CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-398

CHEMISTRY REVIEW(S)

NDA 21-398

COMBIGAN™
(Brimonidine Tartrate 0.2% / Timolol 0.5%)
Ophthalmic Solution

Allergan Inc.

Lin Qi, Ph.D.

Division of Anti-infective and Ophthalmic Drug Products

Chemistry Review Data Sheet

1. NDA 21-398

2. REVIEW #: Labeling

3. REVIEW DATE: September 27, 2007

4. REVIEWER: Lin Qi

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	17-Sep-2001
Amendment (BC)	15-Jan -2002
Amendment (BC)	31-Jan –2002
Amendment (BC)	22-Feb -2002
Amendment (AZ)	13-Sep-2004
Amendment (AZ)	29-Jun-2006
Amendment (BZ)	04-Aug-2006
Amendment (BZ)	03-Oct-2006
Amendment (BC)	27-Oct-2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (BL)	06-Jun-2007

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Allergan Inc.
Address:	2525 Dupont Drive P.O.Box 19534 Irvine, CA 92623-9534
Representative:	Lewis Gryziewicz, Director of Regulatory Affairs
Telephone:	714-246-6088

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	COMBIGAN™
b) Non-Proprietary Name (USAN):	Brimonidine Tartrate 0.2%/Timolol 0.5% Ophthalmic Solution
c) Code Name/#:	AGN 190342-LF/AGN 196156-H/Formula 9262X
d) Chem. Type/Submission Priority:	
• Chem. Type:	4
• Submission Priority:	S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Selective alpha-2 adrenergic agonist. Indicated for reduction of elevated intraocular pressure in patient with glaucoma or ocular hypertension.

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 0.2%/0.5% (w/v)(Brimonidine Tartrate/Timolol)

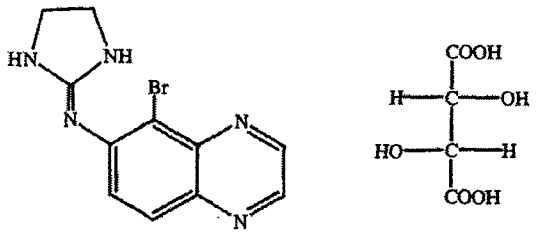
13. ROUTE OF ADMINISTRATION: Topical, ophthalmic, one drop per eye twice daily

14. Rx/OTC DISPENSED: _X_Rx ___OTC

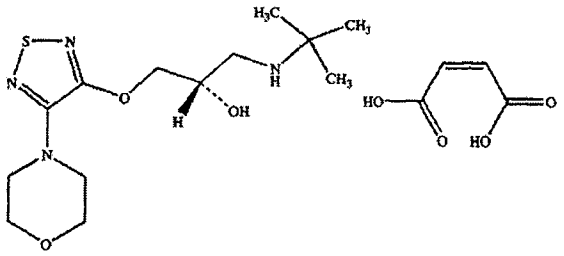
15. _____SPOTS product – Form Completed

__X__Not a SPOTS product

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



Brimonidine Tartrate : 5-Bromo-6-(2-imidazolin-2-ylamino)quinoxaline L-tartrate
$C_{15}H_{16}N_5O_6Br$, MW 442.24, [59803-98-4]



Timolol Maleate: (–)-1-(t-Butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)-oxy]-2-propanol maleate (1: 1)
$C_{17}H_{28}N_4O_7S$, MW 432.49, [26921-17-5]. See USP24 page 1663 for detail.

The Chemistry Review for NDA 21-398

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the quality assurance perspective, this NDA is recommended for approval.

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

N/A

II. Summary of Chemistry Assessments

This review includes labeling review and establishment inspection results. The facilities were found acceptable (See Attachment 1).

III. Administrative

A. Reviewer's Signature

Signed electronically in DFS

B. Endorsement Block

ChemistName/Date: LQi
ChemistryBranchChiefName/Date: NSchmuff
ProjectManagerName/Date: LAthey

C. CC Block

CC listed in DFS

15 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 6

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
9/27/2007 03:06:13 PM
CHEMIST

Norman Schmuff
9/28/2007 12:18:09 PM
CHEMIST

NDA 21-398

COMBIGAN™
(Brimonidine Tartrate 0.2% / Timolol 0.5%)
Ophthalmic Solution

Allergan Inc.

Lin Qi, Ph.D.

Division of Anti-infective and Ophthalmic Drug Products

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Chemistry Review Data Sheet

1. NDA 21-398

2. REVIEW #: 3

3. REVIEW DATE: November 7, 2006

4. REVIEWER: Lin Qi

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	17-Sep-2001
Amendment (BC)	15-Jan -2002
Amendment (BC)	31-Jan –2002
Amendment (BC)	22-Feb -2002
Amendment (AZ)	13-Sep-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (AZ)	29-Jun-2006
Amendment (BZ)	04-Aug-2006
Amendment (BZ)	03-Oct-2006
Amendment (BC)	27-Oct-2006

1. NAME & ADDRESS OF APPLICANT:

Name: Allergan Inc.

Chemistry Review Data Sheet

Address: 2525 Dupont Drive
P.O.Box 19534
Irvine, CA 92623-9534
Representative: Lewis Gryziewicz, Director of Regulatory Affairs

Telephone: 714-246-6088

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: COMBIGAN™
b) Non-Proprietary Name (USAN): Brimonidine Tartrate 0.2%/Timolol 0.5% Ophthalmic Solution
c) Code Name/#: AGN 190342-LF/AGN 196156-H/Formula 9262X
d) Chem. Type/Submission Priority:
- Chem. Type: 4
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Selective alpha-2 adrenergic agonist. Indicated for reduction of elevated intraocular pressure in patient with glaucoma or ocular hypertension.

11. DOSAGE FORM: Solution

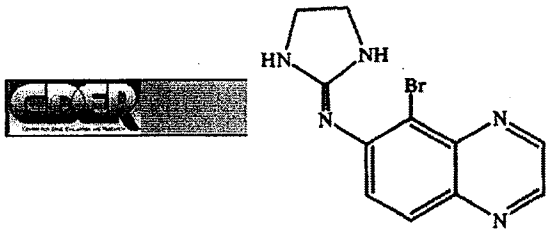
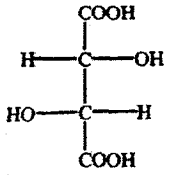
12. STRENGTH/POTENCY: 0.2%/0.5% (w/v)(Brimonidine Tartrate/Timolol)

13. ROUTE OF ADMINISTRATION: Topical, ophthalmic, one drop per eye twice daily

14. Rx/OTC DISPENSED: _X_Rx ___OTC

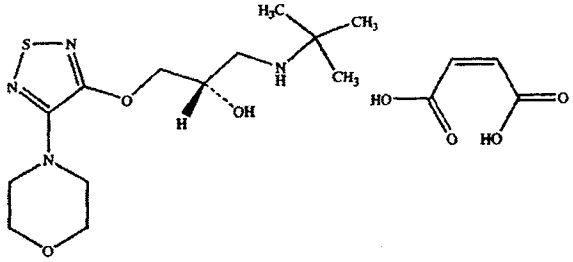
15. _____SPOTS product – Form Completed

__X__Not a SPOTS product

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

Brimonidine Tartrate : 5-Bromo-6-(2-imidazolin-2-ylamino)quinoxaline L-tartrate
$C_{15}H_{16}N_5O_6Br$, MW 442.24, [59803-98-4]



Timolol Maleate: (–)-1-(t-Butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)-oxy]-2-propanol maleate (1: 1)
$C_{17}H_{28}N_4O_7S$, MW 432.49, [26921-17-5]. See USP24 page 1663 for detail.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
11086	I	Allergan, Inc.	Manufacturing site for finished product (Waco,TX)	2	Closed	N/A	No need to review
2461	III	Allergan, Inc.	Supplier of plastic ophthalmic component	1	Adequate	01-Mar-02	USP qualification data are in NDA
[redacted]	I	[redacted]	[redacted]	2	Updated on 5/3/95	N/A	No need to review
[redacted]	I	[redacted]	[redacted]	2	Closed	N/A	No need to review

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
			Tartrate				
[redacted]	II	[redacted]		1	Inadequate Adequate	12-Feb-02 12-Mar-02	[redacted]
	III			1	Adequate	01-Mar-02	
	III			3	Adequate	10-Jan-96	
	III			3	Adequate	14-Feb-01	
				6			
				6			

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	58,460	Brimonidine Tartrate 0.2% /Timolol 0.5%
NDA	20-613	ALPHAGAN® 0.2%
NDA	20-262	ALPHAGAN P 0.15%
ANDA	74-746	Timolol Maleate Oph. Sol. 0.25%
ANDA	74-747	Timolol Maleate Oph. Sol. 0.5%

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES (5 manufacturing sites)	All Acceptable	5-Aug-2006	See Attachment 1
Pharm/Tox			
LNC			
Methods Validation	Revision Acceptable	7-Nov-2006	Lin Qi
OPDRA			
EA			
Microbiology			

The Chemistry Review for NDA 21-398

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the quality assurance perspective, this NDA is recommended for approval.

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

N/A

II. Summary of Chemistry Assessments

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

Brimonidine tartrate (AGN 190342-LF) is currently available in the approved glaucoma product ALPHAGAN® (NDA 20-613) and ALPHGAN®P (NDA 21-262). Timolol is currently available in the approved glaucoma product Timolol Maleate Ophthalmic Solution, USP 0.25% (ANDA 74-746) and Timolol Maleate Ophthalmic Solution, USP 0.5% (ANDA 74-747).

For the majority of chemistry, manufacturing and controls information regarding brimonidine tartrate, the reference is made to the drug substance section of NDA 20-613. The suppliers of brimonidine tartrate are [redacted] There have been no CMC changes involved in brimonidine tartrate since the approval of NDA 20-613.

Timolol maleate is manufactured by [redacted] currently approved in ANDA 74-746. [redacted] for timolol maleate was updated to contain a new version of specification of timolol maleate. The DMF holder was asked by an investigator to include residual solvents testing. The acceptance criteria for [redacted] have been revised to reflect real time data. The NDA applicant has updated the acceptance specification for the drug substance to include the residual solvents.

Brimonidine tartrate and timolol are currently marketed individually as monotherapies for the treatment of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension, which was approved via NDA 20-613 and ANDA 74-746. Applicant has combined brimonidine tartrate and timolol into a single formulation to provide the benefit of adjunctive therapy with a more convenient

dosing regimen. The same excipients but in different ratios are used in this combination product. Even more, the concentration of [redacted] *n the drug product is reduced to achieve* [redacted] *requirement. The benzalkonium chloride (BAK) concentration is also* [redacted] *and the formulation meets USP antimicrobial preservative effectiveness criteria.*

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

The drug product, Brimonidine Tartrate 0.2% / Timolol 0.5% Ophthalmic solution, was clinically evaluated for the reduction of elevated intraocular pressure in patient with glaucoma or ocular hypertension. See Clinical Review and Package Insert for further details.

Brimonidine Tartrate 0.2% / Timolol 0.5% Ophthalmic solution is supplied sterile in white opaque plastic LDPE bottles and tips with blue HIPS caps as follows: [redacted] *5 mL in* [redacted] *bottle (NDC 0023-9211-05), 10 mL in* [redacted] *bottle (NDC 0023-9211-10), 15 mL in 15 ml bottle (NDC 0023-9211-15). The recommended dose for adults is one drop of the drug product in each affected eye(s) twice daily.*

If more than one topical ophthalmic product is to be used, the different product should be instilled at least [redacted] *minutes apart.*

The product should be stored at 15-25°C (59-77°F) and protected from light (Adapted from review #2 by Dr. Yong-de Lu).

C. Basis for Approvability or Not-Approval Recommendation

In this amendment, the applicant provided a CMC section which includes the following information:

- Supporting documentation for a new configuration container closure system, [redacted] bottle to be used for this product
- Stability report including 36 months data on site validation batches (continue to support the proposed 24 month expiration dating period) and revised specification

- [redacted] validation report – referred to the microbiological review of this NDA

Sufficient information were provided on the revised container closure system. Issues regarding the identity and source of the newly observed impurity [redacted] were solved during the review process. [redacted] was established. A revised analytical procedure for impurities in the drug product was provided. The acceptance criterion of [redacted] was established based on the Pharm/Tox qualification study. There are no issues remain unsolved.

III. Administrative

A. Reviewer's Signature

Signed electronically in DFS

B. Endorsement Block

ChemistName/Date: LQi/Nov 7, 2006
ChemistryBranchChiefName/Date: NSchmuff/Nov 7, 2006
ProjectManagerName/Date: LAthey/Nov 7, 2006

C. CC Block

19 Page(s) Withheld

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_____ Deliberative Process

Withheld Track Number: Chemistry- 7

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/s/

Lin Qi
11/13/2006 03:09:01 PM
CHEMIST

Norman Schmuff
11/13/2006 03:19:41 PM
CHEMIST

NDA 21-398

COMBIGAN™
(Brimonidine Tartrate 0.2% / Timolol 0.5%)
Ophthalmic Solution

Allergan Inc.

Yong-de Lu, Ph.D.

Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products

HFD-550

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Chemistry Review Data Sheet

1. NDA 21-398

2. REVIEW #: 2

3. REVIEW DATE: 07-Mar-2005

4. REVIEWER: Yong-de Lu, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	17-Sep-2001
Amendment (BC)	15-Jan -2002
Amendment (BC)	31-Jan –2002
Amendment (BC)	22-Feb -2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (AZ)	13-Sep-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Allergan Inc.

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

Representative: Lewis Gryziewicz, Director of Regulatory Affairs

Telephone: 714-246-6088

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	COMBIGAN™
b) Non-Proprietary Name (USAN):	Brimonidine Tartrate 0.2%/Timolol 0.5% Ophthalmic Solution
c) Code Name/#:	AGN 190342-LF/AGN 196156-H/Formula 9262X
d) Chem. Type/Submission Priority:	
• Chem. Type:	4
• Submission Priority:	S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Selective alpha-2 adrenergic agonist. Indicated for reduction of elevated intraocular pressure in patient with glaucoma or ocular hypertension.

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 0.2%/0.5% (w/v)(Briminidine Tartrate/Timolol)

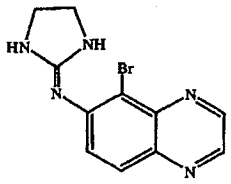
13. ROUTE OF ADMINISTRATION: Topical, ophthalmic, one drop per eye twice daily

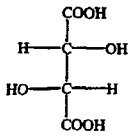
14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. _____SPOTS product – Form Completed

__X__Not a SPOTS product

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





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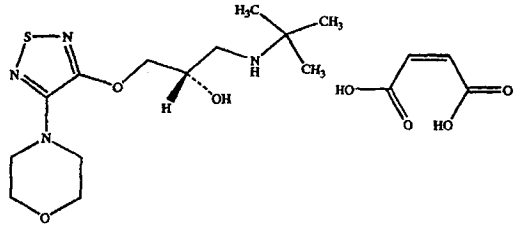
$C_{15}H_{16}N_5O_6Br$, MW 442.24, [59803-98-4]



Timolol Maleate: (–)-1-(t-Butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)-oxy]-2-propanol maleate (1: 1)
C17H28N4O7S, MW 432.49, [26921-17-5]. See USP24 page 1663 for detail.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
11086	I	Allergan, Inc.	Manufacturing site for finished product (Waco,TX)	2	Closed	N/A	No need to review
2461	III	Allergan, Inc.	Supplier of plastic ophthalmic component	1	Adequate	01-Mar-02	USP qualification data are in NDA
[redacted]	I	[redacted]		2	Updated on 5/3/95	N/A	No need to review
	I			2	Closed	N/A	No need to

Chemistry Review Data Sheet

					review
	II				
	III				
	III				
	III				

[1] Action codes for DMF Table:
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[2] 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
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ANDA	74-747	Timolol Maleate Oph. Sol. 0.5%

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES (5 manufacturing sites)	All Acceptable	16-Oct-01	
Pharm/Tox	Approval	23-Jan-02	Zhou Chen (Consulted)
LNC			
Methods Validation	Sent to District Labs	28-Mar-02	
OPDRA			
EA			
Microbiology	Approval	30-Nov-01	Paul Stinavage

The Chemistry Review for NDA 21-398

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for **approval**. The drug product is granted **24 months** expiration dating period.

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

N/A

II. Summary of Chemistry Assessments

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

Brimonidine tartrate (AGN 190342-LF) is currently available in the approved glaucoma product ALPHAGAN® (NDA 20-613) and ALPHGAN®P (NDA 21-262). Timolol is currently available in the approved glaucoma product Timolol Maleate Ophthalmic Solution, USP 0.25% (ANDA 74-746) and Timolol Maleate Ophthalmic Solution, USP 0.5% (ANDA 74-747).

For the majority of chemistry, manufacturing and controls information regarding brimonidine tartrate, the reference is made to the drug substance section of NDA 20-613. The suppliers of brimonidine tartrate are [redacted] There have been no CMC changes involved in brimonidine tartrate since the approval of NDA 20-613.

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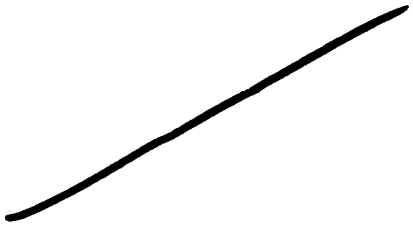
Brimonidine tartrate and timolol are currently marketed individually as monotherapies for the treatment of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension, which was approved via NDA 20-613 and

ANDA 74-746. Applicant has combined brimonidine tartrate and timolol into a single formulation to provide the benefit of adjunctive therapy with a more convenient dosing regimen. The same excipients but in different ratios are used in this combination product. Even more, the concentration of [redacted] in the drug product is reduced to achieve [redacted] requirement. The benzalkonium chloride (BAK) concentration [redacted] and the formulation meets USP antimicrobial preservative effectiveness criteria.



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

The drug product, Brimonidine Tartrate 0.2% / Timolol 0.5% Ophthalmic solution, was clinically evaluated for the reduction of elevated intraocular pressure in patient with glaucoma or ocular hypertension. See Clinical Review and Package Insert for further details.

Brimonidine Tartrate 0.2% / Timolol 0.5% Ophthalmic solution is supplied sterile in white opaque plastic LDPE bottles and tips with blue HIPS caps as follows: [redacted], 5 mL in [redacted] bottle (NDC 0023-9211-05), 10 mL in [redacted] bottle (NDC 0023-9211-10), 15 mL in 15 ml bottle (NDC 0023-9211-15). The recommended dose for adults is one drop of the drug product in each affected eye(s) twice daily.

If more than one topical ophthalmic product is to be used, the different product should be instilled at least [redacted] minutes apart.

The product should be stored at 15-25°C (59-77°F) and protected from light.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments has ultimately provided adequate information on the chemistry, manufacturing and controls for the production of Brimonidine Tartrate 0.2% / Timolol 0.5% Ophthalmic Solution. The acceptance criteria for benzalkonium chloride, osmolality and impurities concentration have

been tightened to reflect the actual data observed in the long term stability study of the drug product. Meanwhile, the acceptance criteria of the residual solvents for timolol maleate have been revised.

A Microbiology consult review recommended an approval (review #1 11/30/01) action. Based on profile, all 5 manufacturing and testing sites were accepted by the Office of Compliance.

Based on the **24 months** long-term stability data for three (3) primary registration batches the proposed 24-month expiration dating for the drug product is acceptable.

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 21-398
HFD-550/Chem Team Leader/LNg
HFD-830/CWChan
HFD-550/MED/JHarris
HFD-550/Chem Reviewer/YLu
HFD-550/CSO/MPuglisi
HFD-550/MED/WChambers

6 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 8

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/s/

Yong-De Lu
3/7/05 04:27:07 PM
CHEMIST

Linda Ng
3/8/05 08:48:11 AM
CHEMIST

CHEMISTRY REVIEW

NDA 21-398

COMBIGAN™
(Brimonidine Tartrate 0.2% / Timolol 0.5%)
Ophthalmic Solution

Allergan Inc.

Yong-de Lu, Ph.D.

Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products

HFD-550

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Chemistry Review Data Sheet

1. NDA 21-398

2. REVIEW #: 1

3. REVIEW DATE: 07-Mar-2002

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	17-Sep-2001
Amendment (BC)	15-Jan -2002
Amendment (BC)	31-Jan –2002
Amendment (BC)	22-Feb -2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Allergan Inc.
Address:	2525 Dupont Drive P.O.Box 19534 Irvine, CA 92623-9534
Representative:	Lewis Gryziewicz, Director of Regulatory Affairs
Telephone:	714-246-6088

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	COMBIGAN™
b) Non-Proprietary Name (USAN):	Brimonidine Tartrate 0.2%/Timolol 0.5% Ophthalmic Solution
c) Code Name/#:	AGN 190342-LF/AGN 196156-H/Formula 9262X
d) Chem. Type/Submission Priority:	
• Chem. Type:	4
• Submission Priority:	S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Selective alpha-2 adrenergic agonist. Indicated for reduction of elevated intraocular pressure in patient with glaucoma or ocular hypertension.

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 0.2%/0.5% (w/v)(Briminidine Tartrate/Timolol)

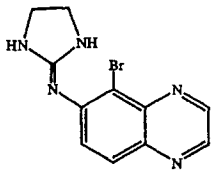
13. ROUTE OF ADMINISTRATION: Topical, ophthalmic, one drop per eye twice daily

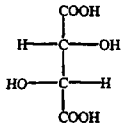
14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. _____ SPOTS product – Form Completed

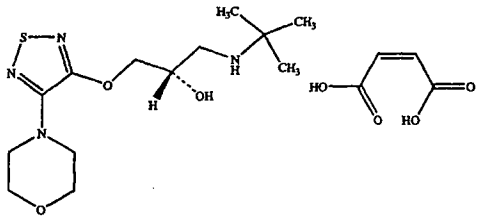
___X___ Not a SPOTS product

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





Brimonidine Tartrate : 5-Bromo-6-(2-imidazolin-2-ylamino)quinoxaline L-tartrate
$C_{15}H_{16}N_5O_6Br$, MW 442.24, [59803-98-4]



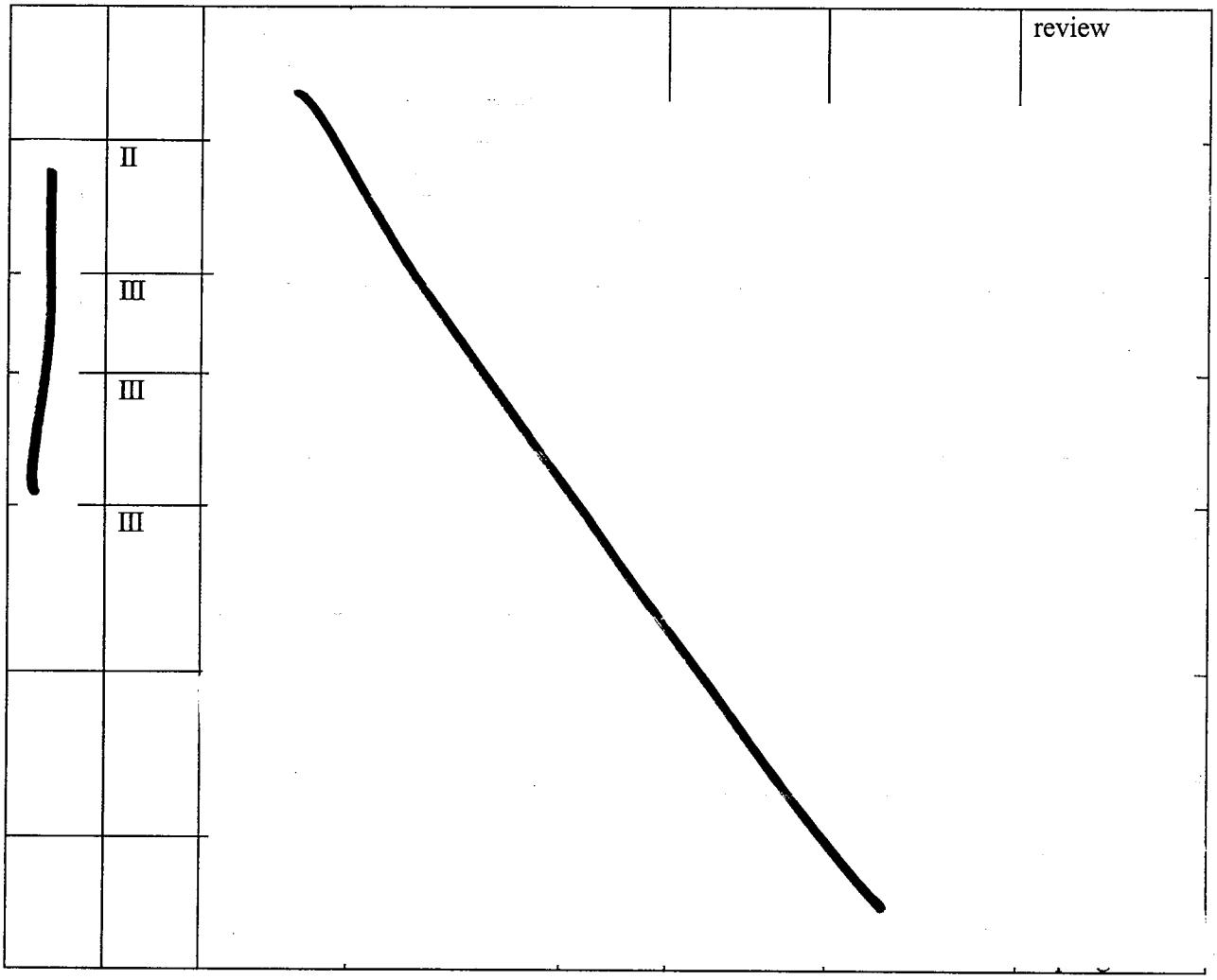
Timolol Maleate: (–)-1-(t-Butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)-oxy]-2-propanol maleate (1: 1)
C17H28N4O7S, MW 432.49, [26921-17-5]. See USP24 page 1663 for detail.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
11086	I	Allergan, Inc.	Manufacturing site for finished product (Waco,TX)	2	Closed	N/A	No need to review
2461	III	Allergan, Inc.	Supplier of plastic ophthalmic component	1	Adequate	01-Mar-02	USP qualification data are in NDA
[redacted]	I	[redacted]	[redacted]	2	Updated on 5/3/95	N/A	No need to review
[redacted]	I	[redacted]	[redacted]	2	Closed	N/A	No need to

Chemistry Review Data Sheet



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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	58,460	Brimonidine Tartrate 0.2% /Timolol 0.5%
NDA	20-613	ALPHAGAN® 0.2%
NDA	20-262	ALPHAGAN P 0.15%
ANDA	74-746	Timolol Maleate Oph. Sol. 0.25%
ANDA	74-747	Timolol Maleate Oph. Sol. 0.5%

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES (5 manufacturing sites)	All Acceptable	16-Oct-01	
Pharm/Tox	Approval	23-Jan-02	Zhou Chen (Consulted)
LNC			
Methods Validation	Sent to District Labs	28-Mar-02	
OPDRA			
EA			
Microbiology	Approval	30-Nov-01	Paul Stinavage

The Chemistry Review for NDA 21-398

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for **approval**. The drug product is granted [redacted] expiration dating period.

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

N/A

II. Summary of Chemistry Assessments

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

Brimonidine tartrate (AGN 190342-LF) is currently available in the approved glaucoma product ALPHAGAN® (NDA 20-613) and ALPHGAN®P (NDA 21-262). Timolol is currently available in the approved glaucoma product Timolol Maleate Ophthalmic Solution, USP 0.25% (ANDA 74-746) and Timolol Maleate Ophthalmic Solution, USP 0.5% (ANDA 74-747).

For the majority of chemistry, manufacturing and controls information regarding brimonidine tartrate, the reference is made to the drug substance section of NDA 20-613. The suppliers of brimonidine tartrate are [redacted] There have been no CMC changes involved in brimonidine tartrate since the approval of NDA 20-613.

Timolol maleate is manufactured by [redacted] currently approved in ANDA 74-746. [redacted] for timolol maleate was updated on to contain a new version of specification of timolol maleate. The DMF holder was asked by an investigator to include residual solvents testing. The acceptance criteria for [redacted] have been revised to reflect real time data. The NDA applicant has updated the acceptance specification for the drug substance to include the residual solvents.

Brimonidine tartrate and timolol are currently marketed individually as monotherapies for the treatment of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension, which was approved via NDA 20-613 and

ANDA 74-746. Applicant has combined brimonidine tartrate and timolol into a single formulation to provide the benefit of adjunctive therapy with a more convenient dosing regimen. The same excipients but in different ratios are used in this combination product. Even more, the concentration of [redacted] in the drug product is reduced to achieve [redacted] requirement. The benzalkonium chloride (BAK) concentration is [redacted] and the formulation meets USP antimicrobial preservative effectiveness criteria.

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

The drug product, Brimonidine Tartrate 0.2% / Timolol 0.5% Ophthalmic solution, was clinically evaluated for the reduction of elevated intraocular pressure in patient with glaucoma or ocular hypertension. See Clinical Review and Package Insert for further details.

Brimonidine Tartrate 0.2% / Timolol 0.5% Ophthalmic solution is supplied sterile in white opaque plastic LDPE bottles and tips with blue HIPS caps as follows: [redacted], 5 mL in [redacted] bottle (NDC 0023-9211-05), 10 mL in [redacted] bottle (NDC 0023-9211-10), 15 mL in 15 ml bottle (NDC 0023-9211-15). The recommended dose for adults is one drop of the drug product in each affected eye(s) twice daily.

If more than one topical ophthalmic product is to be used, the different product should be instilled at least [redacted] minutes apart.

The product should be stored at 15-25°C (59-77°F) and protected from light.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments has ultimately provided adequate information on the chemistry, manufacturing and controls for the production of Brimonidine Tartrate 0.2% / Timolol 0.5% Ophthalmic Solution. The acceptance criteria for benzalkonium chloride, osmolality and impurities concentration have

been tightened to reflect the actual data observed in the long term stability study of the drug product. Meanwhile, the acceptance criteria of the residual solvents for timolol maleate have been revised.

A Microbiology consult review recommended an approval (review #1 11/30/01) action. Based on profile, all 5 manufacturing and testing sites were accepted by the Office of Compliance.

The applicant proposed 24-month expiration dating for the drug product. However, based on the analysis of the available stability data for the product packaged in the commercial container/closure system, only [redacted]xpiration dating is granted. An extention to 24-month expiration dating period will not be granted until the 24-month long term stability data become available and found adequate.

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 21-398
HFD-550/Chem Team Leader/LNg
HFD-830/CWChan
HFD-550/MED/JHarris
HFD-550/Chem Reviewer/YLu
HFD-550/CSO/MPuglisi
HFD-550/MED/WChambers

48 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 9

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

/s/

Yong-De Lu
3/29/02 01:43:04 PM
CHEMIST

Linda Ng
3/29/02 02:25:11 PM
CHEMIST