

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### *APPLICATION NUMBER:*

**022548Orig1s002**

*Trade Name:* ZYMAXID

*Generic or Proper Name:* gatifloxacin

*Sponsor:* Allergan INC

*Approval Date:* September 8, 2016

*Indication:* for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:  
*Haemophilus influenzae, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus mitis group, Streptococcus oralis, Streptococcus pneumonia*

# CENTER FOR DRUG EVALUATION AND RESEARCH

## 022548Orig1s002

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022548Orig1s002**

**APPROVAL LETTER**



NDA 22548/S002

**SUPPLEMENT APPROVAL**

Allergan, Inc  
Attention: Hillary Keir  
Sr. Associate, Regulatory Affairs  
2525 Dupont Drive  
P. O. Box 19534  
Irvine, CA 92623-95234

Dear Ms. Keir:

Please refer to your Supplemental New Drug Application (sNDA) dated and received March 11, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ZYMAXID (gatifloxacin ophthalmic solution), 0.5%.

This Prior Approval supplemental new drug application provides for revisions to the Package Insert to comply with the Pregnancy and Lactation Labeling Rule (PLLR) as well as updates to the 6.2 Postmarketing Experience section.

**APPROVAL & LABELING**

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling text for the package insert, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Judit Milstein, Chief, Project Management Staff at 301-796-0763.

Sincerely,

*{See appended electronic signature page}*

Wiley A. Chambers, MD  
Deputy Director  
Division of Transplant and Ophthalmology Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

ENCLOSURE: Content of Labeling

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/s/  
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WILEY A CHAMBERS  
09/08/2016

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022548Orig1s002**

**LABELING**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use ZYMAXID® safely and effectively. See full prescribing information for ZYMAXID®.

**ZYMAXID® (gatifloxacin ophthalmic solution) 0.5% for topical ophthalmic use**

**Initial U.S. Approval: 1999**

**RECENT MAJOR CHANGES**

Contraindications, Hypersensitivity (4) 09/2016

Warnings and Precautions, Hypersensitivity (5.1) 09/2016

**INDICATIONS AND USAGE** ZYMAXID® is

a quinolone antimicrobial indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms: *Haemophilus influenzae*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus mitis* group, *Streptococcus oralis*, *Streptococcus pneumoniae* (1)

**DOSAGE AND ADMINISTRATION**

Day 1: Instill one drop every two hours in the affected eye(s) while awake, up to 8 times on Day 1.

Days 2 through 7: Instill one drop two to four times daily in the affected eye(s) while awake on Days 2 through 7. (2)

**DOSAGE FORMS AND STRENGTHS**

Ophthalmic solution: 0.5% gatifloxacin (5mg/mL) (3)

**CONTRAINDICATIONS**

ZYMAXID® is contraindicated in patients with a history of hypersensitivity to gatifloxacin, to other quinolones, or to any of the components in this medication. (4)

**WARNINGS AND PRECAUTIONS**

- Hypersensitivity (5.1)
- Growth of Resistant Organisms with Prolonged Use (5.2)
- Corneal Endothelial Cell Injury (5.3)

**ADVERSE REACTIONS**

Most common adverse reactions occurring in ≥ 1 % of patients included worsening of conjunctivitis, eye irritation, dysgeusia, and eye pain. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-433-8871 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 09/2016

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\*Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

ZYMAXID® is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:

- Aerobic gram-positive bacteria:  
*Staphylococcus aureus*  
*Staphylococcus epidermidis*  
*Streptococcus mitis* group\*  
*Streptococcus oralis*\*  
*Streptococcus pneumoniae*
- Aerobic gram-negative bacteria:  
*Haemophilus influenzae*

\*Efficacy for these organisms were studied in fewer than 10 infections.

### 2 DOSAGE AND ADMINISTRATION

- Day 1: Instill one drop every two hours in the affected eye(s) while awake, up to 8 times.
- Day 2 through Day 7: Instill one drop two to four times daily in the affected eye(s) while awake.

### 3 DOSAGE FORMS AND STRENGTHS

Ophthalmic solution: 0.5% gatifloxacin (5 mg/mL)

### 4 CONTRAINDICATIONS

ZYMAXID® is contraindicated in patients with a history of hypersensitivity to gatifloxacin, to other quinolones, or to any of the components in this medication [see *Warnings and Precautions (5.1)*].

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Hypersensitivity

Some patients receiving topical ophthalmic gatifloxacin experienced hypersensitivity reactions including anaphylactic reactions, angioedema (including pharyngeal, laryngeal, or facial edema), dyspnea, urticaria, and itching, even following a single dose. Rare cases of Stevens-Johnson Syndrome were reported in association with topical ophthalmic gatifloxacin use. If an allergic reaction to gatifloxacin occurs, discontinue the drug [see *Patient Counseling Information (17)*].

#### 5.2 Growth of Resistant Organisms with Prolonged Use

Prolonged use of ZYMAXID® may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, discontinue use and institute alternative therapy. Whenever clinical judgment dictates, examine the patient with the aid of magnification, such as slit lamp biomicroscopy and where appropriate, fluorescein staining.

### **5.3 Corneal Endothelial Cell Injury**

ZYMAXID® is for topical ophthalmic use. ZYMAXID® may cause corneal endothelial cell injury if introduced directly into the anterior chamber of the eye.

## **6 ADVERSE REACTIONS**

The following serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity [*see Contraindications (4) and Warnings and Precautions (5.1)*]
- Growth of Resistant Organisms With Prolonged Use [*see Warnings and Precautions (5.2)*]
- Corneal Endothelial Cell Injury [*see Warnings and Precautions (5.3)*]

### **6.1 Clinical Studies Experience**

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In clinical studies of patients with bacterial conjunctivitis treated with ZYMAXID® (N=717), the most frequently reported adverse reactions occurring in  $\geq 1$  % of patients were: worsening of the conjunctivitis, eye irritation, dysgeusia, and eye pain.

Additional adverse reactions reported with other formulations of gatifloxacin ophthalmic solution in other clinical studies included chemosis, conjunctival hemorrhage, dry eye, eye discharge, eyelid edema, headache, increased lacrimation, keratitis, red eye, papillary conjunctivitis, and reduced visual acuity.

### **6.2 Postmarketing Experience**

The following adverse reactions have been identified during post-approval use of ZYMAXID® or with other formulations of gatifloxacin ophthalmic solution. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions included anaphylactic reactions and angioedema (including pharyngeal, oral or facial edema), blepharitis, dyspnea, eye pruritus, eye swelling (including corneal and conjunctival edema), hypersensitivity, including signs and symptoms of eye allergy and allergic dermatitis, nausea, pruritus (including pruritus generalized, rash, urticaria), and vision blurred.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

There are no available data on the use of ZYMAXID® in pregnant women to inform a drug-associated risk. Administration of oral gatifloxacin to pregnant rats and rabbits throughout organogenesis did not produce adverse development outcomes at clinically relevant doses. Administration of gatifloxacin to rats during late gestation through lactation did not produce adverse maternal, fetal or neonatal effects at clinically relevant doses.

## Data

### *Animal Data*

Oral administration of gatifloxacin to pregnant rats throughout organogenesis produced teratogenic effects in rat fetuses, including skeletal/craniofacial malformations, delayed ossification, atrial enlargement, and reduced fetal weight, at doses greater than or equal to 150 mg/kg/day (approximately 600-fold higher than the maximum recommended human ophthalmic dose [MRHOD] for ZYMAXID<sup>®</sup> of 0.04 mg/kg/day, on a mg/m<sup>2</sup> basis). No teratogenic effects were observed in rat or rabbit fetuses at doses of gatifloxacin up to 50 mg/kg/day (approximately 200- and 400-fold higher than the MRHOD, respectively, on a mg/m<sup>2</sup> basis).

In a perinatal/postnatal study in rats, oral administration of gatifloxacin during late gestation through lactation produced an increase in late gestation fetal loss and neonatal/perinatal mortality at 200 mg/kg/day (approximately 800-fold higher than the MRHOD on a mg/m<sup>2</sup> basis).

## **8.2 Lactation**

### Risk Summary

There is no information regarding the presence of ZYMAXID<sup>®</sup> in human milk, the effect of gatifloxacin on breastfed infants, or the effect of gatifloxacin on milk production. Gatifloxacin was found in the breast milk of rats following oral administration of gatifloxacin during lactation. However, systemic levels of gatifloxacin following topical ocular administration are low [*see Clinical Pharmacology (12.3)*], and it is not known whether gatifloxacin would be present in maternal milk at measurable levels following topical ocular administration. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZYMAXID<sup>®</sup> and any potential adverse effects on the breastfed child from ZYMAXID<sup>®</sup>.

## **8.4 Pediatric Use**

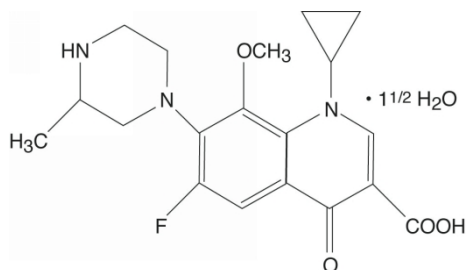
The safety and effectiveness of ZYMAXID<sup>®</sup> in infants below one year of age have not been established. ZYMAXID<sup>®</sup> has been demonstrated in clinical trials to be safe and effective for the treatment of bacterial conjunctivitis in pediatric patients one year or older [*see Clinical Studies (14)*].

## **8.5 Geriatric Use**

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

## 11 DESCRIPTION

ZYMAXID® is a quinolone antimicrobial topical ophthalmic solution for the treatment of bacterial conjunctivitis. Its chemical name is (±)-1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid, sesquihydrate. Its molecular formula is  $C_{19}H_{22}FN_3O_4 \cdot 1\frac{1}{2} H_2O$  and its molecular weight is 402.42. Its chemical structure is:



ZYMAXID® is a clear, pale yellow, sterile, preserved aqueous solution with an osmolality of 260-330 mOsm/kg and a pH of 5.1-5.7.

ZYMAXID® contains the active ingredient gatifloxacin 0.5% (5 mg/mL) and the inactive ingredients benzalkonium chloride 0.005%, edetate disodium, sodium chloride and purified water. ZYMAXID® may contain hydrochloric acid and/or sodium hydroxide to adjust pH.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Gatifloxacin is a quinolone antimicrobial [see *Microbiology* (12.4)].

### 12.3 Pharmacokinetics

Gatifloxacin ophthalmic solution 0.5% was administered to one eye of 6 healthy male subjects each in an escalated dosing regimen starting with a single 2 drop dose, then 2 drops 4 times daily for 7 days, and finally 2 drops 8 times daily for 3 days. At all time points, serum gatifloxacin levels were below the lower limit of quantification (5 ng/mL) in all subjects.

### 12.4 Microbiology

Gatifloxacin is an 8-methoxyfluoroquinolone with a 3-methylpiperazinyl substituent at C7. The antibacterial action of gatifloxacin results from inhibition of DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription, and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division. The mechanism of action of fluoroquinolones including gatifloxacin is different from that of aminoglycoside, macrolide, and tetracycline antibiotics. Therefore, gatifloxacin may be active against pathogens that are resistant to these antibiotics and these antibiotics may be active against pathogens that are resistant to gatifloxacin. There is no cross-resistance between gatifloxacin and the aforementioned classes of antibiotics. Cross-resistance has been observed between systemic gatifloxacin and some other fluoroquinolones.

Resistance to gatifloxacin *in vitro* develops via multiple-step mutations. Resistance to gatifloxacin *in vitro* occurs at a general frequency of  $1 \times 10^{-7}$  to  $10^{-10}$ .

Gatifloxacin has been shown to be active against most isolates of the following organisms both microbiologically and clinically, in conjunctival infections:

Aerobic gram-positive bacteria:

*Staphylococcus aureus*  
*Staphylococcus epidermidis*  
*Streptococcus mitis* group\*  
*Streptococcus oralis*\*  
*Streptococcus pneumoniae*

- Aerobic gram-negative bacteria:  
*Haemophilus influenzae*

\*Efficacy for these organisms were studied in fewer than 10 infections.

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

##### *Carcinogenesis*

There was no increase in neoplasms among B6C3F1 mice given gatifloxacin in the diet for 18 months at doses averaging 81 mg/kg/day in males and 90 mg/kg/day in females. These doses are approximately 175-fold higher than the maximum recommended ophthalmic dose (MRHOD) of 0.04 mg/kg/day ZYMAXID® in a 60 kg human (on a mg/m<sup>2</sup> basis).

A statistically significant increase in the incidence of large granular lymphocyte (LGL) leukemia was seen in male rats treated with 100 mg/kg/day (approximately 405-fold higher than the MRHOD, on a mg/m<sup>2</sup> basis). Fischer 344 rats have a high spontaneous background rate of LGL leukemia and the incidence in high-dose males only slightly exceeded the historical control range established for this strain. There was no increase in neoplasms among Fischer 344 rats given gatifloxacin in the diet for 2 years at doses averaging 47 mg/kg/day in males and 139 mg/kg/day in females (approximately 190- and 560-fold higher than the MRHOD, respectively), on a mg/m<sup>2</sup> basis.

##### *Mutagenesis*

In genetic toxicity tests, gatifloxacin was positive in 1 of 5 strains used in bacterial reverse mutation assays: Salmonella strain TA102. Gatifloxacin was positive in *in vitro* mammalian cell mutation and chromosome aberration assays. Gatifloxacin was positive in *in vitro* unscheduled DNA synthesis in rat hepatocytes but not human leukocytes. Gatifloxacin was negative in *in vivo* micronucleus tests in mice, cytogenetics test in rats, and DNA repair test in rats. The genotoxic findings are similar to findings obtained with other quinolones and may be due to the pharmacologic inhibitory effects of high concentrations of gatifloxacin on eukaryotic type II DNA topoisomerase.

### *Impairment of Fertility*

Oral administration of gatifloxacin produced no adverse effects on fertility or reproduction in rats at doses up to 200 mg/kg/day (approximately 800-fold higher than the MRHOD, on a mg/m<sup>2</sup> basis).

## **14 CLINICAL STUDIES**

In two randomized, double-masked, multicenter clinical trials, where patients 1-89 years of age were dosed for 5 days, ZYMAXID® was clinically superior to its vehicle on day 6 in patients with conjunctivitis and positive conjunctival cultures. Clinical outcomes for the trials demonstrated clinical success (resolution of conjunctival hyperemia and conjunctival discharge) in 58% (193/333) of patients for the gatifloxacin-treated groups versus 45% (148/325) for the vehicle-treated groups. Microbiological outcomes for the same clinical trials demonstrated a statistically superior eradication rate for causative pathogens of 90% (301/333) for gatifloxacin vs. 70% (228/325) for vehicle. Please note that microbiological eradication does not always correlate with clinical outcome in anti-infective trials.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

ZYMAXID® (gatifloxacin ophthalmic solution) 0.5% is supplied sterile in a white, low density polyethylene (LDPE) bottle with a controlled dropper tip, and a tan, high impact polystyrene (HIPS) cap in the following size:

2.5 mL in 5 mL bottle: NDC 0023-3615-25

*Storage:* Store at 15°-25°C (59°-77°F). Protect from freezing.

## **17 PATIENT COUNSELING INFORMATION**

### Avoiding Contamination of the Product

Instruct patients to avoid contaminating the applicator tip with material from the eye, fingers, or other source.

### Potential for Hypersensitivity Reactions

Advise patients to discontinue use immediately and contact the physician at the first sign of a rash or hypersensitivity reaction [*see Warnings and Precautions (5.1) and Contraindication (4)*].

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022548Orig1s002**

**OTHER REVIEW(S)**

Clinical Review  
PLLR Conversion Labeling Review

**NDA 22-548/S-002**  
**SDN-130**

**Submission Date:** September 6, 2016  
**Receipt Date:** September 6, 2016  
**Review Date:** September 7, 2016

**Applicant:** Allergan, Inc.  
2525 Dupont Drive  
P.O. Box 19534  
Irvine, CA 92623-9534  
714-246-5868

**Applicant's**  
**Representatives:** Hillary Keir  
Senior Associate, Global Regulatory Affairs  
714-246-3015

**Drug:** ZYMAXID (gatifloxacin ophthalmic solution) 0.5%

**Pharmacologic**  
**Category:** prostaglandin analog

**Submitted:**

The applicant has submitted an amendment to the Prior Approval Supplement for changes in the package insert to convert it to conform to the PLLR.

Following is the Division's proposed labeling sent to the applicant on August 29, 2016. The applicant has included additional minor edits to the labeling.

The Division has no edits to the submitted labeling.

The supplement is recommended for approval.

Rhea A. Lloyd, MD  
Medical Officer

APPEARS THIS WAY ON  
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/s/  
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RHEA A LLOYD  
09/07/2016

WILLIAM M BOYD  
09/07/2016

Clinical Review  
PLLR Conversion Labeling Review

**NDA 22-548/S-002**  
**SDN-116**  
**SDN-123**

**Submission Date:** March 11, 2016  
**Receipt Date:** March 11, 2016  
**Submission Date:** June 2, 2016  
**Receipt Date:** June 2, 2016  
**Review Date:** August 9, 2016

**Applicant:**

Allergan, Inc.  
2525 Dupont Drive  
P.O. Box 19534  
Irvine, CA 92623-9534  
714-246-5868

**Applicant's**  
**Representatives:**

Hillary Keir  
Senior Associate, Global Regulatory Affairs  
714-246-3015

**Drug:**

ZYMAXID (gatifloxacin ophthalmic solution) 0.5%

**Pharmacologic**  
**Category:**

prostaglandin analog

**Submitted:**

The applicant has submitted a Prior Approval Supplement for changes in the package insert to convert it to conform to the PLLR.

Following is the currently approved labeling.

The applicant's proposed additions are noted by underline and deletions by within the review.

The reviewer's additions are noted by underline and deletions by within the review.

**FULL PRESCRIBING INFORMATION****1 INDICATIONS AND USAGE**

(b) (4)

**Reviewer's Comment:**

*The Acting Associate Director of Labeling (ADL) has made editorial revisions to 1 INDICATIONS AND USAGE. Acceptable.*

**2 DOSAGE AND ADMINISTRATION**

(b) (4)

**Reviewer's Comment:**

*The Acting Associate Director of Labeling (ADL) has made editorial revisions to 2 DOSAGE AND ADMINISTRATION. The dosing instructions have been placed in bulleted form to improve clarity. Acceptable.*

**3 DOSAGE FORMS AND STRENGTHS**

(b) (4)

**Reviewer's Comment:**

*The Acting ADL has made editorial revisions to 2 DOSAGE AND ADMINISTRATION. The dosage form and strength information has been revised to be consistent with best labeling practice. Acceptable.*

**4 CONTRAINDICATIONS**

(b) (4)

**Reviewer's Comment:**

*The applicant has proposed the addition of a contraindication in patients with a history of hypersensitivity to gatifloxacin, to other quinolones, or to any components in the drug product. The applicant has submitted case report forms which describe ocular and non-ocular dermal symptoms associated with hypersensitivity, and allergic reaction. This revision is acceptable.*

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Hypersensitivity**

(b) (4)

#### **Reviewer's Comment:**

*The applicant has proposed the addition of 5.1 Hypersensitivity to be consistent with the most recent approved labeling for ZYMAR (gatifloxacin ophthalmic solution) 0.3% and has provided additional information regarding 4 CONTRAINDICATIONS. The applicant has submitted case report forms in support of these additions. Additional editorial revisions were made by the Acting ADL. The revisions are acceptable.*

### **5.2 Growth of Resistant Organisms with Prolonged Use**

(b) (4)

#### **Reviewer's Comment:**

*The Acting ADL has made editorial revisions to 5.2 Growth of Resistant Organisms with Prolonged Use. The revisions are acceptable.*

### **5.3 Corneal Endothelial Cell Injury**

(b) (4)

#### **Reviewer's Comment:**

(b) (4)

*Acceptable.*

*5.3 Avoidance of Contact Lens Wear has been deleted.*

*The section title should be revised to read 'Corneal Endothelial Cell Injury' and the phrase, 'because it may harm the corneal endothelial cells' should be added to be consistent with the corresponding warning in the ZYMAR labeling.*

## **6 ADVERSE REACTIONS**

(b) (4)

**Reviewer's Comment:**

*Section 6 ADVERSE REACTIONS should be revised to include information regarding other serious adverse reactions described elsewhere in the labeling.*

**6.1 Clinical Studies Experience**

(b) (4)

**Reviewer's Comment:**

*The applicant has proposed editorial revisions to 6.1 Clinical Studies Experience to clarify that the listed adverse reactions were seen in clinical studies. Additionally, the applicant has proposed the addition of 'red eye' to the list of adverse reactions seen in clinical studies with gatifloxacin ophthalmic solution and to be consistent with the most recently approved ZYMAR package insert. These revisions are acceptable.*

**6.2 Postmarketing Experience**

(b) (4)

**Reviewer's Comment:**

*The applicant has proposed the addition of 6.2 Postmarketing Experience. The adverse reactions include 'hypersensitivity, including signs and symptoms of eye allergy and allergic dermatitis' is supported by the submitted case report forms. However, since these additions are included in the revisions in 4 CONTRAINDICATIONS and 5.1 HYPERSENSITIVITY, they should not be included here.*

*The applicant has proposed the addition of adverse reactions reported with other formulations of gatifloxacin ophthalmic solution. This listing is consistent with the most recently approved ZYMAR package insert. These revisions are acceptable.*

**Reviewer's Comment:**

*The applicant has deleted 7 DRUG INTERACTIONS to be consistent with the most recently approved ZYMAR package insert. This deletion is acceptable.*

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

(b) (4)



### **8.2 Lactation**

(b) (4)



**Reviewer's Comment:**

*The applicant has revised 8.1 Pregnancy and included 8.2 Lactation to be in compliance with the Pregnancy, Lactation, and Reproductive Potential Labeling Rule. The applicant's proposed*

wording of 8.1 Pregnancy and 8.2 Lactation have been revised by the Pharmacology Toxicology reviewer. Acceptable.

Additional editorial revisions have been made by the Acting ADL including replacing (b) (4) with 'adverse development outcomes' as suggested by the labeling team because it is a general term that encompasses all outcomes (b) (4). Acceptable.

#### 8.4 Pediatric Use

(b) (4)

#### 8.5 Geriatric Use

(b) (4)

### 11 DESCRIPTION

(b) (4)

#### Reviewer's Comment:

In 11 DESCRIPTION, the Acting ADL has revised the established pharmacologic class and made additional editorial revisions. Acceptable.

### 12 CLINICAL PHARMACOLOGY

#### 12.1 Mechanism of Action

(b) (4)

#### 12.3 Pharmacokinetics

## 12.4 Microbiology

(b) (4)

### **Reviewer's Comment:**

*In 12 CLINICAL PHARMACOLOGY, the Acting ADL has revised the established pharmacologic class and made additional editorial revisions. Acceptable.*

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

**Reviewer's Comment:**

*The applicant has revised 13 NONCLINICAL TOXICOLOGY to be in compliance with the Pregnancy, Lactation, and Reproductive Potential Labeling Rule. The applicant's proposed wording has been revised by the Pharmacology Toxicology reviewer. Acceptable.*

*Additional minor editorial revisions have also been made by the Division. Acceptable.*

**14 CLINICAL STUDIES**

(b) (4)

**16 HOW SUPPLIED/STORAGE AND HANDLING**

(b) (4)

(b) (4)



**17 PATIENT COUNSELING INFORMATION**

(b) (4)



**Reviewer's Comment:**

*The applicant has revised 17 PATIENT COUNSELING INFORMATION to include 'Potential for Hypersensitivity Reactions' consistent with revisions to 4 CONTRAINDICATIONS and 5.1 HYPERSENSITIVITY, and with the most recently approved ZYMAR package insert. Acceptable.*

*The statements in 17 PATIENT COUNSELING INFORMATION have been revised to be the declarative.*

(b) (4)



**Recommendations:**

The supplement is not recommended for approval.

Revised labeling consistent with the revisions found within this review should be submitted.

Rhea A. Lloyd, MD  
Medical Officer



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/s/  
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RHEA A LLOYD  
08/09/2016

WILLIAM M BOYD  
08/10/2016

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
**PUBLIC HEALTH SERVICE**  
**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION - Prior Approval**  
**Supplement: Labeling**

**NDA Application number:** 022548 (Initial U.S. Approval: 1999)

**Supporting document/s:** 116

**Sponsor's letter date:** March 11, 2016

**CDER stamp date:** March 11, 2016

**Product:** ZYMAXID™ (gatifloxacin ophthalmic solution)  
0.5%

**Indication:** anti-infective indicated for the treatment of  
bacterial conjunctivitis

**Sponsor:** Allergan, Inc.

**Review Division:** DTOP

**Reviewer:** Lori E. Kotch, PhD, DABT

**Supervisor/Team Leader:** Lori E. Kotch, PhD, DABT

**Division Director:** Renata Albrecht, MD

**Project Manager:** Judit Milstein

*Template Version: September 1, 2010*

## 1 Executive Summary

Prior Approval Supplement: Labeling –PLLR Conversion for ZYMAXID™ (NDA 022548) approved on 18 May 2010.

## 2 Drug Information

### CAS Registry Number (Optional)

112811-59-3

### Generic Name:

Gatifloxacin ophthalmic solution, 0.5%

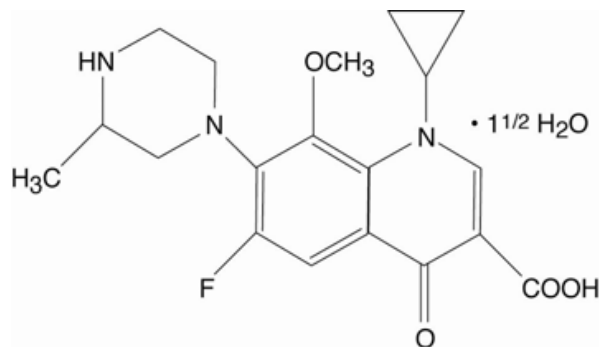
### Chemical Name:

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

### Molecular Formula/Molecular Weight:

$C_{19}H_{22}FN_3O_4 \cdot 1\frac{1}{2}H_2O$ ; Molecular weight = 402.42

### Structure or Biochemical Description



### Pharmacologic Class:

anti-infective

### Formulation:

ZYMAXID™ contains Active: gatifloxacin 0.5% (5 mg/mL); Inactives: benzalkonium chloride 0.005%; edetate disodium; purified water; and sodium chloride. May contain hydrochloric acid and/or sodium hydroxide to adjust pH.

**Dosage and Administration:**

- Patients 1 year of age or older: Instill one drop every two hours in the affected eye(s) while awake, up to 8 times on Day 1.
- Instill one drop two to four times daily in the affected eye(s) while awake on Days 2 through 7.

### **3 Sponsor's Proposed Labeling Changes**

The Sponsor's major labeling changes included recalculation of exposure margins in sections 8 and 13 to be consistent with Divisional policy; the Sponsor has changed exposure margins in the nonclinical sections of the label to reflect calculation of Human Equivalent Doses (HEDs) on a mg/m<sup>2</sup> basis (based on BSA scaling), rather than a direct comparison of animal and human doses on a mg/kg basis. These changes are considered appropriate, given lack of available exposure data (AUC) to establish margins based on systemic plasma/blood levels.

Minor changes to Sponsor-proposed exposure margin values are proposed by the FDA reviewer to eliminate excessive rounding. Additional text changes were proposed by FDA Reviewer to enhance readability, and to ensure consistency across labels within the Division.

### **4 Nonclinical Recommendations**

The following table represents the Sponsor's proposed labeling changes (in left column), compared to the original label<sup>1</sup>; and the FDA reviewer's recommended labeling changes in the right column.

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<sup>1</sup> [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2010/022548s000lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022548s000lbl.pdf)

Sponsor's Proposed Changes	FDA Reviewer Recommended Changes
<div style="background-color: #cccccc; width: 100%; height: 100%; display: flex; align-items: center; justify-content: center;"> <span>(b) (4)</span> </div>	<p><b>8 USE IN SPECIFIC POPULATIONS</b></p> <p><b>8.1 Pregnancy</b></p> <p><u>Risk Summary</u></p> <p>There are no available data on the use of ZYMAXID® in pregnant women to inform a drug-associated risk. Administration of oral gatifloxacin to pregnant rats and rabbits throughout organogenesis did not produce (b) (4) at clinically relevant doses. Administration of gatifloxacin to rats during late gestation through lactation did not produce adverse maternal, fetal or neonatal effects at clinically relevant doses.</p> <p>(b) (4)</p> <p>(b) (4) <i>[It is recommended that this sentence be removed</i> (b) (4) (b) (4)</p> <p>(b) (4)</p> <p>(b) (4) <i>[defer to clinical regarding whether to add this sentence.</i> (b) (4) (b) (4)</p>
	<p><u>Data</u></p> <p><i>Animal Data</i></p> <p>Oral administration of gatifloxacin to pregnant rats throughout organogenesis produced teratogenic effects in rat fetuses, including skeletal/craniofacial malformations, delayed ossification, atrial enlargement, and reduced fetal weight, at doses greater than or equal to 150 mg/kg/day (approximately 600-fold higher than the maximum recommended human ophthalmic dose [MRHOD] for ZYMAXID® of 0.04 mg/kg/day, on a mg/m<sup>2</sup> basis). No</p>

(b) (4)

teratogenic effects were observed in rat or rabbit fetuses at doses of gatifloxacin up to 50 mg/kg/day (approximately 200- and 400-fold higher than the MRHOD, respectively).

In a perinatal/postnatal study in rats, oral administration of gatifloxacin during late gestation through lactation produced an increase in late gestation fetal loss and neonatal/perinatal mortality at 200 mg/kg/day (approximately 800-fold higher than the MRHOD).

## 8.2 Lactation

### Risk Summary

There is no information regarding the presence of **ZYMAXID**<sup>®</sup> in human milk, the effects on the breastfed infants, or the effects on milk production. Gatifloxacin was found in the breast milk of rats following oral administration of gatifloxacin during lactation. However, systemic levels of gatifloxacin following topical ocular administration are low [see *Pharmacology section 12.3*], and it is not known whether gatifloxacin would be present in maternal milk at measurable levels following topical ocular administration.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for **ZYMAXID**<sup>®</sup> and any potential adverse effects on the breastfed child from **ZYMAXID**<sup>®</sup>

(b) (4)

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### *Carcinogenesis*

There was no increase in neoplasms among B6C3F1 mice given gatifloxacin in the diet for 18 months at doses averaging 81 mg/kg/day in males and 90 mg/kg/day in females. These doses are approximately 175-fold higher than the maximum recommended ophthalmic dose (MRHOD) of 0.04 mg/kg/day **ZYMAXID**<sup>®</sup> in a 60 kg human (on a mg/m<sup>2</sup> basis).

(b) (4)

A statistically significant increase in the incidence of large granular lymphocyte (LGL) leukemia was seen in males treated with 100 mg/kg/day (405-fold higher than the MRHOD). Fischer 344 rats have a high spontaneous background rate of LGL leukemia and the incidence in high-dose males only slightly exceeded the historical control range established for this strain. There was no increase in neoplasms among Fischer 344 rats given gatifloxacin in the diet for 2 years at doses averaging 47 mg/kg/day in males and 139 mg/kg/day in females (190- and 560-fold higher than the MRHOD, respectively).

#### *Mutagenesis*

In genetic toxicity tests, gatifloxacin was positive in 1 of 5 strains used in bacterial reverse mutation assays: Salmonella strain TA102. Gatifloxacin was positive in *in vitro* mammalian cell mutation and chromosome aberration assays. Gatifloxacin was positive in *in vitro* unscheduled DNA synthesis in rat hepatocytes but not human leukocytes. Gatifloxacin was negative in *in vivo* micronucleus tests in mice, cytogenetics test in rats, and DNA repair test in rats. The genotoxic findings are similar to findings obtained with other quinolones and may be due to the pharmacologic inhibitory effects of high concentrations of gatifloxacin on eukaryotic type II DNA topoisomerase.

#### *Impairment of Fertility*

Oral administration of gatifloxacin produced no adverse effects on fertility or reproduction in rats at doses up to 200 mg/kg/day (b)(4)-fold higher than the MRHOD, on a mg/m<sup>2</sup> basis).

Internal SharePoint working document <sup>2</sup>

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<sup>2</sup> SharePoint at: <http://sharepoint.fda.gov/orgs/CDER-OND/dtopndas/NDA%2022548%20Zymazid/Forms/AllItems.aspx?InitialTabId=Ribbon.Library&VisibilityContext=WSSListAndLibrary>

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LORI E KOTCH  
07/18/2016

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022548Orig1s002**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**From:** Milstein, Judit  
**To:** ["keir\\_hillary@allergan.com"](mailto:keir_hillary@allergan.com)  
**Subject:** Your NDA 22548/S002-Request for additional information  
**Date:** Thursday, May 19, 2016 1:48:00 PM

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NDA 22548/S-002

ZYMAXID (gatifloxacin ophthalmic solution), 0.5%

Submission dated March 11, 2016

Dear Ms. Keir,

We are reviewing your labeling supplement S002, dated March 11, 2016 and have the following request for additional information:

Please submit the case report forms to support the proposed revisions to the ZYMAXID package insert or state where they may be found in prior submissions.

In order to proceed with the timely review of your submission, we request that you respond by June 3, 2016.

Thank you

Judit Milstein

Chief, Project Management Staff

DTOP/OAP/CDER

Food and Drug Administration

10903 New Hampshire Avenue

Building 22, Room 6180

Silver Spring, MD 20993

Phone: 301-796-0763

Fax: 301-796-9881

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/s/  
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JUDIT R MILSTEIN

05/19/2016

NDA 22548/S002 Request for additional clinical information