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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**™.

INDICATIONS AND USAGE

ZYMAXID™ ophthalmic solution is a topical fluoroquinolone anti-infective indicated for the treatment of patients 1 year of age or older with 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

Gatifloxacin ophthalmic solution 5.0 mg/mL. (3)

CONTRAINDICATIONS

Hypersensitivity to gatifloxacin, to other quinolones, or to any other ingredient in this product. (4)

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 ≥ 1 % of patients included eye irritation and dysgeusia. (6)

FULL PRESCRIBING INFORMATION:

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FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

ZYMAXID™ (gatifloxacin ophthalmic solution) 0.5% solution is indicated for the treatment of patients 1 year of age or older with 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

Gatifloxacin ophthalmic solution 5.0 mg/mL.

4. CONTRAINDICATIONS

ZYMAXID™ is contraindicated in patients with a history of hypersensitivity to gatifloxacin, to other quinolones, or to any other ingredient in this product.

5. WARNINGS AND PRECAUTIONS

5.1 Topical Ophthalmic Use Only

ZYMAXID™ solution should not be introduced directly into the anterior chamber of the eye. **ZYMAXID**™ is not for injection.

5.2 Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolones. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial edema), airway obstruction, dyspnea, urticaria, and itching. There have been extremely rare reports of Steven-Johnson Syndrome and anaphylactic reaction reported in association with topical gatifloxacin use. If an allergic reaction to gatifloxacin occurs, discontinue the drug and contact your physician. Serious acute hypersensitivity reactions may require immediate emergency treatment. Oxygen and airway management should be administered as clinically indicated.

5.3 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 judgement dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and where appropriate, fluorescein staining.

5.4 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**™. **ZYMAXID**™ contains the preservative benzalkonium chloride, which may be absorbed by and cause discoloration of soft contact lenses. Patients wearing soft (hydrophilic) contact lenses should be instructed to remove contact lenses prior to administration of **ZYMAXID**™ and wait at least 15 minutes following administration before reinserting soft contact lenses.

5.5 Handling the Container

Patients should be instructed to avoid allowing the tip of the bottle to contact the eye or surrounding structures, fingers, or any other surface.

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 ≥ 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, red eyes, papillary conjunctivitis, and reduced visual acuity.

6.2 Postmarketing Experience

The following reactions have been identified during postmarketing use of **ZYMAXID**™ or with other formulations of gatifloxacin ophthalmic solution in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to gatifloxacin ophthalmic solutions or a combination of these factors, include: anaphylactic reaction, angioedema (including pharyngeal, oral or facial edema), blepharitis, conjunctival/ocular hyperemia, dysphnea, eye irritation, eye pain, 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.

7. DRUG INTERACTIONS

Specific drug interaction studies have not been conducted with **ZYMAXID**™ ophthalmic solution. **ZYMAXID**™ is a topical drug with effects expected to be predominantly local. Due to minimal blood concentrations of gatifloxacin following ocular dosing (≤ 5 ng/mL), no systemic drug-drug interactions are anticipated.

8. OVERDOSE

ZYMAXID™ is intended for topical use only. Due to the low systemic concentrations after topical ophthalmic application, the likelihood of systemic intoxication from topical overdose is remote. In the event of accidental ingestion, the patient should be carefully observed, and given symptomatic and supportive treatment.

9. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

As with any ocular medication, if transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machinery.

10. USE IN SPECIFIC POPULATIONS

10.1 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.

10.2 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.

10.3 Pediatric Use

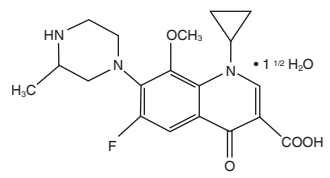
The safety and effectiveness of **ZYMAXID**™ in infants below one year of age have not been established. **ZYMAXID**™ has been demonstrated in clinical trials to be safe and effective for the treatment of bacterial conjunctivitis in pediatric patients one year or older (see **CLINICAL STUDIES, 14**).

10.4 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, 12.3**).

12.2 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.

12.3 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 1×10^{-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 versus 70% (228/325) for vehicle. Please note that microbiological eradication does not always correlate with clinical outcome in anti-infective trials.

15. 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 and 5 mL. Not all pack sizes may be marketed.

Storage: Store below 30°C. Protect from freezing. For external use only. Discard 28 days after opening.

Manufactured by:
Allergan Sales, LLC
Waco, Texas 76712, U.S.A.

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Keyline
Black

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