

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-548Orig1s000**

**CHEMISTRY REVIEW(S)**

**NDA 22-548**

**ZYMAXID (Gatifloxacin Ophthalmic Solution) 0.5%**

**Allergan, Inc.**

**Lin Qi**

**Division of Anti-Infective and Ophthalmology Product**

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# Chemistry Review Data Sheet

1. NDA 22-548
2. REVIEW #: 2
3. REVIEW DATE: April 26, 2010
4. REVIEWER: Lin Qi
5. PREVIOUS DOCUMENTS:

Previous Documents

IND 59,408

Document Date

12/3/1999

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Amendment

Amendment

Amendment

Amendment

Amendment

Amendment

Document Date

7/30/2009

8/31/2009

10/2/2009

11/24/2009

1/8/2010

2/26/2009

4/20/2010

7. NAME & ADDRESS OF APPLICANT:

Name: Allergan, Inc.

Address: 2525 Dupont Drive  
Irvine, CA 92612

Representative: Joanne Lemmo

Telephone: 714-246-5844

Email: [Lemmo\\_joanne@allergan.com](mailto:Lemmo_joanne@allergan.com)

Fax: 714-246-4051

## Chemistry Review Data Sheet

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: ZYMAXID
- b) Non-Proprietary Name (USAN): Gatifloxacin
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 5
  - Submission Priority: S

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

## 10. PHARMACOL. CATEGORY: Anti-infective

## 11. DOSAGE FORM: Ophthalmic Solution

## 12. STRENGTH/POTENCY: 0.5%

## 13. ROUTE OF ADMINISTRATION: Topical, ophthalmic

14. Rx/OTC DISPENSED:  Rx  OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

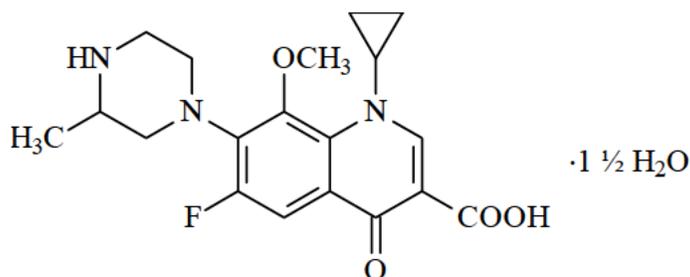
Not a SPOTS product

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

Chemical Name: (±)-1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid, sesquihydrate

## Chemistry Review Data Sheet

Structural Formula:

Molecular Formula:  $C_{19}H_{22}FN_3O_4 \cdot 1 \frac{1}{2} H_2O$ 

Molecular Weight: 402.42

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	3		Aug 25, 2009	LOA 1/17/00
	III			1		Mar 4, 2010 Lin Qi	LOA 5/15/09
	II			1		Mar 4, 2010 Lin Qi	LOA 5/13/09

<sup>1</sup> 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")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

## Chemistry Review Data Sheet

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Cross reference	NDA 21-493	Drug Substance, Same Applicant

## 18. STATUS:

**ONDC:**

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics			
EES	Acceptable		CDER Office of Compliance
Pharm/Tox			
Biopharm			
LNC			
Methods Validation			
OPDRA			
EA			
Microbiology	Approval		Robert Mello

# The Chemistry Review for NDA 22-548

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. An "Acceptable" site recommendation from the Office of Compliance has been made. The labels have adequate information as required. Therefore, from the CMC perspective, this NDA 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)

The drug substance, gatifloxacin (also referred to as AGN-198782), is a white to pale yellow (b)(4) powder. Gatifloxacin has two pKa values of 5.9 and 9.3. The chemical name is (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate. The molecular weight of gatifloxacin sesquihydrate is 402.4 g/mol. Gatifloxacin is the same drug substance as is currently used in ZYMAR (gatifloxacin ophthalmic solution 0.3%) in NDA 21-493. The drug substance is manufactured at (b)(4). Refer to NDA 21-493 and DMF (b)(4) for drug substance information.

The drug product, gatifloxacin ophthalmic solution 0.5% is a clear, pale yellow, sterile, preserved aqueous solution containing gatifloxacin (0.5% w/v anhydrous basis). The inactive ingredients include sodium chloride, edetate disodium, benzalkonium chloride and purified water (See page 15 for composition). The pH of the bulk solution is adjusted using either 1N sodium hydroxide or 1N hydrochloric acid resulting in a final product release pH of (b)(4). The osmolality of the drug product is at 265 - 315 mOsm/kg at release. All excipients are tested to USP/NF. Except for sodium hydroxide and hydrochloric acid, all excipients are tested for endotoxin. See page 29 for product specification.

Gatifloxacin ophthalmic solution 0.5% will be filled in a 5-mL multiple-dose bottle with a tip manufactured of low density polyethylene (LDPE, (b)(4)) and a cap manufactured of (b)(4). The finished product is labeled with a pressure-sensitive label. The tamper evident security feature for the primary

## Executive Summary Section

packaging container is a (b) (4) seal surrounding the cap. The planned market configurations include a 1 mL fill in a 5-mL bottle (physician sample), a 2.5 mL fill in a 5-mL bottle, (b) (4). The secondary packaging consists of a unit cardboard carton and an insert.

The expiration dating period for the gatifloxacin ophthalmic solution 0.5% is 24 months in the proposed market configuration for the 2.5 mL/5-mL (b) (4) configurations and 12 months in the physician sample configuration (1-mL/5-mL). A storage statement of 'Store at 15°-25°C (59°-77°F). Protect from freezing.' is appropriate and justified by the stability data.

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

The applicant holds an approved NDA 21-493 for ZYMAR (gatifloxacin ophthalmic solution 0.3%) with a four times a day (QID) dosing. In the current application, the applicant developed a higher strength formulation, gatifloxacin ophthalmic solution 0.5%, with a proposed twice a day (BID) dosing for a similar indication which is a broad spectrum antibacterial. The proposed dosage and administration is "Patients 1 year of age or older: Day 1: Instill one drop every two hours in the affected eye(s) while awake, up to 8 times. Days 2 through (b) (4) Instill one drop two times daily in the affected eye(s) while awake, (b) (4) ."

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

The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period. The labels have adequate information as required.

A recommendation from the Office of Compliance on the site acceptability has been made on April 18, 2010 (See attachment). There are no outstanding issues in quality microbiology review and the quality microbiological reviewer recommended approval for this application (See microbiological review dated April 16, 2010 by Dr. Robert Mello). In an amendment dated April 20, 2010, an additional 2.5 mL physician sample was proposed by the applicant and found acceptable by the division per discussions on the wrap-up review meeting dated April 26, 2010. Therefore, from the CMC perspective, this NDA is recommended for approval.

## Executive Summary Section

**III. Administrative****A. Reviewer's Signature**

{See signature in DARRTS.}

**B. Endorsement Block**

ChemistName/Date: Lin Qi/April 26, 2010

ChemistryBranchChiefName/Date: Stephen Miller/April 26, 2010

ProjectManagerName/Date: Jeannie David/April 26, 2010

Constantine Markos/April 26, 2010

**C. CC Block**

{See cc list in DARRTS }

54 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22548	ORIG-1	ALLERGAN	GATIFLOXACIN OPHTHALMIC SOLUTION 0.5%

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/s/

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LIN QI  
04/26/2010

STEPHEN P MILLER  
04/27/2010

**NDA 22-548**

**Gatifloxacin Ophthalmic Solution 0.5%**

**Allergan, Inc.**

**Lin Qi**

**Division of Anti-Infective and Ophthalmology Product**

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# Chemistry Review Data Sheet

1. NDA 22-548
2. REVIEW #: 1
3. REVIEW DATE: March 5, 2010
4. REVIEWER: Lin Qi
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

Do folks list the IND here or somewhere else?

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original	7/30/2009
Amendment	8/31/2009
Amendment	10/2/2009
Amendment	11/24/2009
Amendment	1/8/2010
Amendment	2/26/2009

7. NAME & ADDRESS OF APPLICANT:

Name: Allergan, Inc.

Address: 2525 Dupont Drive  
Irvine, CA 92612

Representative: Joanne Lemmo

Telephone: 714-246-5844

Email: [Lemmo\\_joanne@allergan.com](mailto:Lemmo_joanne@allergan.com)

Fax: 714-246-4051

## Chemistry Review Data Sheet

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: ZYMAXID
- b) Non-Proprietary Name (USAN): Gatifloxacin
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 5
  - Submission Priority: S

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

## 10. PHARMACOL. CATEGORY: Anti-infective

## 11. DOSAGE FORM: Ophthalmic Solution

## 12. STRENGTH/POTENCY: 0.5%

## 13. ROUTE OF ADMINISTRATION: Topical, ophthalmic

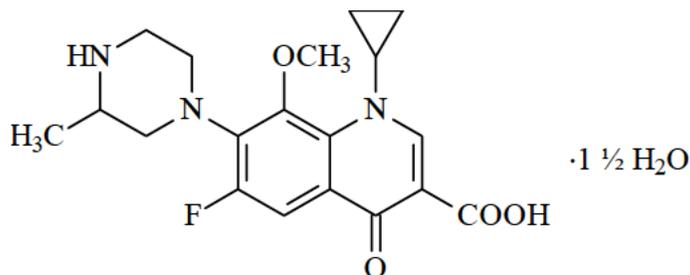
14. Rx/OTC DISPENSED:  Rx  OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#): SPOTS product – Form Completed Not a SPOTS product

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

Chemical Name: (±)-1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid, sesquihydrate

## Chemistry Review Data Sheet

Structural Formula:

Molecular Formula: C<sub>19</sub>H<sub>22</sub>FN<sub>3</sub>O<sub>4</sub> · 1 ½ H<sub>2</sub>O

Molecular Weight: 402.42

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	3		Aug 25, 2009	LOA 1/17/00
	III			1		Mar 4, 2010 Lin Qi	LOA 5/15/09
	II			1		Mar 4, 2010 Lin Qi	LOA 5/13/09

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2 – Type 1 DMF

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6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Cross reference	NDA 21-493	Drug Substance, Same Applicant

### 18. STATUS:

#### ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Pending		CDER Office of Compliance
Pharm/Tox			
Biopharm			
LNC			
Methods Validation			
OPDRA			
EA			
Microbiology	Pending		Robert Mello

# The Chemistry Review for NDA 22-548

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This application is not recommended for approval as there are pending issues related to the GMP status of facilities and a satisfactory quality microbiological review. All other drug product quality (CMC) issues are satisfactory.

#### 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)

The drug substance, gatifloxacin (also referred to as AGN-198782), is a white to pale yellow (b)(4) powder. Gatifloxacin has two pKa values of 5.9 and 9.3. The chemical name is (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate. The molecular weight of gatifloxacin sesquihydrate is 402.4 g/mol. Gatifloxacin is the same drug substance as is currently used in ZYMAR (gatifloxacin ophthalmic solution 0.3%) in NDA 21-493. The drug substance is manufactured at (b)(4). Refer to NDA 21-493 and DMF (b)(4) for drug substance information.

The drug product, gatifloxacin ophthalmic solution 0.5% is a clear, pale yellow, sterile, preserved aqueous solution containing gatifloxacin (0.5% w/v anhydrous basis). The inactive ingredients include sodium chloride, edetate disodium, benzalkonium chloride and purified water (See page 15 for composition). The pH of the bulk solution is adjusted using either 1N sodium hydroxide or 1N hydrochloric acid resulting in a final product release pH of (b)(4). The osmolality of the drug product is at 265 - 315 mOsm/kg at release. All excipients are tested to USP/NF. Except for sodium hydroxide and hydrochloric acid, all excipients are tested for endotoxin. See page 29 for product specification.

Gatifloxacin ophthalmic solution 0.5% will be filled in a 5-mL multiple-dose bottle with a tip manufactured of low density polyethylene (LDPE, (b)(4)) and a cap manufactured of (b)(4). The finished product is labeled with a pressure-sensitive label. The tamper evident security feature for the primary packaging container is a (b)(4) seal surrounding the cap. The planned market

## Executive Summary Section

configurations include a 1 mL fill in a 5-mL bottle (physician sample), a 2.5 mL fill in a 5-mL bottle, (b) (4). The secondary packaging consists of a unit cardboard carton and an insert.

The expiration dating period for the gatifloxacin ophthalmic solution 0.5% is 24 months in the proposed market configuration for the 2.5 mL/5-mL and 5 mL/5-mL configurations and 12 months in the physician sample configuration (1-mL/5-mL). A storage statement of 'Store at 15°-25°C (59°-77°F). Protect from freezing.' is appropriate and justified by the stability data.

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

The applicant holds an approved NDA 21-493 for ZYMAR (gatifloxacin ophthalmic solution 0.3%) with a four times a day (QID) dosing. In the current application, the applicant developed a higher strength formulation, gatifloxacin ophthalmic solution 0.5%, with a proposed twice a day (BID) dosing for a similar indication which is a broad spectrum antibacterial. The proposed dosage and administration is "Patients 1 year of age or older: Day 1: Instill one drop every two hours in the affected eye(s) while awake, up to 8 times. Days 2 through (b) (4) Instill one drop two times daily in the affected eye(s) while awake, (b) (4) ."

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

The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period. The labels have adequate information as required.

However, a recommendation from the Office of Compliance on the site acceptability has not been made as of the date of this review, there are outstanding aspects of the quality microbiology review. Therefore, from the CMC perspective, this NDA is ***not recommended*** for approval until the site acceptability is established and the microbiological aspects are found satisfactory in the product quality microbiological review review.

**III. Administrative****A. Reviewer's Signature**

{See signature in DARRTS.}

## Executive Summary Section

**B. Endorsement Block**

ChemistName/Date: Lin Qi/March 30, 2010

ChemistryBranchChiefName/Date: Stephen Miller/March 30, 2010

ProjectManagerName/Date: Jeannie David/March 30, 2010

Constantine Markos/ March 30, 2010

**C. CC Block**

{See cc list in DARRTS }

50 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22548	ORIG-1	ALLERGAN	GATIFLOXACIN OPHTHALMIC SOLUTION 0.5%

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

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/s/

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LIN QI  
03/30/2010

STEPHEN P MILLER  
04/01/2010