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 use
Initial U.S. Approval: 1999

————————INDICATIONS AND USAGE————————
ZYMAR® is a quinolone antimicrobial indicated 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

————————DOSAGE AND ADMINISTRATION————————
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————————
Ophthalmic solution, 0.3% gatifloxacin (3mg/mL)(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)
- Corneal Endothelial Cell Injury (5.3)

————————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.*

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 0/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZYMAR® 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 these organisms were studied in fewer than 10 infections.

2 DOSAGE AND ADMINISTRATION

- 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

Ophthalmic solution: 0.3% gatifloxacin (3 mg/mL)

4 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 *[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, even following a single dose. There have been rare reports of Stevens-Johnson Syndrome reported in association with topical ophthalmic 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

Prolonged use of **ZYMAR®** 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

ZYMAR® is for topical ophthalmic use. **ZYMAR®** 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 with **ZYMAR®**, 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

Risk Summary

There are no available data on the use of **ZYMAR®** 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 1010-fold higher than the maximum recommended human ophthalmic dose [MRHOD] for **ZYMAR®** of 0.024 mg/kg/day, on a mg/m^2 basis). No teratogenic effects were observed in rat or rabbit fetuses at doses of gatifloxacin up to 50 mg/kg/day (approximately 335- and 675-fold higher than the MRHOD, respectively, on a mg/m^2 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 1350-fold higher than the MRHOD on a mg/m^2 basis).

8.2 Lactation

Risk Summary

There is no information regarding the presence of **ZYMAR®** 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 **ZYMAR®** and any potential adverse effects on the breastfed child from **ZYMAR®**.

8.4 Pediatric Use

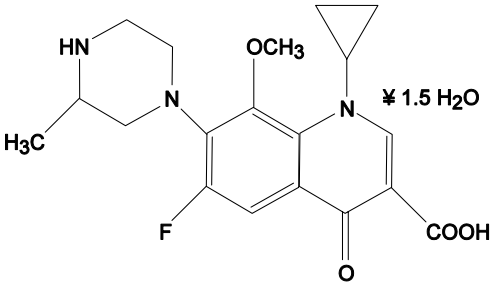
The safety and effectiveness of ZYMAR (gatifloxacin ophthalmic solution) 0.3% have been established in all ages. Use of ZYMAR is supported by evidence from adequate and well controlled studies of ZYMAR in adults, children and neonates [*see Clinical Studies (14)*].

8.5 Geriatric Use

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

11 DESCRIPTION

ZYMAR® 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 $C_{19}H_{22}FN_3O_4 \cdot 1.5\ H_2O$, and its molecular weight is 402.42. Its chemical structure is:



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

ZYMAR® contains the active ingredient gatifloxacin 0.3% (3 mg/mL) and the inactive ingredients benzalkonium chloride 0.005%, edetate disodium, purified water and sodium chloride. **ZYMAR®** 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 Microbiology (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 x 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**:**

- Aerobes, Gram-Positive:
  *Corynebacterium propinquum**
  Staphylococcus aureus
  Staphylococcus epidermidis
  *Streptococcus mitis group**
  Streptococcus pneumoniae

- Aerobes, Gram-Negative:
  Haemophilus influenzae

* Efficacy for these organisms were 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®** 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 (≥ 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 are approximately 290-fold higher than the maximum recommended human ophthalmic dose (MRHOD) of 0.024 mg/kg/day **ZYMAR**® in a 60 kg human (on a mg/m^2 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 675-fold higher than the MRHOD, on a mg/m^2 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 315-fold and 935-foldhigher, respectively, than the MRHOD, on a mg/m^2 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
There were no adverse effects on fertility or reproduction in rats given gatifloxacin orally at doses up to 200 mg/kg/day (approximately 1350-fold higher than the MRHOD, on a mg/m^2 basis).

14 CLINICAL STUDIES
In a randomized, double-masked, multicenter clinical trial, where patients were dosed for 5 days, ZYMAR® 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.

In a randomized, double-masked, multicenter clinical trial of pediatric patients with bacterial conjunctivitis between birth and 31 days of age, patients were dosed with ZYMAR or another anti-infective agent for 7 days. Clinical outcomes for the trial demonstrated clinical cure of 79% (44/56) for the gatifloxacin-treated group.

16 HOW SUPPLIED/STORAGE AND HANDLING
ZYMAR® (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.

Potential for Hypersensitivity Reactions
Advise patients to discontinue use immediately and contact your physician at the first sign of a rash or allergic reaction [*see Warnings and Precautions (5.1)*].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