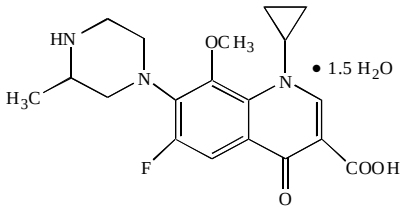
ZYMAR®
(gatifloxacin ophthalmic solution) 0.3% ALLERGAN
sterile

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:



$C_{19}H_{22}FN_3O_4 \bullet 1.5\ H_2O$ 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:
*Cornyebacterium 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 microbiologic 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:
*Cornyebacterium 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 sizes:
2.5 mL in a 6 mL bottle- NDC 0023-9218-03
5 mL in an 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
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Irvine, CA 92612, U.S.A.

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