# CLINICAL PHARMACOLOGY REVIEW

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| **NDA: 22-548** | Submission Date(s): 7/30/09 |
| **Drug** | Gatifloxacin Ophthalmic Solution, 0.5% |
| **Trade Name** | ZYMAXID™ (proposed) |
| **OCP Reviewers** | Ryan P. Owen, Ph.D. |
| **OCP Team Leader** | Charles Bonapace, Pharm.D. |
| **OCP Division** | DCP4 |
| **OND division** | DAIOP (520) |
| **Sponsor** | Allergan |
| **Relevant IND(s)** | 59,408 |
| **Submission Type; Code** | Original NDA; 505(b)(1) application |
| **Formulation; Strength(s)** | Solution containing 5 mg/mL gatifloxacin (0.5%) |
| **Indication** | Bacterial Conjunctivitis |
| **Dosage and Administration** | Day 1: Instill one drop every two hours in the affected eye(s) while awake, up to 8 times<br>Days 2-5: Instill one drop two times daily in the affected eye(s) while awake, approximately 12 hours apart |

## 1. Executive Summary

Gatifloxacin is a fluoroquinolone-class antibiotic. In this NDA, gatifloxacin ophthalmic solution 0.5% is proposed for the treatment of bacterial conjunctivitis. The proposed dosing regimen and route of administration are as follows: On Day 1, instill one drop every two hours in the affected eye(s) while awake, up to 8 times, and on Days 2-5, instill one drop two times daily in the affected eye(s) while awake, approximately 12 hours apart.

Gatifloxacin has been previously approved in the form of topical eye drops (ZYMAR® gatifloxacin ophthalmic solution 0.3%). Gatifloxacin was formerly marketed as an oral antibiotic in 200 and 400 mg doses. The oral formulation of gatifloxacin was pulled from the market in 2006.

The recommended dosing regimen for ZYMAR® is as follows: on Days 1 and 2, instill one drop every two hours in the affected eye(s) while awake, up to 8 times daily, and on Days 3-7, instill one drop up to four times daily while awake.

Gatifloxacin has been reformulated to the higher dosage strength (0.5%) so that the dosing frequency could be reduced while maintaining or improving the anti-microbial properties. The excipients are the same between the 0.3% and the 0.5% formulations. The 0.3% and 0.5% formulations are nearly identical - the 0.5% formulation has an increased gatifloxacin concentration, a reduced pH (to ensure solubility of the drug substance), and a slightly lower sodium chloride concentration (for tonicity).

In a Phase 1 pharmacokinetic trial submitted under the ZYMAR® (Gatifloxacin 0.3%) NDA (NDA 21-493), systemic gatifloxacin concentrations were below the limit of quantitation (5 ng/mL) following dosing of two drops eight times daily for three days with Gatifloxacin 0.5%. Accordingly, the systemic concentrations of gatifloxacin following the proposed dosing regimen of one drop eight times daily on Day 1 and one drop two times daily on Days 2-5 are likely to be undetectable. Although the $C_{max}$ with Gatifloxacin 0.5% may be slightly higher than the ZYMAR® (Gatifloxacin 0.3%) dosing regimen, the total exposure is likely to be less.

### 1.1 Recommendation

A waiver of the requirement for submission of evidence of in vivo bioavailability for the drug product gatifloxacin ophthalmic solution 0.5% is hereby granted under CFR 320.22 (e). Pharmacokinetic information from NDA 21-493 and from the previously marketed oral tablet of gatifloxacin supports this recommendation.

### 1.2 Phase 4 Commitments

No Phase 4 commitments are recommended.

## 1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

This NDA does not contain any new clinical pharmacology studies. Reference is made to the clinical pharmacology program conducted under NDA 21-493. In support of the increased formulation strength of gatifloxacin, the Sponsor has submitted two identical Phase 3 studies which examined the safety and efficacy of the new formulation. Under the previous clinical pharmacology program, systemic concentrations were undetectable (< 5 ng/mL) following a total topical daily dose of 2.56 mg/day for three days.

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Office of Clinical Pharmacology
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Charles R. Bonapace, Pharm.D.
Team Leader

## 2. Question-Based Review

### 2.1 General attributes of the drug

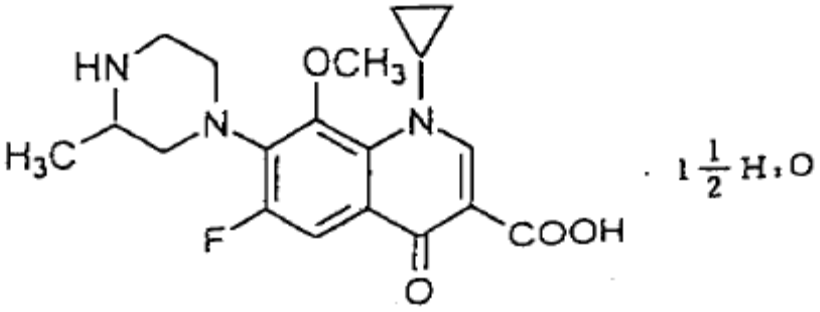
This submission is an NDA for a topically administered ophthalmic drug product; therefore, only the relevant questions from the OCP question-based review template are included below.

#### 2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to the clinical pharmacology and biopharmaceutics review?

The drug substance in the current NDA (gatifloxacin) is the same as in the currently approved NDA 21-493 (ZYMAR®, gatifloxacin ophthalmic solution 0.3%). Gatifloxacin is a white to pale yellow crystal or crystalline powder. The excipients in the drug product include sodium chloride, edentate disodium, and benzalkonium chloride, and sodium hydroxide/hydrochloric acid (to adjust to pH 5.2-5.7). Table 1 describes the function of the excipients.

**Structural Formula:** $C_{19}H_{22}FN_3O_4 \cdot 1.5\ H_2O$

**Chemical Structure:**




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

**Other Names:** AM-1155; Allergan PM #12546

**Chemical Abstract Service Registry Number:** CAS 180200-66-2

**Molecular Weight:** 402.42 g/mol

The quantitative composition of the proposed gatifloxacin ophthalmic solution drug product is shown in Table 1.

**Table 1: Product formulation composition of Gatifloxacin Ophthalmic Solution 0.5%**

| Ingredient | Grade | Function | Concentration |
|---|---|---|---|
| Gatifloxacin Sesquihydrate (% w/v) | N/A | Active Ingredient | 0.5 |
| Benzalkonium Chloride (% w/v) | [redacted] | [redacted] | 0.005 |
| Edetate Disodium (% w/v) | | | [redacted] |
| Sodium Chloride (% w/v) | | | |
| Hydrochloric Acid [redacted] or Sodium Hydroxide [redacted] | NF/Ph Eur | pH adjustment | |
| Purified Water[a] | USP/Ph Eur | [redacted] | |

a Purified Water meets bacterial endotoxins specification for Water for Injection

Source: 3.2.P.1

### 2.1.2 What are the proposed mechanism(s) of action and therapeutic indications(s)?

Gatifloxacin is a fluororquinolone antibiotic. The mechanism of action for fluoroquinolones is via the inhibition of bacterial enzymes DNA gyrase and topoisomerase IV, which ultimately results in cell death. The proposed indication for gatifloxacin ophthalmic solution 0.5% is the treatment of bacterial conjunctivitis.

### 2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dosing regimen for gatifloxacin ophthalmic solution 0.5% is as follows: On Day 1, instill one drop in the affected eye(s) every two hours while awake, up to eight times. On Days 2-5, instill one drop two times daily in the affected eye(s) while awake, approximately 12 hours apart.

## 2.2 General clinical pharmacology

### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

No clinical pharmacology studies were conducted in support of this NDA. The pharmacokinetics of gatifloxacin have been previously examined under the NDA for ZYMAR® (gatifloxacin ophthalmic solution 0.3%, NDA 21-493). The clinical program for gatifloxacin ophthalmic solution 0.5% consisted of two identically-designed Phase 3 studies. Both Phase 3 studies were multi-center, randomized, double-masked, parallel group studies which compared gatifloxacin ophthalmic solution 0.5% to vehicle in patients diagnosed with bacterial conjunctivitis. The study medication was administered to the qualified eye(s) up to 8 times on the first day, and twice daily on Days 2 through 5.

### 2.2.2 What are the PK characteristics of the drug?

The systemic exposure of gatifloxacin ophthalmic solution 0.5% has been studied in a clinical pharmacology study submitted under NDA 21-493. In a Phase 1 study in healthy volunteers, 0.5% gatifloxacin was administered as 2 drops eight times daily for 3 days (total daily dose = 2.56 mg). The resulting systemic concentrations were below the limit of quantitation for the assay (5 ng/mL). The current proposed regimen is one drop eight times daily on Day 1, followed by one drop two times daily on Days 2-5. That would mean the total daily dose on Day 1 would be 1.28 mg, and on Days 2-5, the total daily dose would be 0.32 mg/day. Over the course of the two treatment regimens, the Phase 1 study would result in a total dose of 7.68 mg over three days (which was undetectable), and the current proposed dosing regimen would result in a total dose of 2.56 over 5 days, which is also likely to be undetectable. The concentrations observed following oral administration of 400 mg gatifloxacin were approximately 800 times higher than the lower limit of quantitation (5 ng/mL) in the 0.5% gatifloxacin PK study. Therefore, the systemic exposures resulting from the proposed dosing regimen for gatifloxacin ophthalmic solution 0.5% will likely not be measurable, and are not likely to pose any risk for systemic toxicities.

**2.3 Intrinsic Factors**

Not applicable

**2.4 Extrinsic Factors**

Not applicable

**2.5 General Biopharmaceutics**

Not applicable

**2.6 Analytical section**

Not applicable

## 3. LABELING RECOMMENDATIONS

## 4. APPENDICES

Not applicable.

| 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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RYAN P OWEN
03/15/2010

CHARLES R BONAPACE
03/16/2010