



IMPORTANT GATIFLOXACIN UPDATE

ZYMAR® discontinuation

- Starting February 28, 2011, Allergan, Inc., will no longer manufacture or distribute ZYMAR® (gatifloxacin ophthalmic solution) 0.3%
- Please alert ZYMAR® prescribers that it is no longer available

ZYMAXID®: Exclusive gatifloxacin offering

- ZYMAXID® (gatifloxacin ophthalmic solution) 0.5% will continue to be available
- ZYMAXID® will be the exclusive gatifloxacin offering of Allergan in the United States
- ZYMAXID® is designed to deliver more drug to the ocular surface in 2 ways¹:
 - Greater concentration of active agent (gatifloxacin) compared to the ZYMAR® (gatifloxacin ophthalmic solution) 0.3% formulation^{1,2}
 - Up to 4 times daily dosing¹

Overview of ZYMAR® and ZYMAXID®

| | ZYMAR® Ophthalmic Solution ² | ZYMAXID® Ophthalmic Solution ¹ |
|-------------------------|--|---|
| Dosing | Days 1 and 2: Q2H (up to 8 times daily) Days 3 through 7: QID | Day 1: Q2H (up to 8 times daily) Day 2 through 7: BID to QID |
| Active Ingredient | <i>gatifloxacin 0.3%</i> | <i>gatifloxacin 0.5%</i> |
| Preservative | <i>benzalkonium chloride 0.005%</i> | Same preservative |
| Key information: | How ZYMAR® is supplied: 5 mL fill in 10 mL bottle NDC #: 0023-9218-05 | How ZYMAXID® is supplied: 2.5 mL fill in 5 mL bottle NDC #: 0023-3615-25 |

Please contact your wholesaler to stock ZYMAXID® ophthalmic solution on your shelves.

INDICATION: ZYMAXID®

ZYMAXID® (gatifloxacin ophthalmic solution) 0.5% is a topical fluoroquinolone anti-infective 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*,^{*} and *Streptococcus pneumoniae*.

^{*}Efficacy for this organism was studied in fewer than 10 infections.

INDICATION: ZYMAR®

ZYMAR® ophthalmic solution is 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*,^{*} and *Streptococcus pneumoniae*.

^{*}Efficacy for this organism was studied in fewer than 10 infections.

DOSAGE AND ADMINISTRATION: ZYMAXID®

Patients 1 year of age or older: Instill 1 drop every 2 hours in the affected eye(s) while awake, up to 8 times on day 1. Instill 1 drop 2 to 4 times daily in the affected eye(s) while awake on days 2 through 7.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS: ZYMAXID®

ZYMAXID® solution should not be introduced directly into the anterior chamber of the eye. As with other anti-infectives, prolonged use of ZYMAXID® may result in overgrowth of nonsusceptible organisms, including fungi.

Please see additional Important Safety Information on reverse side.

ZYMAXID®
(gatifloxacin ophthalmic solution) 0.5%

IMPORTANT GATIFLOXACIN UPDATE

Managed Care Coverage

Approximately **83%** of prescriptions written for ZYMAXID® are currently covered by managed care organizations³

- Allergan, Inc., will notify physicians, pharmacies, and managed care organizations of this change to minimize any disruption and ensure that ZYMAXID® ophthalmic solution is available for your customers

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS: ZYMAXID® (continued)

If superinfection occurs, discontinue use and institute alternative therapy. Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis or during the course of therapy with ZYMAXID®.

ADVERSE REACTIONS: ZYMAXID®

The most frequently reported adverse reactions occurring in $\geq 1\%$ of patients in the gatifloxacin study population (N = 717) were: worsening of the conjunctivitis, eye irritation, dysgeusia, and eye pain. Additional adverse events reported with other formulations of gatifloxacin ophthalmic solution include chemosis, conjunctival hemorrhage, dry eye, eye discharge, eyelid edema, headache, increased lacrimation, keratitis, papillary conjunctivitis, and reduced visual acuity.

ADVERSE REACTIONS: ZYMAR®

The most frequently reported adverse events in the overall study population were conjunctival irritation, increased lacrimation, keratitis, and papillary conjunctivitis. These events occurred in approximately 5% to 10% of patients.

Please see accompanying full prescribing information for ZYMAR® and ZYMAXID®.

1. ZYMAXID® Prescribing Information. 2. ZYMAR® Prescribing Information. 3. Wolters Kluwer Pharma Solutions. *Source*® Dynamic Claims, January 2011.



©2011 Allergan, Inc., Irvine, CA 92612 www.allergan.com *marks owned by Allergan, Inc. ZYMAR® and ZYMAXID® are licensed from Kyorin Pharmaceutical Co., Ltd., Tokyo, Japan. *Source* is a registered trademark owned by Wolters Kluwer Pharma Solutions. APC65JL11 110784

ZYMAXID®
(gatifloxacin ophthalmic solution) 0.5%

ZYMAXID™

(gatifloxacin ophthalmic solution) 0.5%

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%
Initial U.S. Approval: 1999

INDICATIONS AND USAGE

ZYMAXID™ ophthalmic solution is a topical fluoroquinolone anti-infective 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*

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

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. (2)

DOSAGE FORMS AND STRENGTHS

5 mL size bottle filled with 2.5 mL of gatifloxacin ophthalmic solution, 0.5%. (3)

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- Topical Ophthalmic Use Only (5.1)
- Growth of Resistant Organisms with Prolonged Use (5.2)
- Avoidance of Contact Lenses. Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with Zymaxid (5.3)

ADVERSE REACTIONS

Most common adverse reactions occurring in $\geq 1\%$ 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.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 05/2010

FULL PRESCRIBING INFORMATION: Contents*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Topical Ophthalmic Use Only
- 5.2 Growth of Resistant Organisms with Prolonged Use
- 5.3 Avoidance of Contact Lens Wear

6 ADVERSE REACTIONS

- 6.1 Clinical Studies Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics
- 12.4 Microbiology

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

- 17.1 Avoiding Contamination of the Product
- 17.2 Avoidance of Contact Lens Wear

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZYMAXID™ (gatifloxacin ophthalmic solution) 0.5% solution 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 this organism was studied in fewer than 10 infections.

2 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 DOSAGE FORMS AND STRENGTHS

Five (5) mL bottle containing 2.5 mL of a 0.5% sterile topical ophthalmic solution.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Topical Ophthalmic Use Only

ZYMAXID™ solution should not be introduced directly into the anterior chamber of the eye.

5.2 Growth of Resistant Organisms with Prolonged Use

As with other anti-infectives, prolonged use of ZYMAXID™ (gatifloxacin ophthalmic solution) 0.5% 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 or during the course of therapy with ZYMAXID™ (see PATIENT COUNSELING INFORMATION, 17.2).

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 ZYMAXID™, the most frequently reported adverse reactions occurring in $\geq 1\%$ of patients in the gatifloxacin study population (N=717) were: worsening of the conjunctivitis, eye irritation, dysgeusia, and eye pain.

Additional adverse events reported with other formulations of gatifloxacin ophthalmic solution include chemosis, conjunctival hemorrhage, dry eye, eye discharge, eyelid edema, headache, increased lacrimation, keratitis, papillary conjunctivitis, and reduced visual acuity.

7 DRUG INTERACTIONS

Specific drug interaction studies have not been conducted with ZYMAXID™ ophthalmic solution.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Teratogenic Effects: There were no teratogenic effects observed in rats or rabbits following oral gatifloxacin doses up to 50 mg/kg/day (approximately 1000-fold higher than the maximum recommended ophthalmic dose). However, skeletal/craniofacial malformations or delayed ossification, atrial enlargement, and reduced fetal weight were observed in fetuses from rats given ≥ 150 mg/kg/day (approximately 3000-fold higher than the maximum recommended ophthalmic dose). In a perinatal/postnatal study, increased late post-implantation loss and neonatal/perinatal mortalities were observed at 200 mg/kg/day (approximately 4000-fold higher than the maximum recommended ophthalmic dose).

Because there are no adequate and well-controlled studies in pregnant women, ZYMAXID™ 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 ZYMAXID™ is administered to a nursing woman.

8.4 Pediatric Use

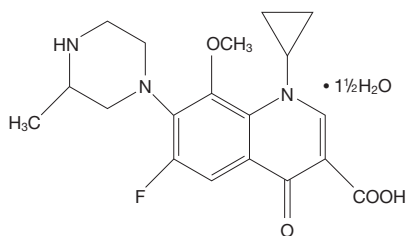
The safety and effectiveness of ZYMAXID™ in infants below one year of age have not been established. ZYMAXID™ has been demonstrated in clinical trials to be safe and effective for the treatment of bacterial conjunctivitis in pediatric patients one year or older (see CLINICAL STUDIES, 14).

8.5 Geriatric Use

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

11 DESCRIPTION

ZYMAXID™ sterile ophthalmic solution is an 8-methoxyfluoroquinolone anti-infective 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 **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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Gatifloxacin is a fluoroquinolone antibacterial (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 fluorquinolones 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 1×10^{-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 as described in the INDICATIONS AND USAGE, Section 1.

Aerobic Gram-Positive Bacteria:

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

Aerobic Gram-Negative Bacteria:

Haemophilus influenzae

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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 1600-fold and 1800-fold higher, respectively, than the maximum recommended ophthalmic dose of 0.05 mg/kg/day in a 50 kg human.

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 (900- and 2800-fold higher, respectively, than the maximum recommended 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 approximately 2000-fold higher than the maximum recommended 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.

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.

There were no adverse effects on fertility or reproduction in rats given gatifloxacin orally at doses up to 200 mg/kg/day (approximately 4000-fold higher than the maximum recommended ophthalmic dose for ZYMAXID™).

14 CLINICAL STUDIES

In two randomized, double-masked, multicenter clinical trials, where patients 1-89 years of age were dosed for 5 days, ZYMAXID™ solution 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 hyperaemia and conjunctival discharge) of 58% (193/333) 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 sizes:

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

17.1 Avoiding Contamination of the Product

Patients should be instructed to avoid contaminating the applicator tip with material from the eye, fingers, or other source.

17.2 Avoidance of Contact Lens Wear

Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis.

© 2010 Allergan, Inc.
Irvine, CA 92612, U.S.A.
™ and ® marks owned by Allergan, Inc.
Licensed from Kyorin Pharmaceuticals Co., Ltd.
U.S. Patents 5,880,283 and 6,333,045
APC24ER10
72366US10B

 ALLERGAN

ZYMAR[®]

(gatifloxacin ophthalmic solution) 0.3%

sterile

DESCRIPTION

ZYMAR[®] (gatifloxacin ophthalmic solution) 0.3% is a sterile ophthalmic solution. It is an 8-methoxy fluoroquinolone anti-infective for topical ophthalmic use.

Structure and Empirical Formula:

C₁₇H₂₂FN₃O₄ • 1.5 H₂O Mol Wt 402.42

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

Contains Active: gatifloxacin 0.3% (3 mg/mL).

Preservative: benzalkonium chloride 0.005%.

Inactives: edetate disodium; purified water and sodium chloride. May contain hydrochloric acid and/or sodium hydroxide to adjust pH to approximately 6.

ZYMAR[®] is a sterile, clear, pale yellow colored isotonic unbuffered solution. It has an osmolality of 260-330 mOsm/kg.

CLINICAL PHARMACOLOGY

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.

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 as described in the INDICATIONS AND USAGE section.

Aerobes, Gram-Positive:

*Corynebacterium propinquum**

Staphylococcus aureus

Staphylococcus epidermidis

*Streptococcus mitis**

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[®] 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 2µg/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

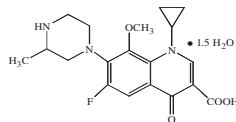
Anaerobic Microorganisms:

Bacteroides fragilis

Clostridium perfringens

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.



INDICATIONS AND USAGE

ZYMAR[®] 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**

Streptococcus pneumoniae

Aerobic Gram-Negative Bacteria:

Haemophilus influenzae

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

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.

WARNINGS

NOT FOR INJECTION.

ZYMAR[®] solution should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.

In patients receiving systemic quinolones, including gatifloxacin, serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial edema), airway obstruction, dyspnea, urticaria, and itching. If an allergic reaction to gatifloxacin occurs, discontinue the drug. Serious acute hypersensitivity reactions may require immediate emergency treatment. Oxygen and airway management should be administered as clinically indicated.

PRECAUTIONS

General: As with other anti-infectives, prolonged use 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.

Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis.

Information for Patients: Avoid contaminating the applicator tip with material from the eye, fingers or other source.

Systemic quinolones, including gatifloxacin, have 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.

Drug Interactions: Specific drug interaction studies have not been conducted with ZYMAR[®] ophthalmic solution. However, the systemic administration of some quinolones has been shown to elevate plasma concentrations of theophylline, interfere with the metabolism of caffeine, and enhance the effects of the oral anticoagulant warfarin and its derivatives, and has been associated with transient elevations in serum creatinine in patients receiving systemic cyclosporine concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

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 2000-fold higher than the maximum recommended ophthalmic dose of 0.04 mg/kg/day in a 50 kg human.

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 (1000 and 3000-fold higher, respectively, than the maximum recommended 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 approximately 2000-fold higher than the maximum recommended 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.

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.

There were no adverse effects on fertility or reproduction in rats given gatifloxacin orally at doses up to 200 mg/kg/day (approximately 4500-fold higher than the maximum recommended ophthalmic dose for ZYMAR[®]).

Pregnancy: Teratogenic Effects. Pregnancy Category C:

There were no teratogenic effects observed in rats or rabbits following oral gatifloxacin doses up to 50 mg/kg/day (approximately 1000-fold higher than the maximum recommended ophthalmic dose). However, skeletal/craniofacial malformations or delayed ossification, atrial enlargement, and reduced fetal weight were observed in fetuses from rats given ≥150 mg/kg/day (approximately 3000-fold higher than the maximum recommended ophthalmic dose). In a perinatal/postnatal study, increased late post-implantation loss and neonatal/perinatal mortalities were observed at 200 mg/kg/day (approximately 4500 times the maximum recommended ophthalmic dose).

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

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 gatifloxacin is administered to a nursing woman.

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

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

ADVERSE REACTIONS

Ophthalmic Use: The most frequently reported adverse events in the overall study population were conjunctival irritation, increased lacrimation, keratitis, and papillary conjunctivitis. These events 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 irritation, eye pain, eyelid edema, headache, red eye, reduced visual acuity and taste disturbance.

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.

HOW SUPPLIED

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 a 10 mL bottle - NDC 0023-9218-05

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

ANIMAL PHARMACOLOGY

Quinolone antibacterials have been shown to cause bone or cartilage changes in immature animals. There was no evidence of bone cartilage changes following ocular administration of gatifloxacin in rabbits or dogs.

Rx only

Based on package insert 71706JUS12P revised August 2004.

© 2007 Allergan, Inc.
Irvine, CA 92612, U.S.A.
® marks owned by Allergan, Inc.
Licensed from Kyorin Pharmaceuticals Co., Ltd.
U.S. Patents 4,980,470 and 5,880,283