

NDA 21493/S-010

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## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**ZYMAR® (gatifloxacin ophthalmic solution) 0.3%**  
**For Topical Ophthalmic Administration**  
**Initial U.S. Approval: 1999**

### INDICATIONS AND USAGE

ZYMAR® ophthalmic solution is a topical quinolone antimicrobial for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:

*Haemophilus influenzae*, *Corynebacterium propinquum*\*,  
*Staphylococcus aureus*, *Staphylococcus epidermidis*,  
*Streptococcus mitis group*\*, *Streptococcus pneumoniae*

\* Efficacy for this organism was studied in fewer than 10 infections. (1)

### DOSAGE AND ADMINISTRATION

The recommended dosage regimen for the treatment of bacterial conjunctivitis is:

Days 1 and 2: Instill one drop every two hours in the affected eye(s) while awake, up to 8 times daily.  
Days 3 through 7: Instill one drop up to four times daily while awake. (2)

### DOSAGE FORMS AND STRENGTHS

10 mL size bottle filled with 5 mL of gatifloxacin ophthalmic solution, 0.3%. (3)

### CONTRAINDICATIONS

ZYMAR® solution 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)
- Avoidance of Contact Lenses (5.3)
- Corneal Endothelial Cell Injury (5.4)

### ADVERSE REACTIONS

Most common adverse reactions occurring in 5-10 % of patients included conjunctival irritation, increased lacrimation, keratitis, and papillary conjunctivitis. (6)

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

See 17 for PATIENT COUNSELING INFORMATION.

Revised: XX/2015

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

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

**ZYMAR**<sup>®</sup> (gatifloxacin ophthalmic solution) 0.3% solution is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:

#### **Aerobic Gram-Positive Bacteria:**

*Corynebacterium propinquum*\*

*Staphylococcus aureus*

*Staphylococcus epidermidis*

*Streptococcus mitis* group\*

*Streptococcus pneumoniae*

#### **Aerobic Gram-Negative Bacteria:**

*Haemophilus influenzae*

\* Efficacy for this organism was studied in fewer than 10 infections.

### 2 DOSAGE AND ADMINISTRATION

The recommended dosage regimen for the treatment of bacterial conjunctivitis is:

Days 1 and 2: Instill one drop every two hours in the affected eye(s) while awake, up to 8 times daily.

Days 3 through 7: Instill one drop up to four times daily while awake.

### 3 DOSAGE FORMS AND STRENGTHS

Ten (10) mL bottle containing 5 mL of a 0.3% sterile topical ophthalmic solution.

### 4 CONTRAINDICATIONS

**ZYMAR**<sup>®</sup> solution 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

Patients receiving topical gatifloxacin have experienced hypersensitivity reactions including anaphylactic reactions, angioedema (including pharyngeal, laryngeal, or facial edema), dyspnea, urticaria, and itching. There have been rare reports of Stevens-Johnson Syndrome reported in association with topical gatifloxacin use. If an allergic reaction to gatifloxacin occurs, discontinue the drug and contact your physician [*see Patient Counseling Information (17)*].

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

As with other antimicrobials, prolonged use of **ZYMAR**<sup>®</sup> (gatifloxacin ophthalmic solution) 0.3% may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, discontinue use and institute alternative therapy. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

#### 5.3 Avoidance of Contact Lens Wear

Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis [*see Patient Counseling Information (17)*].

#### 5.4 Corneal Endothelial Cell Injury

**ZYMAR**<sup>®</sup> solution should not be introduced directly into the anterior chamber of the eye because it may harm the corneal endothelial cells.

## **6 ADVERSE REACTIONS**

### **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 with **ZYMAR**<sup>®</sup>, the most frequently reported adverse reactions in the overall study population were: conjunctival irritation, increased lacrimation, keratitis, and papillary conjunctivitis. These reactions occurred in approximately 5-10% of patients. Other reported reactions occurring in 1-4% of patients were chemosis, conjunctival hemorrhage, dry eye, eye discharge, eye pain, eyelid edema, headache, red eye, reduced visual acuity and taste disturbance.

An additional adverse reaction reported with gatifloxacin ophthalmic solution in other clinical studies includes worsening of the conjunctivitis.

### **6.2 Postmarketing Experience**

The following adverse reactions have been identified during post-approval use of gatifloxacin ophthalmic solution 0.3%. 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 include: anaphylactic reactions and angioedema (including pharyngeal, oral or facial edema), blepharitis, dyspnea, eye pruritus, eye swelling (including corneal and conjunctival edema), hypersensitivity, nausea, pruritus (including pruritus generalized), rash, urticaria, vision blurred.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### **Pregnancy Category C.**

There were no teratogenic effects observed in rats or rabbits following oral gatifloxacin doses up to 50 mg/kg/day. This dose produced systemic exposure that is approximately 450 times and 1850 times the plasma exposure (based on  $C_{max}$ ) at the maximum recommended human ophthalmic dose, respectively. However, skeletal/craniofacial malformations or delayed ossification, atrial enlargement, and reduced fetal weight were observed in fetuses from rats given  $\geq 150$  mg/kg/day (approximately - 1230 times the plasma exposure at the maximum recommended human ophthalmic dose). In a perinatal/postnatal study, increased late post-implantation loss and neonatal/perinatal mortalities were observed at 200 mg/kg/day (approximately 1400 times the plasma exposure at the maximum recommended human ophthalmic dose). The above exposure multiples are based on a human systemic concentration of gatifloxacin that is estimated to be below the limit of quantification (5 ng/mL) at steady-state in humans, following ocular administration [*see Clinical Pharmacology (12.3)*].

Because there are no adequate and well-controlled studies in pregnant women, **ZYMAR**<sup>®</sup> solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### **8.3 Nursing Mothers**

Gatifloxacin is excreted in the breast milk of rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when **ZYMAR**<sup>®</sup> is administered to a nursing woman.

## 8.4 Pediatric Use

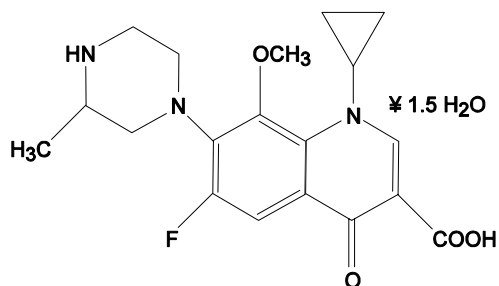
Safety and effectiveness in infants below the age of one year have not been established.

## 8.5 Geriatric Use

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

## 11 DESCRIPTION

**ZYMAR**<sup>®</sup> (gatifloxacin ophthalmic solution) 0.3% is a sterile ophthalmic solution. It is an 8-methoxy quinolone antimicrobial for topical ophthalmic use. 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<sub>19</sub>H<sub>22</sub>FN<sub>3</sub>O<sub>4</sub> · 1.5 H<sub>2</sub>O, and its molecular weight is 402.42. Its chemical structure is:



**ZYMAR**<sup>®</sup> is a clear, pale yellow, sterile, preserved aqueous solution with an osmolality of 260-330 mOsm/kg and a pH of approximately 6.

**ZYMAR**<sup>®</sup> contains **Active:** gatifloxacin 0.3% (3 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.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Gatifloxacin is a quinolone antimicrobial drug [see *Clinical Pharmacology*, 12.4].

### 12.3 Pharmacokinetics

Gatifloxacin ophthalmic solution 0.3% or 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 between  $1 \times 10^{-7}$  to  $10^{-10}$ .

Gatifloxacin has been shown to be active against most strains of the following organisms both *in vitro* and clinically, in conjunctival infections as described in the INDICATIONS AND USAGE, (1).

**Aerobes, Gram-Positive:**

*Corynebacterium propinquum*\*

*Staphylococcus aureus*

*Staphylococcus epidermidis*

*Streptococcus mitis* group\*

*Streptococcus pneumoniae*

**Aerobes, Gram-Negative:**

*Haemophilus influenzae*

\* Efficacy for this organism was studied in fewer than 10 infections.

The following *in vitro* data are available, **but their clinical significance in ophthalmic infections is unknown.** The safety and effectiveness of ZYMAR<sup>®</sup> in treating ophthalmic infections due to the following organisms have not been established in adequate and well-controlled clinical trials.

The following organisms are considered susceptible when evaluated using systemic breakpoints. However, a correlation between the *in vitro* systemic breakpoint and ophthalmological efficacy has not been established. The following list of organisms is provided as guidance only in assessing the potential treatment of conjunctival infections. Gatifloxacin exhibits *in vitro* minimal inhibitory concentrations (MICs) of 2 mcg/mL or less (systemic susceptible breakpoint) against most ( $\geq 90\%$ ) strains of the following ocular pathogens.

**Aerobes, Gram-Positive:**

*Listeria monocytogenes*

*Staphylococcus saprophyticus*

*Streptococcus agalactiae*

*Streptococcus pyogenes*

*Streptococcus viridans* Group

*Streptococcus* Groups C, F, G

**Aerobes, Gram-Negative:**

*Acinetobacter lwoffii*

*Enterobacter aerogenes*

*Enterobacter cloacae*

*Escherichia coli*

*Citrobacter freundii*

*Citrobacter koseri*

*Haemophilus parainfluenzae*

*Klebsiella oxytoca*

*Klebsiella pneumoniae*

*Moraxella catarrhalis*  
*Morganella morganii*  
*Neisseria gonorrhoeae*  
*Neisseria meningitidis*  
*Proteus mirabilis*  
*Proteus vulgaris*  
*Serratia marcescens*  
*Vibrio cholerae*  
*Yersinia enterocolitica*

**Other Microorganisms:**

*Chlamydia pneumoniae*  
*Legionella pneumophila*  
*Mycobacterium marinum*  
*Mycobacterium fortuitum*  
*Mycoplasma pneumoniae*

**Anaerobic Microorganisms:**

*Bacteroides fragilis*  
*Clostridium perfringens*

### 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 produced systemic exposure that is approximately - 45 times and 60 times the plasma exposure (based on C<sub>max</sub>) at the maximum recommended human ophthalmic dose, respectively.

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 85 times and 230 times, respectively, the plasma exposure at the maximum recommended human ophthalmic dose). A statistically significant increase in the incidence of large granular lymphocyte (LGL) leukemia was seen in males treated with a high dose of 100 mg/kg (approximately 170 times the plasma exposure at the maximum recommended human ophthalmic dose). 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.

The above exposure multiples are based on a human systemic concentration of gatifloxacin that is estimated to be below the limit of quantification (5 ng/mL) at steady-state in humans, following ocular administration [*see Clinical Pharmacology (12.3)*].

##### *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 findings may be due to the inhibitory effects of high concentrations on eukaryotic type II DNA topoisomerase.

### *Impairment of Fertility*

There were no adverse effects on fertility or reproduction in rats given gatifloxacin orally at doses up to 200 mg/kg/day (approximately 1400 times the plasma exposure at the maximum recommended human ophthalmic dose).

## **14 CLINICAL STUDIES**

In a randomized, double-masked, multicenter clinical trial, where patients were dosed for 5 days, **ZYMAR**<sup>®</sup> solution was superior to its vehicle on day 5-7 in patients with conjunctivitis and positive conjunctival cultures. Clinical outcomes for the trial demonstrated clinical cure of 77% (40/52) for the gatifloxacin-treated group versus 58% (28/48) for the placebo-treated group. Microbiological outcomes for the same clinical trial demonstrated a statistically superior eradication rate for causative pathogens of 92% (48/52) for gatifloxacin vs. 72% (34/48) for placebo. Please note that microbiological eradication does not always correlate with clinical outcome in anti-infective trials.

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

**ZYMAR**<sup>®</sup> (gatifloxacin ophthalmic solution) 0.3% 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:

5 mL in 10 mL bottle - NDC 0023-9218-05

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

## **17 PATIENT COUNSELING INFORMATION**

### **Avoiding Contamination of the Product**

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

### **Avoidance of Contact Lens Wear**

Advise patients not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis.

### **Potential for Hypersensitivity Reactions**

Topical gatifloxacin has been associated with hypersensitivity reactions, even following a single dose. Discontinue use immediately and contact your physician at the first sign of a rash or allergic reaction.

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