalent to Allergan's ALPHAGAN P. This drug product has a clear, greenish-yellow color. It has an osmolality of 250-350 mOsmol/kg and a pH of 6.6 – 7.4.

POLYQUAD was selected as the antimicrobial preservative and povidone _____ as the _____ Potassium chloride, calcium chloride, and magnesium chloride were chosen based on their natural concentrations found in human tears. Sodium chloride serves as the _____ and _____ Hydrochloric acid and/or sodium hydroxide were used to adjust pH.



Executive Summary Section

The drug product will be packaged in Alcon's standard white _____ bottles with fill volumes of 5 mL (in the 8 mL bottle), 10 mL (in the 10 mL bottle) and 15 mL (in the 15 mL bottle). All sizes employ the same natural _____ and a purple polypropylene (PP) closure. Tamper evidence is provided by a _____ around the neck and closure of the _____. The packaging components for Brimonidine Tartrate Ophthalmic Solution, 0.15% are the same as those approved for use in Brimonidine Tartrate Ophthalmic Solution, 0.2% (ANDA 76-254).

The Brimonidine Tartrate Ophthalmic Solution, 0.15% has satisfactory stability when stored at 25°C and require no additional labeled storage precautions and the data collected thus far (18 months) support a proposed shelf-life of 24 months for all three sizes: 5mL/8 mL, 10 mL/10 mL, and 15 mL/15 mL.

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

Brimonidine Tartrate Ophthalmic Solution, 0.15% is described as a stable, preserved, multi-dose formulation that is indicated for lowering intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. The route of administration and the dosing regimen for Brimonidine Tartrate Ophthalmic Solution, 0.15%, will be identical to that of Alphagan P. The recommended dose is one drop of Brimonidine tartrate Ophthalmic Solution, 0.15% in the affected eye(s) three-times-daily, approximately 8 hours apart. The proposed expiry dating period is two years for the drug product.

C. Basis for Approvability or Not-Approval Recommendation

Many information request letters were sent to the applicant via facsimile. Some issues were resolved and summarized in the review, for example, the addition of the second identity test in the drug product specification, justification of the expiry dating period of brimonidine tartrate reference standard, and the qualification of reference standard. Some issues remain outstanding, such as, _____

_____ The firm will update the Agency on this two issues as post-approval agreements before August 31, 2005.

III. Administrative

A. Reviewer's Signature

Linda Ng, Ph.D.

B. Endorsement Block

Norman Schmuft, Ph.D., Acting DNDCIII Deputy Director

C. CC Block

Raphael R. Rodriguez, Project Manager
Wiley Chambers, Deputy Division Director HFD-550

5 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/

Linda Ng
2/24/05 12:37:26 PM
CHEMIST
CMC recommends AP with agreements

Norman Schmuff
2/24/05 01:31:36 PM
CHEMIST

Appears This Way
On Original



NDA 21-764

Brimonidine Tartrate Ophthalmic Solution, 0.15%

Alcon, Inc.

Lin Qi, 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	8
I. Recommendations.....	8
A. Recommendation and Conclusion on Approvability	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments.....	8
A. Description of the Drug Product(s) and Drug Substance(s)	8
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation.....	9
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	10
P DRUG PRODUCT	27
A APPENDICES	55
R REGIONAL INFORMATION.....	60
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	60
A. Labeling & Package Insert	60
B. Environmental Assessment Or Claim Of Categorical Exclusion	61
III. List Of Deficiencies to be Communicated.....	61
IV. Issues to be Addressed in the Next Review	64



Chemistry Review Data Sheet

1. NDA 21-764
2. REVIEW #: 1
3. REVIEW DATE: 02-Feb-2005
4. REVIEWER: Lin Qi
5. PREVIOUS DOCUMENTS:

Previous Documents
Original IND 64,330

Document Date
27-Nov-2002

6. SUBMISSION(S) BEING REVIEWED:

Previous Documents
Original NDA
Amendment
Amendment
Amendment
Amendment
Amendment
Amendment

Document Date
27-Apr-2004
11-May-2004
15-Oct-2004
03-Jan-2005
20-Jan-2005
01-Feb-2005
03-Feb-2005



CHEMISTRY REVIEW



Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Alcon, Inc.
Address: P.O. Box 62
Bosch 69
CH-6331, Hunenberg
Switzerland
Alcon Research, Ltd.
Representative: 6201 South Freeway
Fort worth, Texas 76134-2099
Telephone: 817-551-4877
Facsimile: 817-551-4630

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN): Brimonidine Tartrate
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Filed under 505 (b)(2) of the Federal Food, Drug and Cosmetic Act: Allergan's ALPHAGAN P (brimonidine tartrate ophthalmic solution) 0.15%

10. PHARMACOL. CATEGORY: Alpha-2 adrenergic agonist

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 0.15% (one drop in the affected eye(s) three-times-daily, approximately 8 hours apart)

13. ROUTE OF ADMINISTRATION: Ophthalmic

14. Rx/OTC DISPENSED: Rx OTC



CHEMISTRY REVIEW



Chemistry Review Data Sheet

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

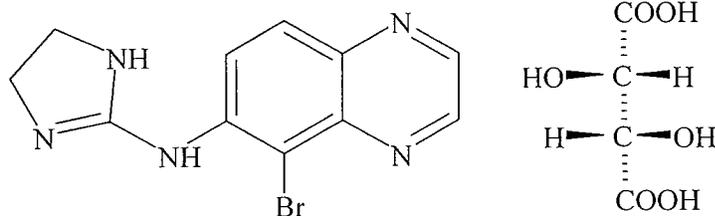
____ SPOTS product – Form Completed

X Not a SPOTS product

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

CHEMICAL NAME: 5-Bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate

STRUCTURAL FORMULA:



MOLECULAR FORMULA: $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$

MOLECULAR WEIGHT: 442.23

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
							See chemistry review section P.2.4
							See chemistry review section P.2.4
							See chemistry review section P.2.4



CHEMISTRY REVIEW



Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
							See chemistry review section P.2.4
							See chemistry review section P.2.4
							See microbiology review
							See microbiology review
							See chemistry review section P.2.4

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	21-262	ALPHAGAN P referenced through Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act
ANDA	76-254	Referenced for the manufacturing process of brimonidine tartrate used in Brimonidine Tartrate Ophthalmic Solution, 0.2%



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	10/22/04	S. FERGUSON(HFD-322)
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	See Section R3 (p. 60)		
OPDRA			
EA	Categorical Exclusion claimed		
Microbiology	Approval recommended	8/26/04	Bryan S. Riley, Ph.D.

Appears This Way
On Original



The Chemistry Review for NDA 21-764

The Executive Summary

I. Recommendations

- A. **Recommendation and Conclusion on Approvability:** From the chemistry, manufacturing, and controls perspective, this NDA is 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)

Drug substance, brimonidine tartrate, is a relative selective alpha-2 adrenergic agonist for ophthalmic use. The concentration of the substance, 0.15%, was chosen to be quantitatively identical to that of ALPHAGAN P. Brimonidine tartrate 1.5 mg/mL equals to brimonidine free base 1.0 mg/mL. The physical and chemical characterization of brimonidine tartrate drug substance has been performed and referred to Alcon's ANDA 76-254 for Brimonidine Tartrate Ophthalmic Solution, 0.2%.

Drug substance, brimonidine tartrate is manufactured by _____ The manufacturing process, process controls, process validation, manufacturing process development, the characterization of the drug substance, controls of the drug substance, and analytical procedures for the drug substance referred to Alcon's ANDA 76-254 for Brimonidine Tartrate Ophthalmic Solution, 0.2%.

Brimonidine Tartrate Ophthalmic Solution, 0.15% is developed as a product that is pharmaceutically and therapeutically equivalent to Allergan's ALPHAGAN P. This drug product has a clear, greenish-yellow color. It has an osmolality of 250-350 mOsmol/kg and a pH of 6.6 – 7.4.

POLYQUAD was selected as the antimicrobial preservative and povidone _____ as the _____. Potassium chloride, calcium chloride, and magnesium chloride were chosen based on their natural concentrations found in human tears. Sodium chloride serves as the _____ and _____ and the _____ Hydrochloric acid and/or sodium hydroxide were used to adjust pH.



Executive Summary Section

The drug product will be packaged in Alcon's standard white _____ bottles with fill volumes of 5 mL (in the 8 mL bottle), 10 mL (in the 10 mL bottle) and 15 mL (in the 15 mL bottle). All sizes employ the same natural _____ and a purple polypropylene (PP) closure. Tamper evidence is provided by a _____ around the neck and closure of the _____. The packaging components for Brimonidine Tartrate Ophthalmic Solution, 0.15% are the same as those approved for use in Brimonidine Tartrate Ophthalmic Solution, 0.2% (ANDA 76-254).

The Brimonidine Tartrate Ophthalmic Solution, 0.15% has satisfactory stability when stored at _____ to 25°C and require no additional labeled storage precautions and the data collected thus far (18 months) support a proposed shelf-life of 24 months for all three sizes: 5mL/8 mL, 10 mL/10 mL, and 15 mL/15 mL.

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

Brimonidine Tartrate Ophthalmic Solution, 0.15% is described as a stable, preserved, multi-dose formulation that is indicated for lowering intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. The route of administration and the dosing regimen for Brimonidine Tartrate Ophthalmic Solution, 0.15%, will be identical to that of Alphagan P. The recommended dose is one drop of Brimonidine tartrate Ophthalmic Solution, 0.15% in the affected eye(s) three-times-daily, approximately 8 hours apart. The proposed expiry dating period is two years for the drug product.

C. Basis for Approvability or Not-Approval Recommendation

A few information request letters were sent to the applicant via facsimile. Some issues were resolved and summarized in the review, for example, the addition of the second identity test in the drug product specification, justification of the expiry dating period of brimonidine tartrate reference standard, and the qualification of reference standard. Some issues remain outstanding, such as, _____

III. Administrative

A. Reviewer's Signature

Lin Qi, Review Chemist

B. Endorsement Block

Linda Ng, Chemistry Team Leader

C. CC Block

Raphael R. Rodriguez, Project Manager
Wiley Chambers, Deputy Division Director HFD-550

55 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Chemistry-2

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

/s/

Lin Qi
2/3/05 03:06:01 PM
CHEMIST

Linda Ng
2/3/05 03:14:00 PM
CHEMIST

Appears This Way
On Original