CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-493

CHEMISTRY REVIEW(S)

NDA 21-493

ZYMAR™
Gatifloxacin Ophthalmic Solution 0.3%

ALLERGAN, INC.

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

HFD-550

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-493

2. REVIEW #: 2

3. REVIEW DATE: March 18, 2003

4. REVIEWER: Libaniel Rodriguez

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	29-May-2002
BC	23-Sep-2002
BC	13-Feb-03
BC	25-Feb-03

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
BC	10-Mar-03
BC	12-Mar-03

7. NAME & ADDRESS OF APPLICANT:

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

Representative: Elizabeth Bancroft

Telephone: 714 246 4391

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ZYMAR™
b) Non-Proprietary Name (USAN): Gatifloxacin
c) Code Name/# (ONDC only): AGN 198782
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: Section 505(b)(1) of the Food, Drug and Cosmetic Act.

10. PHARMACOL. CATEGORY: Antibacterial

11. . DOSAGE FORM: Ophthalmic Solution

12. STRENGTH/POTENCY: 0.3%

13. ROUTE OF ADMINISTRATION: Topical Ophthalmic

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note25]:

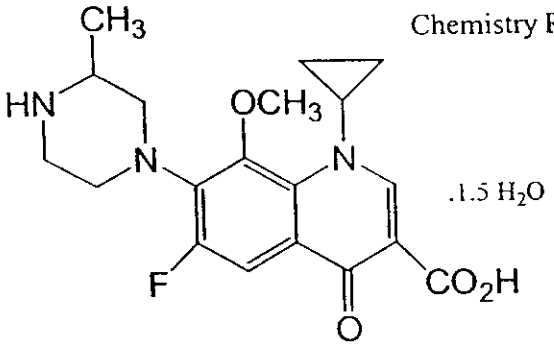
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Structural Formula:

Chemistry Review Data Sheet



Molecular Formula

$C_{19}H_{22}FN_3O_4 \cdot 1.5H_2O$

Chemical Name

(±)-1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinoline-carboxylic acid, sesquihydrate. *CAS-180200-66-2.*

Molecular Weight

402.42

Chemical Abstracts Numbers

180200-66-2 racemate as sesquihydrate

160738-57-8 racemate, no hydration specified

11211-59-3 without stereochemical designation and hydration specified

USAN name

Gatifloxacin

Allergan Code Number (AGN #)

AGN 198782

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	All Facilities Acceptable	13-Feb-03	Office of Compliance
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Pending	19-Mar-03	Philadelphia and San Juan District Laboratories.
OPDRA			
EA			
Microbiology	Approval	16-Jul-02	Paul Stinavage

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-493

The Executive Summary

A. Recommendations

A. Recommendation and Conclusion on Approvability

From the point of view of CMC, 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)

Zymar drug product is a sterile, clear, yellow- — color, isotonic solution containing 0.3% w/v gatifloxacin and 0.005% w/v benzalkonium chloride as the preservative. Excipients include sodium chloride ——— edetate disodium ——— and purified water as the vehicle. The pH of the final solution is adjusted to — using — hydrochloric acid and/or —sodium hydroxide. The buffering action of gatifloxacin maintains the finished product pH of ~ . All the excipients are USP/NF compendial grade materials. Zymar is ——— ——— into multi-dose eye drop bottles in the following configurations, ——), 2.5 mL/6 mL bottle and 5.0 mL/8 mL bottle. The bottles and tips are made of low density polyethylene (LDPE) and are colored white. The cap is made of high impact polystyrene (HIPS) and is colored beige/tan to comply with the AAO color scheme for anti-infectives. The bottles and tips are sterilized with ——— , the caps are sterilized with ——
The commercial product will be manufactured at Allergan's manufacturing facilities in Waco, Texas and Westport, Ireland. Both facilities were found acceptable on profile by the Office of Compliance.

The drug substance gatifloxacin is a fluoroquinolone antibacterial agent developed by Kyorin Pharmaceutical Co., Ltd (Tokyo, Japan). Gatifloxacin drug substance was approved in two other NDAs, 21-062 tablets and 21-062 intravenous injection on December 27, 1999. All the relevant information for gatifloxacin drug substance was submitted to the FDA in Kyorin's ~ . A letter of authorization from Kyorin for Allergan to include the information in their application by reference, dated March 18, 2002 is appropriately included in the application. — was reviewed and found adequate by this reviewer in September 22, 2002.

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

Gatifloxacin 0.3% ophthalmic solution is intended for the treatment of acute bacterial conjunctivitis in pediatric and adult patients. It is supplied in multiple-dose eyedropper bottles. The recommended duration of treatment is 7 days. One drop is instilled in the affected eye every two hours while awake for the first two days. The remaining days application should be 4 times per day every four hours. There are no special preparations prior to the application of this product to the eye.

The recommended expiry for this drug product based on the data submitted is 24 months for the 2.5 mL/6 mL and 5 mL/8 mL package configurations and [redacted] mL package configuration

C. Basis for Approvability or Not-Approval Recommendation

Many issues were raised and resolved during this review cycle. For example, tightening of a proposed acceptance criterion to reflect actual data. It was also noticed that the registration stability batches did not have the same color cap as the commercial batches, therefore, stability data for the commercial batches with the correct color cap was requested. The application was amended with two stability data updates for both the registration and commercial batches. The first update, [redacted] months of stability data for the registration batches, [redacted] months for the commercial batchess, showed many failures for [redacted] for the commercial batches. At this point Allergan found that the method used for this measurement was not adequate and replaced for their backup method. The backup method yielded results within acceptance criteria for the batches that had failed previously. The second upgrade, [redacted] months of stability data for the registration batches and [redacted] months for the commercial batches, had all the parameters measured within acceptance criteria. However, with this update Allergan reported , [redacted] This occurred at the [redacted] and [redacted] months stability stations for all the primary registration lots and most of the sublots. The report did not contain any data or results from any study about the [redacted] or a satisfactory explanation and solution to this problem. Receipt of the studies, explanation and solution of the problem is one of the reasons for the approvability of this of this application. The second reason is the proposed [redacted]

[redacted]

On March 12, 2003, Allergan amended the application with the submission of a fill volume study to adequately demonstrate that the [redacted] at the base of the tip was not a cause for significant loses of drug product. The amendment also contained a very

detailed technical study to determine the cause of the ~~~ The results of the study indicated that ~~~ .

~~~ Appropriate container/closure integrity tests and results were also included in this studies. Based on the updated stability data and the reports above, it can be concluded that the quality of the drug product has not been compromised by the formation of the ~~~

III. Administrative

A. Reviewer's Signature

Libaniel Rodriguez, Review Chemist

B. Endorsement Block

Linda Ng, Chemistry Team Leader

C. CC Block

Chi Wan Chen, DD HFD-830
Wiley Chambers, DDD HFD-550
Lori Gorski, Project Manager HFD-550

APPEARS THIS WAY
ON ORIGINAL
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✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/s/

Libaniel Rodriguez
3/19/03 12:35:51 PM
CHEMIST
Review # 2 Approval

Linda Ng
3/19/03 03:22:04 PM
CHEMIST

NDA 21-493

ZYMAR™

ALLERGAN, INC.

Libaniel Rodriguez, Ph. D.
DAAODP

APPEARS THIS WAY
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Table of Contents

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1. NDA 21-493

2. REVIEW #: 1

3. REVIEW DATE: February 25, 2003

4. REVIEWER: Libaniel Rodriguez

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	29-May-2002
BC	23-Sep-2002
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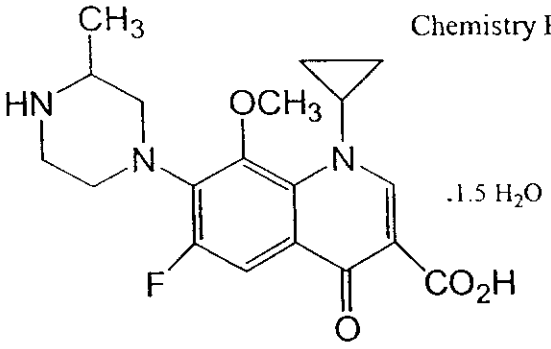

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USAN name

Gatifloxacin

Allergan Code Number (AGN #)

AGN 198782

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	22/08/2002	
	III			1	Adequate	01/10/2002	
	III			3	Adequate	08/08/2000	
	III			3	Adequate	27/03/2002	
	III			3 6	Adequate	14/02/2001	

[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	21-061	Tablets
NDA	21-062	injection
IND	59408	Active

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	All Facilities Acceptable	13-Feb-03	Office of Compliance
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	In Progress		
OPDRA			
EA			
Microbiology	Approval	16-Jul-02	Paul Stinavage

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The Chemistry Review for NDA 21-493

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III. Administrative

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Libaniel Rodriguez, Review Chemist /07-Feb-03

B. Endorsement Block

Linda Ng, Chemistry Team Leader /07-Feb-03

C. CC Block

Chi Wan Chen DD HFD-830
Wiley Chambers DDD HFD-550

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/s/

Libaniel Rodriguez
3/7/03 03:41:14 PM
CHEMIST
Approvable CMC

Linda Ng
3/7/03 04:19:40 PM
CHEMIST
PM to note deficiencies on last page