PRODUCT MONOGRAPH

Pr ZYMAR™

(Gatifloxacin)

Ophthalmic Solution

0.3%

Antibacterial Agent

Allergan Inc.
Markham, Ontario
L3R 9S1

Date of Preparation:
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Control No.: 081899

PRODUCT MONOGRAPH

PrZYMAR™

(Gatifloxacin)
Ophthalmic Solution

0.3%

THERAPEUTIC CLASSIFICATION

Antibacterial Agent

ACTIONS AND CLINICAL PHARMACOLOGY

Mechanism of Action

ZYMAR™ (gatifloxacin) ophthalmic solution 0.3% is a sterile solution for topical ophthalmic use. Gatifloxacin is an 8-methoxy synthetic fluoroquinolone antibacterial agent with *in vitro* activity against gram-negative and gram-positive, aerobic and anaerobic and clinically important atypical microorganisms.

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 (see **MICROBIOLOGY**).

Clinical Pharmacology

Pharmacokinetics

Ocular Administration

Gatifloxacin ophthalmic solutions 0.3% and 0.5% were administered to 1 eye of 6 healthy male subjects each (see **PHARMACOLOGY**, **Human Pharmacokinetics, Table 6**). At all time points, serum gatifloxacin levels were below the lower limit of quantification (5 ng/mL) in all subjects. Pharmacokinetic

parameters for ophthalmic dosing could not therefore be calculated. There is no human pharmacokinetic data available with respect to tear concentration following ocular administration.

Systemic Administration

Gatifloxacin is well absorbed from the gastrointestinal tract after oral administration and can be given without regard to food. The absolute bioavailability of gatifloxacin is 96%. Peak plasma concentrations of gatifloxacin usually occur 1-2 hours after oral dosing (see **PHARMACOLOGY, Human Pharmacokinetics, *Systemic Administration***)

INDICATIONS AND CLINICAL USE

ZYMAR™ (gatifloxacin) ophthalmic solution 0.3% is indicated for the treatment of patients 1 year of age and older with bacterial conjunctivitis caused by susceptible strains of the following bacteria:

Aerobic Gram-positive bacteria:

Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumoniae

Aerobic Gram-negative bacteria:

Haemophilus influenzae

CONTRAINDICATIONS

ZYMAR™ (gatifloxacin) ophthalmic solution 0.3% is contraindicated in individuals who have shown hypersensitivity to gatifloxacin, to other quinolones, or to any of the components in this medication. (See **PHARMACEUTICAL INFORMATION**).

WARNINGS

NOT FOR INJECTION INTO THE EYE. FOR TOPICAL OPHTHALMIC USE ONLY.

ZYMAR™ (gatifloxacin) ophthalmic solution 0.3% should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.

In patients receiving systemic quinolones, 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.

As with all antibiotics, serious and sometimes fatal events, some due to hypersensitivity and some due to uncertain etiology, have been reported in patients receiving systemic quinolone therapy. These events may be severe and generally occur following administration of multiple doses. Clinical manifestations may include one or more of the following: fever, rash or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome); vasculitis, arthralgia, myalgia, serum sickness; allergic pneumonitis, interstitial nephritis; acute renal insufficiency or failure; hepatitis, jaundice, acute hepatic necrosis or failure; anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

PRECAUTIONS

General

As with other anti-infectives, prolonged use of ZYMAR™ (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.

Hypersensitivity

As with all topical ophthalmic drugs, there is a potential for a systemic reaction. Urticaria has been reported in patients receiving ZYMAR™ (see **ADVERSE REACTIONS**).

Systemic quinolones have been associated with hypersensitivity reactions, even following a single dose.

Contact Lenses

Patients should not wear contact lenses while they have signs and symptoms of bacterial conjunctivitis.

Arthropathy

As with other members of the quinolone class, gatifloxacin has caused arthropathy and/or chondrodysplasia in juvenile rats and dogs when given systemically. (See **TOXICOLOGY, Special Toxicity Studies**).

Arthrotoxic and osteotoxic potential of ZYMAR™ was not assessed in animals.

Drug Interactions

Specific drug interaction studies have not been conducted with ZYMAR™ ophthalmic solution. Limited information is available on the concurrent use of ZYMAR™ with other ophthalmic products.

Probenecid

Systemic administration of gatifloxacin (single oral 200 mg dose) with probenecid (500 mg BID x 1 day) resulted in a 42% increase in AUC and 44% longer half-life of gatifloxacin.

Digoxin

Overall, only modest increases in Cmax and AUC of digoxin were noted (12% and 19%, respectively) in 8 of 11 healthy volunteers who received concomitant administration of gatifloxacin (400 mg oral tablet, once daily for 7 days) and digoxin (0.25 mg orally, once daily for 7 days). In 3 of 11 subjects, however, a significant increase in digoxin concentrations was observed. In these 3 subjects, digoxin Cmax increased by 18%, 29%, and 58% while digoxin AUC increased by 66%, 104%, and 79%, and digoxin clearance decreased by 40%, 51%, and 45%.

Systemic studies have also shown that gatifloxacin is chelated by polyvalent ions, such as iron, magnesium, zinc and aluminum.

No significant pharmacokinetic interactions occur when cimetidine, midazolam, theophylline, warfarin, or glyburide is administered concomitantly with oral gatifloxacin.

Use in Pregnancy

There are no adequate and well-controlled studies of ZYMAR™ in pregnant women. This drug should not be used in pregnant women unless, in the physician's opinion, the potential benefit to the mother justifies the potential risk to the fetus.

ZYMAR™ solution has not been studied in pregnant animals. Oral and intravenous studies in pregnant animals indicate that gatifloxacin crosses the placenta and that reproductive and fetal effects occur at doses of $\geq$150 mg/kg/day, which cause maternal toxicity (see **TOXICOLOGY**).

Use in Nursing Mothers

It is not known whether gatifloxacin is excreted in human milk, although gatifloxacin has been shown to be excreted in the breast milk of rats. Because gatifloxacin may be excreted in human milk, a decision should be made either to discontinue nursing or to discontinue the administration of ZYMAR™, taking into account the importance of ZYMAR™ therapy to the mother and the possible risk to the infant.

Use in Children

The safety and efficacy of ZYMAR™ in infants below the age of one year have not been established. ZYMAR™ ophthalmic solution has been used to treat conjunctivitis in 14 infants between 1-2 years of age and 47 children between 3-12 years of age.

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

Information To Be Provided To The Patient

Physicians should instruct their patients to:

" avoid contaminating the applicator tip with material from the eye (or surrounding structures), fingers or other sources.

" refrain from wearing contact lenses if they have signs and symptoms of bacterial conjunctivitis.

" discontinue use of drug immediately and to contact their physician at the first sign of a rash or allergic reaction.

ADVERSE REACTIONS

In clinical studies 364 patients were treated with ZYMAR™ (gatifloxacin) ophthalmic solution 0.3% for up to 5 days. Treatment-related adverse events were reported for 14.6% (53/364) of patients. The most frequently reported treatment-related adverse events occurring in 0.5% to 5% of patients treated with gatifloxacin are listed below:

Table 1: Percent of Patients in Phase 3 Trials with Treatment-Related Adverse Events Reported by 0.5% to 5% of Patients in the Active Treatment Arm

Body System **Preferred Term**	**Gatifloxacin** **N = 364**
Ocular	
superficial punctate keratitis	4.4%
eye irritation	1.9%
dry eye	1.6%
eyelid oedema	1.4%
lacrimation increased	1.4%
visual acuity reduced	1.1%
eye pain	0.8%
conjunctivitis papillary	0.8%
eye discharge	0.5%
Other (Non Ocular)	
erythema	0.8%
dermatitis, contact	0.5%
taste disturbance	1.4%
rhinorrhoea	0.5%
edema	0.5%

Other treatment-related adverse events occurring in less than 0.5% of patients included, conjunctival disorder, conjunctivitis, chemosis, conjunctival cyst, conjunctival hemorrhage, corneal deposits, eye disorder, photophobia, subepithelial opacities, blurred vision, dermatitis, generalized urticaria, nausea, sore throat, sneezing, dizziness, and iritis.

ZYMAR™ was discontinued due to an adverse event, either related or unrelated to the drug, in 1.6% (6/364) of patients.

Post-Marketing Experience
Adverse events reported include macular edema, eye redness, eyelid edema, keratoconjunctivitis, blepharitis allergic, endophthalmitis, corneal disorder, eye irritation, uveitis, corneal ulcer, allergic reactions including pruritis and angioneurotic edema and neurological events including headache, tinnitus, tremor and oral parasthesia. Rare cases of corneal melts and perforation have been reported in patients with multiple confounding factors including preexisting large corneal ulcer, corneal thinning, undiagnosed dacryocystitis, and use of multiple topical medications. Thus, it is difficult to determine the relationship of the events to ZYMAR™.

In one case, an elderly female with chronic conjunctivitis due to methicillin-resistant *Staphylococcus aureus* and a history of dacrocystitis, reported corneal perforation. This patient was using multiple concomitant antibiotics and had demonstrated evidence of a corneal defect associated with the infection prior to using ZYMAR™ and continued using ZYMAR™ during a successful post operative repair healing period.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

A topical overdosage of ZYMAR™ (gatifloxacin) ophthalmic solution 0.3% is considered to be a remote possibility. Discontinue medication when heavy or protracted use is suspected. A topical overdosage may be flushed from the eye(s) with warm tap water.

If a 10 kg child swallowed the contents of a 5 mL bottle of ZYMAR™ (15 mg of drug) it would be exposed to 1.5 mg/kg of gatifloxacin. This is equivalent to 25% of the recommended adult systemic therapeutic dose of gatifloxacin of 400 mg/day for a 70 kg adult (6.0 mg/kg).

DOSAGE AND ADMINISTRATION

The recommended dosage regimen for ZYMAR™ (gatifloxacin) ophthalmic solution 0.3% in the treatment of patients 1 year of age and older with 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 to 7: Instill one drop four times daily while awake.

Doses should be evenly spaced throughout the day.

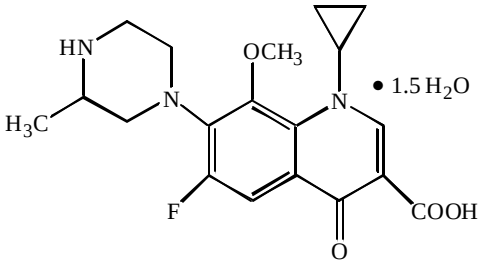
PHARMACEUTICAL INFORMATION

Drug Substance

Common name:gatifloxacin

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

Structural formula:



Molecular formula: $C_{19}H_{22}FN_3O_4 \cdot 1.5\ H_2O$

Molecular weight: 402.42

Description: Gatifloxacin is a sesquihydrate crystalline powder and is white to pale yellow in colour. It exists as a racemate, with no net optical rotation. The solubility of the gatifloxacin in water is pH dependent. It is slightly soluble in ethanol and water and freely soluble in acetic acid. Gatifloxacin melts at approximately 183°C.

Composition

Each mL of ZYMAR™ (gatifloxacin) ophthalmic solution 0.3% contains:
Active Ingredients: gatifloxacin 0.3% (3 mg/mL)
Inactive Ingredients: edetate disodium; purified water and sodium chloride. May contain hydrochloric acid and/or sodium hydroxide to adjust pH.

Preservatives: benzalkonium chloride 0.005%

ZYMAR™ is a sterile, clear, pale yellow coloured isotonic unbuffered solution formulated at a target pH of 6.

Stability and Storage Conditions

ZYMAR™ ophthalmic solution 0.3% should be stored at 15°C to 25°C. Protect from freezing.

AVAILABILITY OF DOSAGE FORMS

ZYMAR™ (gatifloxacin) ophthalmic solution 0.3% is supplied sterile in a white, low density polyethylene bottle with a controlled dropper tip and a tan, high density polyethylene (HIPS) cap. ZYMAR™ is supplied in 1.0 mL, 2.5 mL and 5.0 mL sizes.

INFORMATION FOR THE CONSUMER

Please read this package insert carefully <u>before</u> using ZYMAR™ (gatifloxacin) ophthalmic solution 0.3%. It provides useful information about this medication and effects you may experience. If you have any questions or need further explanation, please ask your doctor or pharmacist.

<u>Remember:</u> This medication is prescribed for the particular condition that you have. Never give this medication to others. Do not use it for any other condition.

What kind of medication is ZYMAR™ and how does it work?

ZYMAR™ is an antibiotic eye drop used to treat bacterial eye infections. ZYMAR™ kills many kinds of bacteria that can cause infections of the eye and is ineffective against viruses.

What is ZYMAR™ for?

ZYMAR™ is used to treat the signs and symptoms of bacterial conjunctivitis.

What are the ingredients of ZYMAR™?

ZYMAR™ contains the antibiotic, gatifloxacin, which is a member of the group of antibiotics known as "quinolones". ZYMAR™ also contains the following non-medicinal ingredients: edetate disodium, purified

water, sodium chloride and benzalkonium chloride, as preservative. It may also contain hydrochloric acid and or sodium hydroxide.

Who should not use ZYMAR™ ?
Do not use ZYMAR™ if you:

- have ever had an allergic reaction to TEQUIN™ (gatifloxacin) Tablets or I.V., or any medicine in the group of antibiotics known as "quinolones", such as CIPRO® (ciprofloxacin), LEVAQUIN® (levofloxacin), AVELOX® (moxifloxacin), OCUFLOX® (ofloxacin), or NOROXIN® (norfloxacin).
- are allergic to any component of ZYMAR™ (See, What are the ingredients of ZYMAR™?).
- ZYMAR™ is not recommended for children under 1 year of age.

Before using ZYMAR™ you should discuss with your doctor the following:

- If you have allergies to any medications.
- If you wear contact lenses.
- If you are using any other eye drops.
- If you are pregnant or intend to become pregnant
- If your are breast-feeding or intend to breast-feed

How to use ZYMAR™ ?:

- ZYMAR™ was prescribed by your doctor to treat your specific medical problem and is for your use only. Do not share it with others.
- The usual dose of ZYMAR™ is: On days 1 and 2, instill one drop every two hours in the affected eye(s) while awake, up to 8 times daily. On days 3 to 7, instill one drop four times daily while awake. Doses should be evenly spaced throughout the day.
- Your doctor may have told you to use ZYMAR™ in a different way to that recommended in this leaflet. If so, follow your doctor's instructions about when and how to use the eye drops. Read the directions on your prescription label carefully. Ask your doctor or pharmacist to explain anything that you do not understand.

- Do not wear contact lenses when you are suffering bacterial conjunctivitis.
- Do not change the dosage of the drug without consulting your physician. If you stop treatment contact your physician immediately.
- Do not start taking any other ophthalmic medicines unless you have discussed the matter with your physician.
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- If you develop any eye irritation or any new eye problems such as dryness of the eye, swelling or redness of the eyelid, tearing, or decreased vision, contact your physician immediately.
- If you suspect that ZYMAR™ is causing an allergic reaction, i.e. itchy skin or increased inflammation, stop its use and contact your physician as soon as possible.
- You must not use the bottle if the tamper-proof seal on the bottle neck is broken before you first use it.
- Follow the following steps to help you use ZYMAR™ properly:

1. Wash your hands. Tilt your head back and look at the ceiling.
2. Gently pull down the lower eyelid to create a small pocket.
3. Turn the bottle upside down and squeeze it gently to release one drop into each eye that needs treatment.
4. Let go of the lower lid, and close your eye for 30 seconds.

If a drop misses your eye, try again.

To help prevent infections, do not let the tip of the bottle touch your eye or anything else. Put the cap back on and close the bottle immediately after you have used it.

Missed Doses:

- If you forget to apply your eye drops at your normal time, simply apply them as soon as you remember. Then go back to the original schedule as directed by your doctor. **Don't try to catch up on missed drops by applying more than one dose at a time.**

Possible side effects of ZYMAR™ and what to do about them:

a) Stop use of the product and consult a doctor if:

- You experience inflamed or itchy skin, swelling or redness of the skin or hives (urticaria), which may indicate you are allergic to an ingredient in ZYMAR™, immediately discontinue the product and contact your doctor as soon as possible.

b) Other side effects:

- Some eye related side effects which have occurred when using ZYMAR™ include eye irritation, dry eye, swelling and redness of the eyelid, tearing or eye discharge, decreased vision, or eye pain. Other, non eye related side effects include unusual or after-taste and runny nose. Rare side effects include swelling or other disorders of the area around the cornea, spots on the cornea, sensitivity to light, blurred vision, nausea, sore throat, sneezing and dizziness. If any of these events persist or cause you concern, consult your doctor.

- Tell your physician or pharmacist promptly about any unusual symptom.

Storing ZYMAR™:

- Keep the dispensing container tightly closed when not in use. Store between 15°C to 25°C, protect from freezing.
- Discard container 28 days after opening.
- Do not use ZYMAR™ after the expiration date (marked "EXP") on the bottle and the box.
- Keep away from children.

Special Notes:

- If ZYMAR™ is swallowed, contact your doctor or poison control centre.

- If you accidentally add too many drops to the eye, ZYMAR™ may be flushed from the eye(s) with warm water.
- Vision may be temporarily blurred or unstable for a period after administration of ZYMAR™ ophthalmic solution. Use caution if driving or performing duties requiring clear vision.

***How Supplied**:*
ZYMAR™ is supplied sterile in a white, low density polyethylene bottle with a controlled dropper tip and a tan, high density polyethylene (HIPS) cap. ZYMAR™ is available in 1.0 mL, 2.5 mL and 5.0 mL sizes.

MICROBIOLOGY

Gatifloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive aerobic and anaerobic microorganisms. Gatifloxacin also has *in vitro* activity against clinically important atypical microorganisms. 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 penicillins, cephalosporins, aminoglycosides, macrolides and tetracyclines. 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 aforementioned classes of antibiotics.

Cross-resistance has been observed between systemic gatifloxacin and some other fluoroquinolones.

From *in vitro* synergy tests, gatifloxacin as with other fluoroquinolones is antagonistic with rifampicin against enterococci. Resistance to gatifloxacin *in vitro* develops slowly via multiple-step mutation. Resistance to gatifloxacin *in vitro* occurs at a general frequency of between 1×10^{-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 INDICATIONS and CLINICAL USE.

Table 2: *In vitro* Activity of Gatifloxacin against the indicated Bacterial Isolates from Clinical Trials

Bacterial Species	**No. of Isolates**	**MIC_{90} (: g/mL)**
Gram-Positive Aerobic Bacteria		

Bacterial Species	No. of Isolates	MIC_{90} (: g/mL)
Staphylococcus aureus	71	0.25
Staphylococcus epidermidis	94	2
Streptococcus pneumoniae	78	0.5
Gram-Negative Aerobic Bacteria		
Haemophilus influenzae	93	0.03

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.

Table 3: *In vitro* Activity Against Bacterial Conjunctivitis Pathogens and Ocular Pathogens

Organism (number of isolates)	MIC50 or MIC50 Range (µg/mL)	MIC90 or MIC90 Range (µg/mL)
AEROBES, GRAM-POSITIVE		
Bacillus species (14)	0.09 (9)	0.032 - 0.120 (5)
Enterococcus faecalis (16)	%	0.25 - 1.0
Staphylococcus capitis (11)	%	2
Staphylococcus warneri (13)	%	0.19-2.0
Streptococcus mitis (26)	%	0.5
Streptococcus oralis (14)	%	1
Streptococcus, viridans group (24)	0.25 (10)	0.38 - 1.0 (14)
CoagNeg Staphylococcus (20)	0.09 - 2	%
AEROBES, GRAM-NEGATIVE		
Moraxella catarrhalis (18)	%	0.023 - 0.06
Pseudomonas aeruginosa (39)	%	1.95 - 32
Serratia marcescens (29)	%	0.25 - 1.0

* Data not available

Susceptibility Tests

There are currently no NCCLS approved standards for assessing *in vitro* susceptibility of conjunctival isolates to topical antibiotics, including gatifloxacin. Standardized systemic susceptibility tests may not be appropriate to predict clinical effectiveness in treating conjunctivitis.

PHARMACOLOGY

Preclinical Pharmacology

Pharmacokinetics

Ocular Administration

The table below summarizes the single- and multiple dose pharmacokinetic studies conducted to study the ocular absorption, distribution, metabolism and excretion of gatifloxacin following topical ophthalmic administration.

Table 4: Preclinical Ocular Pharmacokinetic Studies

Study Description	Species/ Strain	No./ Sex	Ophthalmic Dose and Regimen	Tissue/Samples[2] Examined and Sampling Times	Results
Study 1: A single dose pharmacokinetic study conducted to investigate the ocular absorption, distribution, and metabolism of gatifloxacin following topical ophthalmic administration in rabbits.	Adult rabbit (pigmented, and non-pigmented)/ Dutch and Japanese White	57/M (4/TP[1])	[^{14}C]-Gatifloxacin 0.5 mg (0.5%)/animal administered as 50 : l/eye given as two 25 : l instillations within 5 mins. Bilateral Single dose	**Tissues**: cornea, conjunctiva, extraocular muscle (EOM), sclera, iris and ciliary body (ICB), aqueous humor (AH), lens, vitreous humor (VH), retina, choroid and plasma At 0.5, 1, 2, 4, 8, 24 hrs and 7, 28, and 84 days after instillation in Dutch rabbits. At 1, 4, and 24 hrs after instillation for Japanese rabbits	-The results show that [^{14}C]-Gatifloxacin distributed rapidly into ocular tissues following ophthalmic instillation in all rabbits, and achieved relatively high concentrations in the cornea and conjunctiva. -Radioactivity concentrations in conjunctiva, cornea, ICB, and AH were greater than in the lens, VH, and retina. -Differences between Dutch and Japanese White rabbits were seen in ICB and choroid. Radioactivity concentrations in ICB and choroid in Dutch rabbits were higher than those in Japanese White rabbits at all sampling times and at 24 hrs post dose were 180 and 32 times those in Japanese White rabbits, respectively. -These results indicate an affinity of [14C]-gatifloxacin to melanin-containing tissues. **Mean PK Parameters**[3] **Dutch Rabbits** / **Japanese White Rabbits** Tmax (hr) / Cmax (ng-eq/g)/ $T_{½}$ (hr)[4] / Tmax (hr) / Cmax (ng-eq/g)/ $T_{½}$(hr) Plasma: 0.5*/63/ 0.81 / 1*/16/ NC Cornea: 0.5*/8951/ 4.6 / 1*/3269/ 2.8 Conjunctiva: 0.5*/1768/ 5.6 / 1*/1077/ 2.8 EOM: 0.5*/530/ 5.3 / 1*/158/ 4.7 Sclera: 0.5*/719/ 3.6 / 1*319/ 4.3 ICB: 8/7562/ 528 / 1*/435/ 5.8 AH: 1/987/ 4.1 / 1*/480/ 3.2 Lens: ½2/ 24 / 1*/18/ 45.6 VH: ½0/ 12 / 1*/9/ 3.6 Retina: 0.5*/125/ 9.4 / 24**/97/ NC Choroid: 24/2264/ 984 / 1*/191/ 33.6
Study 2: A single dose pharmacokinetic study conducted to investigate the	Adult rabbit (pigmented)/ Dutch	30/M (3/TP)	Gatifloxacin 0.3 mg (0.3%)/animal administered as 50 : l/eye given as two 25 : l	**Tissues**: plasma, blood, anterior aqueous conjunctiva, extraocular muscle, cornea, iris/ciliary body,	-Cmax[3] for [14C]-Gatifloxacin in ocular tissues was reached in most tissues by 2 hrs post dose. -Highest radioactivity concentrations: cornea, ICB -Lowest radioactivity concentrations: vitreous body, lens -Radioactivity concentrations declined slowly from all melanin-containing tissues

Study Description	Species/ Strain	No./ Sex	Ophthalmic Dose and Regimen	Tissue/Samples[2] Examined and Sampling Times	Results
ocular distribution, and excretion of gatifloxacin following topical ophthalmic administration in rabbits.			instillations within 5 mins. Bilateral Single dose	crystalline lens, vitreous body, retinochoroid, sclera, lacrimal gland, accessory lacrimal gland, nasal mucosa, and tongue. At 0.5, 1, 2, 4, 8 and 24 hrs and 7, 28, and 84 days after instillation for ocular tissue and plasma/blood examination. At 0.5, 1, 4, and 24 hrs, and 7 and 28 days after instillation for examination of various body tissues/organs **Samples (from 3 rabbits)** urine, feces Collected once between 0-24 hrs after instillation, and once every 24 thereafter (up to 168 hrs)	after 8 hours post-dose, indicating binding of [^{14}C]-Gatifloxacin to melanin is reversible. **Pharmacokinetic Parameters of Radioactivity in Tissue** **Tissue** **AUC (: g eq.Ahr AmL^{-1})** Cornea 32.7 (0-28 days)/33.0 (0-4) ICB 1900 (0-84 days)/2030 (0-4) Retina and Choroid 533 (0-84 days)/705 (0-4) Sclera 76.4 (0-84 days)/81.6 (0-4) Plasma Data not available -At the end of a 168 hour collection period, 62.3% of the dose was recovered in feces and 35.1% of the dose was recovered in urine (total >97%), demonstrating that with the exception of small amounts bound to melanin containing tissues, gatifloxacin is almost completely excreted. **Cumulative Excretion of ^{14}C-gatifloxacin (mean% of dose±SD)** **Time** (hr) **Urine / Feces** 0-24 30.8±8.3 / 54.7±9.9 48 33.8±8.8 / 60.9±11.5 72 34.6±8.9 / 61.8±11.3 96 34.7±9.0 / 62.2±11.3 120 35.0±9.0 / 62.3±11.2 144 35.1±9.1 / 62.3±11.2 168 35.1±9.1 / 62.3±11.2

Study Description	Species/ Strain	No./ Sex	Ophthalmic Dose and Regimen	Tissue/Samples[2] Examined and Sampling Times	Results
Study 3: A repeat dose pharmacokinetics study conducted to investigate the ocular distribution of gatifloxacin following topical ophthalmic administration in rabbits.	Adult rabbit (pigmented)/ Dutch	30/M (3/TP)	Gatifloxacin 0.3 mg (0.3%) TID for 15 days (total of 43 instillation)/each dose per animal was administered as 50 : l/eye given as two 25 : l instillations within 5 mins. Bilateral Repeated dose	**Tissues:** plasma, blood, anterior aqueous conjunctiva, extraocular muscle, cornea, iris, ciliary body, crystalline lens, vitreous body, retinochoroid, sclera, lacrimal gland, accessory lacrimal gland, nasal mucosa, tongue, liver and skin. **Day 4**: 1 hr post instillation #10 **Day 8**: 1 hr post instillation #22 **Day 15**: 1, 2, 4, 8, and 24 hrs and 7, 28, and 84 days post instillation #43 (last dose)	-With the exception of lens, sclera, ICB and retina/choroid, ^{14}C-gatifloxacin concentrations in ocular tissues did not increase after repeated TID dosing in Dutch rabbits. -Concentrations in lens and sclera appeared to be reaching steady state after 22 doses, but the concentrations in melanin containing tissues continued to increase even after a total of 43 doses, indicating accumulation of gatifloxacin occurs during multiple dose administration, especially in melanin containing tissues. **Tissue** **T½ (day)** [5] **Cmax (ng-eq/g or mL)** **AUC (: g eq.Ahr AmL^{-1})**[5] Plasma Data not available 29±4 Data not available Cornea 5.3 (2hr-28 days) 4322±1387 84.0 (0-28 days)/ 88.0 (0-4) ICB 17 (4hr-84 days) 40286±4254 13900 (0-84 days)/ 14700 (0-4) Retina+Choroid 24 (2hr-84 days) 13144±1232 6210 (0-84 days)/ 7170 (0-4) Sclera 21 (24 hr-84 days) 1815±567 655 (0-84 days)/ 721 (0-4)

[1] = timepoint; * = first sampling timepoint; ** = Last sampling timepoint,

[2] = Gatifloxacin concentrations in tear film were not studied in animals.

[3]Cmax and Tmax are observed values

[4] The intervals for which half-life was calculated was Tmax-24hr with the execption of the following tissues in the Dutch Rabbit: Plasma Tmax-2hr; Sclera and Retina Tmax-8hr; ICB and choroid Tmax -84 days

[5]Pharmacokinetic parameters of radioactivity in tissue calculated after a 43rd instillation.

Human Pharmacology

Pharmacokinetics

Ocular Administration

Absorption
Systemic absorption of ZYMAR™ following ocular administration was investigated in 12 healthy volunteers. Below is a summary of the pharmacokinetic data from this study.

Table 5: Clinical Ocular Pharmacokinetic Studies

Study Description and Design	Treatment Groups, Dosing Regimen and No. Enrolled/Completed	Demographics	Pharmacokinetic Parameters			
			C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0\text{-}last}$ (ng.hr/mL)	$t_{½}$ (hr)
Phase 1, randomized, single-centre, single-blind, placebo controlled, paired-eye design study of the pharmacokinetics of gatifloxacin ophthalmic solution in healthy volunteers.	**Group 1**: 2 drops Gatifloxacin 0.3% in one eye/ 2 drops Placebo in contralateral eye 1x daily on day 1 4x daily on days 2 to 8 8x daily on days 9 to 11 N=6/6 **Group 2**: 2 drops Gatifloxacin 0.5% in one eye/ 2 drops Placebo in contralateral eye 1x daily on day 1 4x daily on days 2 to 8 8x daily on days 9 to 11 N=6/6	**sex:** all 12 subjects were male **race:** Asian (all volunteers were Japanese) **Mean Age ± SD (range)**: 24.7 ± 4.3 yrs (20-35 yrs)	-Blood samples were collected on: Day 2: at predose Day 5 (after 4th dose): at 0.5, 1, and 2 hrs Day 8 (after 7th dose): at 0.5, 1, and 2 hrs Day 9: at predose Day 11 (after the 8th dose): at 0.5, 1, 2 and 12 hrs -Serum[1] gatifloxacin concentrations in blood samples obtained at 12 time points from each subject were measured with high performance liquid chromatography (HPLC). -The concentration of gatifloxacin were below the limit of detection (#5ng/mL) in all the samples, and therefore pharmacokinetic paramenters could not be determined.			

[1] There is no human pharmacokinetic data available with respect to tear concentration following ocular administration

Systemic Administration

Absorption

The mean (SD) pharmacokinetic parameters of gatifloxacin after single 200 mg oral doses, single and multiple 400 mg oral doses, and single and multiple 1-hour i.v. infusions of 200 and 400 mg are listed below:

Table 6: Oral Administration

	C_{max} (: g/mL)	T_{max} [a] (h)	AUC [b] (: gh/mL)	$T_{½}$ (h)
200 mg -- Healthy Volunteers				
Single dose (n=12)	2.0 ±0.4	1.00 (0.50, 2.50)	14.2 ±0.4	--
400 mg -- Healthy Volunteers				
Single dose (n=202)	3.8 ±1.0	1.00 (0.50, 6.00)	33.0 ±6.2	7.8 ±1.3
Multiple dose (n=18)	4.2 ±1.3	1.50(0.50, 4.00)	34.4 ±5.7	7.1 ±0.6
400 mg -- Patients with Infection				
Multiple dose (n=140) [c]	4.2 ±1.9	--	51.3 ±20.4	--
400 mg -- Single Dose Subjects with Renal Insufficiency				
Cl_{cr} 50-80mL/min (n=8)	4.4 ±1.1	1.13 (0.75, 2.00)	48.0 ±12.7	11.2 ±2.8
Cl_{cr} 30-49mL/min (n=8)	5.1 ±1.8	0.75 (0.50, 6.00)	74.9 ±12.6	17.2 ±8.5
Cl_{cr} < 30mL/min (n=8)	4.5 ±1.2	1.50 (0.50, 6.00)	149.3 ±35.6	30.7 ±8.4
Hemodialysis (n=8)	4.7 ±1.0	1.50 (1.00, 3.00)	180.3 ±34.4	35.7 ±7.0
CAPD (n=8)	4.7 ±1.3	1.75 (0.50, 3.00)	227.0 ±60.0	40.3 ±8.3

[a] Median (Minimum, Maximum)

[b] Single dose: $AUC_{0-¥}$, Multiple dose: AUC_{0-24}

[c] Based on the patient population pharmacokinetic modeling, n=103 for C_{max}

C_{max}: Maximum serum concentration; T_{max} : Time to C_{max} ; AUC: Area under concentration versus time curve; $T_{1/2}$: Serum half-life

Table 7: Intravenous Administration

	C_{max} (: g/mL)	T_{max} [a] (h)	AUC [b] (: g•h/mL)	$T_{½}$ (h)	VD_{ss} (L/kg)
200 mg -- Healthy Volunteers					
Single dose (n=12)	2.2 ±0.3	1.00 (0.67, 1.50)	15.9 ±2.6	11.1 ±4.1	1.9 ±0.1
Multiple dose (n=8)	2.4 ±0.4	1.00 (0.67, 1.00)	16.8 ±3.6	12.3 ±4.6	2.0 ±0.3
400 mg -- Healthy Volunteers					
Single dose (n=30)	5.5 ±1.0	1.00 (0.50, 1.00)	35.1 ±6.7	7.4 ±1.6	1.5 ±0.2
Multiple dose (n=5)	4.6 ±0.6	1.00 (1.00, 1.00)	35.4 ±4.6	13.9 ±3.9	1.6 ±0.5
[a] Median (Minimum, Maximum)					
[b] Single dose: $AUC_{0-¥}$, Multiple dose: AUC_{0-24}					
C_{max} : Maximum serum concentration; T_{max} : Time to C_{max} ; AUC: Area under concentration versus time curve; $T_{1/2}$: Serum half-life; Vd_{ss} : Volume of distribution;					

Metabolism

Following oral or i.v. administration, gatifloxacin undergoes limited biotransformation in humans with less than 1% of the dose excreted in the urine as ethylenediamine and methylethylenediamine metabolites.

In vivo studies in humans (and animals) indicate that gatifloxacin is not an enzyme inducer; therefore, gatifloxacin is unlikely to alter the metabolic elimination of itself or other coadmnistered drugs.

Distribution

Serum protein binding of gatifloxacin is approximately 20% and is concentration independent. Following single and multiple intravenous infusions of 200 mg and 400 mg gatifloxacin, the mean volume of distribution of gatifloxacin at steady-state (Vd_{ss}) ranged from 1.5 to 2.0 L/Kg. Gatifloxacin is widely distributed throughout the body into many tissues and fluids. The distribution of gatifloxacin into tissues results in higher gatifloxacin concentrations in most target tissues than in serum.

Excretion

Gatifloxacin is excreted as unchanged drug primarily by the kidney. More than 70% of the administered dose was recovered as unchanged drug in the urine following oral and intravenous administration, and 5% was recovered in the feces. Renal clearance is independent of dose with mean values ranging from 124 to 161 mL/min. The magnitude of this value, coupled with the significant decrease in the elimination of gatifloxacin seen with concomitant probenecid administration, indicates that gatifloxacin undergoes both glomerular filtration and tubular secretion. Gatifloxacin may also undergo minimal biliary and/or intestinal elimination, since 5% of an intravenous dose was recovered in the feces as unchanged drug.

Ophthalmic Clinical Studies

In a randomized, double-masked, multicentre clinical trial where patients, aged > 1 year, were dosed for 4-6 days, ZYMAR™ ophthalmic solution 0.3% was superior to its vehicle on follow-up assessment (days 5-7) in patients with conjunctivitis and positive conjunctival cultures. Clinical outcomes for the trial demonstrated clinical cure of 76.9% (40/52) for the gatifloxacin treated group versus 58.3% (28/48) for the vehicle treated group on days 5-7. Microbiological outcomes for the same clinical trial demonstrated a statistically superior eradication rate for causative pathogens of 92.3% (48/52) for gatifloxacin vs. 72.3% (34/47) for vehicle on days 5-7. Please note that microbiological eradication does not always correlate with clinical cure in anti-infective trials.

TOXICOLOGY

Topical, Ocular Administration

Subacute and Chronic Toxicity

Gatifloxacin ophthalmic solution was evaluated in repeat dose ocular toxicity studies in rabbits and dogs, up to 1 month and 3 months in duration, respectively. Summaries of these studies are given in tables 8, 9, 10, and 11.

Arthrotoxic and osteotoxic potential of ZYMAR™ was not assessed in animals.

Table 8: Subacute Toxicity Study					
Species/ Strain	Number per Group/Sex/ Age/Initial Body Weight	Treatment Groups	Dosing Regimen/Duration	Evaluated Parameters	Results
Rabbits, Japanese White Albino	3 males 9 weeks old on receipt 1.98 to 2.13 kg	Saline 0.5% gatifloxacin (GFLX)	100 : L 8 times/day (i.e. at an interval of 100 : L/hr), left eye -7 days 100 : L 8 times/day (i.e. at an interval of 100 : L/hr), right eye -4 mg/rabbit/day -7 days	1) Clinical signs: -on days 1 to 7 (prior to first dose), -on day 7 +1 (day after completion of administration) 2) Body weight: -on day 1 (prior the first dose), -on day 7 + 1 (day after completion of administration) 3) Ocular examination, including: -area of corneal opacity -degree of corneal opacity -palpebral redness -palpebral edema -bulbar redness -discharge -nictitating membrane, and -iris appearance, response On day 0 (prior to initiation of administration), and days 1, 4, and 7, 30 min. following last administration 4)Fluorescein staining: -On day 0 (prior to initiation of administration), and days 1, 4, and 7.	1) Clinical signs: no abnormalities in any of the 3 rabbits, at any timepoint. 2) Body weight (mean kg ± SD): no abnormal changes 3) Ocular examination: no abnormalities at any timepoint. 4)Fluorescein staining: -no animal showed any abnormality, in either eye, at any timepoint.

Table 9: Chronic Toxicity					
Species/ Strain	Number per Group/Sex/ Age/Initial Body Weight	Treatment Groups	Dosing Regimen	Evaluated Parameters	Results
Rabbits, Dutch (pigment-ed)	5 males 20 weeks old upon receipt 1.73-1.97 kg	Saline 0.5% Gatifloxacin (GFLX) 1.0% Gatifloxacin (GFLX) Made fresh weekly from gatifloxacin hydrate,	100 ：L 4 times/day, each eye, 28 days 100 ：L 4 times/day, each eye, 28 days -4 mg/rabbit/day -28 days 100 ：L 4 times/day, each eye, 28 days -8 mg/rabbit/day -28 days	1) Clinical signs: twice daily; and once on day 28, prior to necropsy 2)Body weights: once weekly; and once on day 28, prior to necropsy 3)Ocular observations including: -area of corneal opacity -degree of corneal opacity -iris appearance, response -palpebral redness -palpebral chemosis -bulbar redness -condition of nictitating membrane -discharge once before start of study, and once weekly. 4) Ophthalmologic exams, including: -corneal fluorescein exam -lens and vitreous exam -ocular fundus exam once before start of study and once weekly. 5) Electroretinography: once before study initiation and at then at weeks 1 and 4. 6) Hematology, Blood Chemistry, and Urinalysis: once at termination of study 7) Necropsy, Organ Weights and	1) Clinical signs: no remarkable changes noted in either active treatment group vs placebo. 2) Body weight: no significant changes in either active treatment group vs placebo. 3) Ocular observations: no abnormalities on cornea, iris or conjunctivae, in either eye in any groups on any examinations. 4) Ophthalmologic exams: no damages/abnormalities of cornea, lens, vitreous body or fundus of either eye, in any group on any examinations. 5) ERG: no significant changes in the latency and amplitude of *a*- and *b*-wave were noted in either active treatment group compared to placebo. 6)Hematology and Urinalysis no significant changes were noted in either active treatment group compared to placebo Blood Chemistry: -no treatment-related changes 7) Necropsy, Organ weights and Histopathology: -no treatment related changes

				Histopathology: at termination of study	

Table 10: Chronic Toxicity

Species/ Strain	Number per Group/Sex/ Age/Initial Body Weight	Treatment Groups	Dosing Regimen	Evaluated Parameters	Results
Rabbits, Haz (NZW) SPF albino	5 males 13 weeks old at treatment initiation 2.11-2.52 kg	Saline 0.5% Gatifloxacin with 0.005% BAK, 0.01% EDTA	100 ：L 8 times/day, each eye, 30 days 100 ：L 8 times/day, each eye, 30 days -8 mg/rabbit/day -30 days	1) Clinical signs: twice daily 2) Food Consumption: daily 3) Body weights: at randomization, the first day of administration, and once weekly thereafter 4) Ocular observations including: -corneal opacity -degree of corneal opacity -iris values -palpebral redness -palpebral chemosis -discharge once before start of administration, on the first day of administration, and once weekly thereafter. 5) Ophthalmologic exams, including: -tonometry -corneal exam -lens and vitreous exam -ocular fundus exam once before start of administration, on the first day of administration, and once weekly thereafter.	1) Clinical signs: no treatment-related changes noted. 2) Food consumption: no treatment-related changes noted 3) Body weight: no treatment-related changes noted. 4) Ocular observations: no lesions/abnormalities observed. 5) Ophthalmologic exams: no damages/abnormalities of intraocular pressure, cornea, lens, vitreous or fundus observed. 6) Fluorescein Angiography: no treatment-related abnormalities observed 7) ERG: no significant changes were noted during course of treatment. 8) Hematology, Clinical Chemistry, Coagulation: no significant changes were noted in active treatment group vs placebo 9) Necropsy, Organ weights and Histopathology: -no treatment-related macroscopic or microscopic observations.

Table 10: Chronic Toxicity					
Species/ Strain	Number per Group/Sex/ Age/Initial Body Weight	Treatment Groups	Dosing Regimen	Evaluated Parameters	Results
				6) Fluorescein Angiography: once before start of administration, on the first day of administration, and once weekly thereafter. 7) Electroretinography: once before administration and at days 14 and 30 during administration 8) Hematology, Clinical Chemistry, and Coagulation: once prior to administration and at termination 9) Necropsy, Organ Weights and Histopathology: at termination	

Table 11: Chronic Toxicity					
Species/ Strain	Number per Group/Sex/ Age/Body Weight	Treatment Groups	Dosing Regimen/Duration	Evaluated Parameters	Results
Beagle dogs	4/sex/group sacrificed at end of treatment; 2/sex/group sacrificed after	Placebo ophthalmic solution, 0.5% Gatifloxacin	2 drops (80 ：L) 10 times/day, right eye, 1 month 2 drops (80 ：L) 10 times/day, right eye,	1) Mortality checks: twice daily during pre-treatment, treatment and recovery phases. 2) Clinical observations: once daily during pre-treatment, treatment and recovery period.	1) Mortality no mortality 2) Clinical observations: -No drug-related clinical observations. 3) Gross ocular observations:

Table 11: Chronic Toxicity					
Species/ Strain	Number per Group/Sex/ Age/Body Weight	Treatment Groups	Dosing Regimen/Duration	Evaluated Parameters	Results
	1 month recovery period 13-14 months old at start of treatment 7.5-11.7 kg during treatment	Placebo ophthalmic solution, 0.5% Gatifloxacin	4 mg/dog/day for 1 month 2 drops (80 ：L) 32 times/day for 2 days, 16 times/day for 5 days, then 4 times/day for 11 weeks, right eye, 3 months total 2 drops (80 ：L) 32 times/day for 2 days, 16 times/day for 5 days, then 4 times/day for 11 weeks, right eye, 3 months total 12.8 mg/dog/day for 2 days, 6.4 mg/dog/day for 5 days, and 1.6 mg/dog/day for 11 weeks	3) Gross ocular observations including: -conjunctival hyperemia -conjunctival chemosis -ocular discharge twice daily during week 1 of treatment and twice weekly for remainder of treatment period; once weekly during recovery. 4) Body weight: once prior to randomization; once weekly during last two weeks of pre-treatment; once prior to dosing; once weekly during treatment and recovery; prior to necropsy 5) Food consumption daily during last two weeks of pre-treatment; daily throughout treatment and recovery. 6) Ophthalmology exams, including indirect ophthalmoscopy, slit lamp biomicroscopy with fluorescein staining, pupillary reflex, tonometry: once prior to start of treatment; end of week 4 and week 13 of treatment; and end of recovery. 7) Hematology, Clinical Chemistry, Coagulation, Urinalysis: once prior to treatment; once at weeks 4 and 13 of treatment; and end of recovery period.	-After the first three weeks of treatment, there was a slight increase in the frequency of mild hyperemia in the treated eye of drug-treated males. Hyperemia was rare among females. -These findings were not accompanied by gross or microscopic pathology changes. -No drug related hyperemia during recovery period, indicating reversibility of the effect. 4) Body weights - no adverse effect on mean body weight in any drug-treated animals. 5) Food consumption - no adverse effect on mean food consumption in any drug-treated animals. 6) Ophthalmology: Slit lamp and ophthalmoscopic examinations revealed no drug-related ocular effects. No drug-related effects were observed on intraocular pressure or on pupillary light reflex throughout the study. 7) Hematology, Clinical Chemistry, Coagulation, Urinalysis: -No drug-related changes 8) 1 month study: Cmax (ng/mL) = 73.7 (day 7); 65 (day 28) $AUC_{0\text{-}t}$(ng•h/mL) =581 (day 7); 616 (day 28) 3 month study: Cmax (ng/mL) = 162 (day 1); 18 (day 90)

Table 11: Chronic Toxicity					
Species/ Strain	Number per Group/Sex/ Age/Body Weight	Treatment Groups	Dosing Regimen/Duration	Evaluated Parameters	Results
				8) Toxicokinetics: Day 7 and 28 for 1 month treatment groups Day 1 and 90 for 3 month treatment groups. 9) Necropsy, Organ Weights, Gross and Microscopic pathology: termination	$AUC_{0\text{-}t}$(ng.h/mL) = 1980 (day 1); 182 (day 90) 9)Necropsy, Organ Weights, Gross and Microscopic pathology: -no treatment related changes in organ weights -no treatment related macroscopic lesions. -no treatment related histopathological changes -no treatment related changes in corneas, exterior or internal ocular structures.

In Vitro Corneal Epithelial Wound Closure

Some quinolone antibacterials have been shown to alter corneal healing rates dose dependently in nonclinical models. In an *in vitro* model of wound closure in primary cultures of rabbit corneal epithelial cells, wound healing rates with gatifloxacin at 0.2 mM, 0.4 mM and 0.6 mM (75, 150, or 230 : g/mL, respectively) were 88.1, 62.8 or 33.3 percent, respectively, of the wound healing rate for untreated control cultures. Wounds in control cultures closed within 38 hours. In this assay a 5-7 mm diameter mechanical wound was made in a confluent culture of cells. Triplicate cultures were treated with each concentration of gatifloxacin, without preservatives or pharmaceutical excipients, at 37°C for 64 hours. Digital images of the wounds were taken at treatment initiation and at 13, 22, 38, 45 and 64 hrs thereafter. Wound areas were measured and relative rates of wound closure calculated (change in relative wound area per hour as a percent of the control rate).

Oral/Intravenous Administration

Acute Toxicity
In single-dose oral studies, no major adverse effects were seen in rats at doses up to 2000 mg/kg or dogs at a dose of 160 mg/kg. Single intravenous doses up to 120 mg/kg in rats and 15 mg/kg in dogs were well tolerated.

Subacute and Chronic Toxicity
In a series of repeat-dose oral studies, gatifloxacin was given for up to 6 months to rats at doses of 30, 60, 120, and 240 mg/kg/day and dogs a t doses of 6, 12, and 24 mg/kg/day. In rats, gatifloxacin was well tolerated for 6 months at a dose of 30 mg/kg daily. At 60 mg/kg/day, hepatocellular lipid droplets were observed microscopically in the liver, while at 120 mg/kg/day, and higher, similar liver changes and vacuolation of pancreatic $ cells were seen. In dogs, the drug was well tolerated for 6 months at a dose of 6 mg/kg daily. At 12 mg/kg/day and higher, the primary finding was vacuolation of pancreatic $ cells. In a 5 month oral monkey study (15, 30, and 60 mg/kg), drug related changes at 15 and 30 mg/kg/day were limited to vacuolation of the pancreatic $ cells (only observed upon ultrastructural examination). At 60 mg/kg, in addition to the pancreatic changes, decreases in body weight and food consumption were noted. The changes observed in all of the oral studies were generally reversible upon cessation of treatment.

In 1 month intravenous studies, gatifloxacin was well tolerated in rats at doses up to 30 mg/kg daily. Doses of 90 mg/kg daily were overtly toxic, resulting in several deaths. In dogs, no drug-related changes were seen after 1 month of intravenous dosing at 7 mg/kg/day. At 15 mg/kg/day, drug-related findings were limited to emesis and salivation. Doses of 30 mg/kg daily produced numerous clinical signs, changes in clinical-pathology parameters, and a decrease in lymphocytes in the cortex of the thymus. With the exception of some minor irritation at the injection sites in rats, all of the changes observed in these studies were reversible upon cessation of treatment.

Mutagenicity
Gatifloxacin was negative in five *in vivo* genotoxicity studies that included oral and intravenous micronucleus tests in mice, an oral cytogenetics test in rats, and oral DNA repair tests in two strains of rats.

Gatifloxacin was evaluated as positive in three *in vitro* gene-mutation studies and two *in vitro* chromosomal-aberration studies. These findings were not unexpected; similar findings have been obtained with other quinolone antibiotics and are considered to be due to the inhibitory effects that high concentrations of these compounds have on eukaryotic cell type II DNA topoisomerase. This enzyme is related to bacterial DNA gyrase, the target at which all quinolones exert their antibiotic activity.

Carcinogenicity
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.

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. A statistically significant increase in the incidence of large granular lymphocyte (LGL) leukemia was seen in high-dose males (52%) when compared to controls (16%). Although LGL leukemia is commonly seen in the F344 rat, the incidence of this change in high-dose males slightly exceeded the historical control range (5.7 to 40.4%) established for this strain. These findings suggest that gatifloxacin may have exacerbated the onset and development of this commonly occurring neoplasm. The incidence of LGL leukemia in all of the other drug-treated groups was comparable to that in controls. There were no other neoplastic or non-neoplastic lesions observed in the study that were considered directly attributable to treatment with gatifloxacin.

Reproduction and Teratology
Animal data shows that there were no teratogenic effects observed in rats or rabbits following oral gatifloxacin doses up to 50 mg/kg/day. However, skeletal/craniofacial malformations or delayed ossification, atrial enlargement, and reduced fetal weight were observed in fetuses from rats given $150 mg/kg/day. In a perinatal/postnatal study, increased late post-implantation loss and neonatal/perinatal mortalities were observed at 200 mg/kg/day.

Special Toxicity Studies:

Arthrotoxicity
Oral gatifloxacin was evaluated in a series of special toxicity studies. In juvenile rats (doses $600 mg/kg) and dogs ($10 mg/kg), gatifloxacin produced arthrotoxic and osteotoxic effects similar to those seen with

other quinolone antibiotics. Relevance of these findings to the clinical use of gatifloxacin ophthalmic solution is unknown.

Phototoxicity/photosensitization

There was no evidence of phototoxicity and/or photosensitization in numerous oral studies of gatifloxacin in mice and guinea pigs.

Effects on glucose/insulin/pancreatic $ cells

Gatifloxacin produced reversible changes in glucose tolerance, serum insulin levels, and morphology of pancreatic $ cells when given orally to rats for 7 days at a dose of 810 mg/kg/day, but not at 270 mg/kg/day. Similar changes in $ cells were seen in dogs (6 months at 24 mg/kg/day) and monkeys (5 months at 60 mg/kg/day) given gatifloxacin orally.

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