PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]APO-GATIFLOXACIN

Gatifloxacin Ophthalmic Solution

Solution, 0.3% gatifloxacin (as hemihydrate), for ophthalmic use

Antibacterial Agent (ATC Code: S01AE06)

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MAR 23, 2016

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AUG 04, 2023

Submission Control Number: 272580.

RECENT MAJOR LABEL CHANGES

None at the time of the most recent authorization.	

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

APO-GATIFLOXACIN (gatifloxacin ophthalmic solution) 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*

To reduce the development of drug-resistant bacteria and maintain the effectiveness of APO-GATIFLOXACIN and other antibacterial drugs, APO-GATIFLOXACIN should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.

1.1 Pediatrics

Pediatrics (≥ 1 year and ≤ 12 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of gatifloxacin ophthalmic solution in pediatric patients 1 year of age and older has been established; therefore, Health Canada has authorized an indication for pediatric use. See 7.1.3 Pediatrics.

1.2 Geriatrics

Geriatrics (> 65 years of age): No overall differences in safety or effectiveness have been observed between elderly and younger patients.

2 CONTRAINDICATIONS

APO-GATIFLOXACIN is contraindicated in patients who have shown hypersensitivity to gatifloxacin, to other quinolones, or to any ingredient in the formulation, including any non-medicinal ingredient, or components in this container. See 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

- The recommended dosage regimen for APO-GATIFLOXACIN 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 in the affected eye(s) while awake.

  - Doses should be evenly spaced throughout the day.

4.4 Administration

Patients should be instructed to avoid allowing the tip of the bottle to contact the eye or surrounding structures to avoid eye injury and contamination of the eye drops.

Patients wearing soft (hydrophilic) contact lenses should be instructed to remove contact lenses prior to administration of APO-GATIFLOXACIN and wait at least 15 minutes following administration before reinserting soft contact lenses.

4.5 Missed Dose

Patients should be instructed to instill the drops as soon as they remember, and then to return to their regular routine.

5 OVERDOSAGE

A topical overdosage of APO-GATIFLOXACIN 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 APO-GATIFLOXACIN (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).

For management of a suspected drug overdose, including accidental ingestion, contact your regional poison control centre

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
ophthalmic	Solution, 0.3% w/v; Gatifloxacin (as Gatifloxacin hemihydrate)	Benzalkonium chloride 0.005%, as preservative, edetate disodium, sodium chloride and water for injection. May contain hydrochloric acid and/or sodium hydroxide to adjust pH.

APO-GATIFLOXACIN is supplied sterile in a white, low density polyethylene (LDPE) bottle with a controlled dropper tip and a white, high density polyethylene (HDPE) copolymer cap. APO-GATIFLOXACIN is supplied in a 5 mL size.

7 WARNINGS AND PRECAUTIONS

General

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

APO-GATIFLOXACIN should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.

APO-GATIFLOXACIN contains the preservative benzalkonium chloride. See 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

The use of gatifloxacin with other products may lead to drug interactions. For established or potential drug interactions. See 9 DRUG INTERACTIONS.

As with all topical ophthalmic drugs, there is a potential for a systemic reaction.

Driving and Operating Machinery

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.

Immune

Hypersensitivity

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.

Hypersensitivity reactions including anaphylactic reaction, dyspnea, rash, Stevens-Johnson syndrome and urticaria have been reported in association with gatifloxacin ophthalmic solution. See 8 ADVERSE REACTIONS.

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

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.

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.

Musculoskeletal and Connective Tissue

Tendon inflammation and rupture may occur with systemic fluoroquinolone therapy including gatifloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids. Treatment with APO-GATIFLOXACIN should be discontinued at the first sign of tendon inflammation.

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 16 NON-CLINICAL TOXICOLOGY.

Arthrotoxic and osteotoxic potential of gatifloxacin ophthalmic solution was not assessed in animals.

Ophthalmologic

Contact Lenses

Patients should not wear contact lenses while they have signs and symptoms of bacterial conjunctivitis. APO-GATIFLOXACIN contains the preservative benzalkonium chloride, which may be absorbed by and cause discoloration of soft contact lenses.

Susceptibility/Resistance

Development of Drug Resistant Bacteria

Prescribing APO-GATIFLOXACIN in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant organisms.

Potential for Microbial Overgrowth

As with other anti-infectives, prolonged use of APO-GATIFLOXACIN 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.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies of gatifloxacin ophthalmic solution 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.

Gatifloxacin ophthalmic 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 ≥ 150 mg/kg/day, which cause maternal toxicity. See 16 NON-CLINICAL TOXICOLOGY.

7.1.2 Breast-feeding

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 APO-GATIFLOXACIN, taking into account the importance of APO-GATIFLOXACIN therapy to the mother and the possible risk to the infant.

7.1.3 Pediatrics

The safety and efficacy of gatifloxacin ophthalmic solution in infants under 1 year of age have not been established. Gatifloxacin ophthalmic solution has been used to treat conjunctivitis in 14 infants between 1 to 2 years of age and 47 children between 3 to 12 years of age.

7.1.4 Geriatrics

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

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In clinical studies 364 patients were treated with gatifloxacin ophthalmic solution 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 2 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

	Gatifloxacin N = 364
Eye disorders	
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%
General disorders and administration site conditions	
Edema	0.5%
Nervous system disorders	
Taste disturbance	1.4%
Respiratory, thoracic and mediastinal disorders	
Rhinorrhea	0.5%
Skin and subcutaneous tissue disorders	

	Gatifloxacin N = 364
Erythema	0.8%
Dermatitis, contact	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.

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

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

8.5 Post-Market Adverse Reactions

The following additional adverse reactions have been identified during postmarketing use of gatifloxacin ophthalmic solution 0.3% in clinical practice. Because postmarketing reporting of these reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions.

Eye disorders: blepharitis allergic, corneal disorder, corneal ulcer, endophthalmitis, eye edema (including corneal and conjunctival edema), eye redness, eye pruritus, keratoconjunctivitis, macular edema, uveitis.

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 gatifloxacin ophthalmic solution.

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 gatifloxacin ophthalmic solution and continued using gatifloxacin ophthalmic solution during a successful post operative repair healing period.

Immune system disorders: anaphylactic reactions, angioneurotic edema (including pharyngeal, oral or facial edema), hypersensitivity, pruritus allergic, rash, Stevens-Johnson syndrome.

Nervous system disorders: headache, paraesthesia oral, tinnitus, tremor.

Respiratory, thoracic and mediastinal disorders: dyspnea.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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

9.3 Drug-Behavioural Interactions

No formal drug-behavioural interaction studies were conducted with gatifloxacin ophthalmic solution.

9.4 Drug-Drug Interactions

Topical Ophthalmic

Interactions with drugs have not been established.

Systemic

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 C_{max} 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 C_{max} 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.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

APO-GATIFLOXACIN 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 15 MICROBIOLOGY.

10.2 Pharmacodynamics

No pharmacodynamic studies were conducted.

10.3 Pharmacokinetics

Ocular Administration

Gatifloxacin ophthalmic solutions 0.3% and 0.5% were administered to 1 eye of 6 healthy male subjects each (see Table 3). 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.

Absorption

Systemic absorption of gatifloxacin ophthalmic solution following ocular administration was investigated in 12 healthy volunteers. Below is a summary of the pharmacokinetic data from this study.

Table 3 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 parameters could not be determined.			

1 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 to 2 hours after oral dosing.

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 intravenous infusions of 200 and 400 mg are listed below:

Table 4 Oral Administration

	C_{max} (mcg/mL)	T_{max} [a] (h)	AUC [b] (mcg·h/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: $AUC_{0-\infty}$, 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 5 Intravenous Administration

	C_{max} (mcg/mL)	T_{max} [a] (h)	AUC [b] (mcg•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					

	C_{max} (mcg/mL)	T_{max} [a] (h)	AUC [b] (mcg•h/mL)	$T_{½}$ (h)	VD_{ss} (L/kg)
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: $AUC_{0-\infty}$, 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 intravenous 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.

Preclinical Pharmacology

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 6 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 mcL/eye given as two 25 mcL 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 [^{14}C]-gatifloxacin to melanin-containing tissues. **Mean PK Parameters**[3] (T_{max} (hr) / C_{max} (ng-eq/g)/ $T_{½}$ (hr)[4]) **Dutch Rabbits** / **Japanese White Rabbits** 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

Study Description	Species / Strain	No./ Sex	Ophthalmic Dose and Regimen	Tissue/Samples[2] Examined and Sampling Times	Results
					Choroid 24/2264/ 984 1*/191/ 33.6
Study 2: A single dose pharmacokinetic study conducted to investigate the ocular distribution, and excretion of gatifloxacin following topical ophthalmic administration in rabbits.	Adult rabbit (pigmented)/ Dutch	30/M (3/TP)	Gatifloxacin 0.3 mg (0.3%)/animal administered as 50 mcL/eye given as two 25 mcL instillations within 5 mins. Bilateral Single 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, 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	-C_{max}[3] for [^{14}C]-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 after 8 hours post-dose, indicating binding of [^{14}C]-Gatifloxacin to melanin is reversible. **Pharmacokinetic Parameters of Radioactivity in Tissue** **Tissue** — **AUC (mcg eq. xhr xmL^{-1})** Cornea — 32.7 (0-28 days)/33.0 (0-∞) ICB — 1900 (0-84 days)/2030 (0-∞) Retina and Choroid — 533 (0-84 days)/705 (0-∞) Sclera — 76.4 (0-84 days)/81.6 (0-∞) 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

Study Description	Species / Strain	No./ Sex	Ophthalmic Dose and Regimen	Tissue/Samples[2] Examined and Sampling Times	Results
				Collected once between 0-24 hrs after instillation, and once every 24 thereafter (up to 168 hrs)	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 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 mcL/eye given as two 25 mcL 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] C_{max} (ng-eq/g or mL) AUC (mcg eq.·hr·mL^{-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-∞) ICB 17 (4hr-84 days) 40286±4254 13900 (0-84 days)/14700 (0-∞) Retina+Choroid 24 (2hr-84 days) 13144±1232 6210 (0-84 days)/7170 (0-∞) Sclera 21 (24 hr-84 days) 1815±567 655 (0-84 days)/721 (0-∞)

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

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

Study Description	Species / Strain	No./ Sex	Ophthalmic Dose and Regimen	Tissue/Samples[2] Examined and Sampling Times	Results

[3] C_{max} and T_{max} are observed values

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

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

11 STORAGE, STABILITY AND DISPOSAL

APO-GATIFLOXACIN should be stored at room temperature 15°C to 30°C. Protect from freezing. Discard container 28 days after opening.

Keep out of the reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

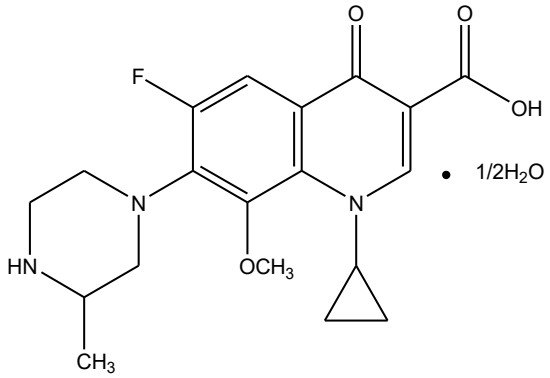
Drug Substance

Proper name: gatifloxacin

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

Molecular formula and molecular mass: $C_{19}H_{22}FN_3O_4$ ½ H_2O and 384.39 g/mol

Structural formula:



Physicochemical properties: Gatifloxacin is a hemihydrate powder and is white to pale yellow colour solid. 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 soluble in acetic acid and water. Gatifloxacin hemihydrate melts at 159°C to 160°C.

APO-GATIFLOXACIN ophthalmic solution is a sterile, clear, pale yellow coloured isotonic unbuffered solution formulated at a pH of 5.5 to 6.5.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Bacterial Conjunctivitis

At the time of authorization, the trial design and study demographics were not included in the Product Monograph.

Study results

In a randomized, double-masked, multicentre clinical trial where patients, aged > 1 year, were dosed for 4 to 6 days, gatifloxacin ophthalmic solution 0.3% was superior to its vehicle on follow-up assessment (days 5 to 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 to 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 to 7. Please note that microbiological eradication does not always correlate with clinical cure in anti-infective trials.

15 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 1 INDICATIONS.

Table 7 *In vitro* Activity of Gatifloxacin against the indicated Bacterial Isolates from Clinical Trials

Bacterial Species	No. of Isolates	MIC_{90} (mcg/mL)
Gram-Positive Aerobic Bacteria		
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 gatifloxacin ophthalmic solution 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 8 *In vitro* Activity against Bacterial Conjunctivitis Pathogens and Ocular Pathogens

Organism (number of isolates)	MIC_{50} or MIC_{50} Range (mcg/mL)	MIC_{90} or MIC_{90} Range (mcg/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.

16 NON-CLINICAL 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, 9, 10, 11 and 12.

Arthrotoxic and osteotoxic potential of gatifloxacin ophthalmic solution was not assessed in animals.

Table 9 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 mcL 8 times/day (i.e. at an interval of 100 mcL/hr), left eye -7 days 100 mcL 8 times/day (i.e. at an interval of 100 mcL/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 10 Chronic Toxicity

Species / Strain	Number per Group/Sex/Age/Initial Body Weight	Treatment Groups	Dosing Regimen	Evaluated Parameters	Results
Rabbits, Dutch (pigmented)	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 mcL 4 times/day, each eye, 28 days 100 mcL 4 times/day, each eye, 28 days -4 mg/rabbit/day -28 days 100 mcL 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	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.

Species / Strain	Number per Group/Sex/Age/Initial Body Weight	Treatment Groups	Dosing Regimen	Evaluated Parameters	Results
				-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 Histopathology: at termination of study	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

Table 11 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	Saline 0.5% Gatifloxacin	100 mcL 8 times/day, each eye, 30 days 100 mcL 8 times/day, each	1) Clinical signs: twice daily 2) Food Consumption: daily 3) Body weights: at randomization, the first day of administration, and	1) Clinical signs: no treatment-related changes noted. 2) Food consumption: no treatment-related changes noted.

Species/ Strain	Number per Group/Sex/ Age/Initial Body Weight	Treatment Groups	Dosing Regimen	Evaluated Parameters	Results
	2.11-2.52 kg	with 0.005% BAK, 0.01% EDTA	eye, 30 days -8 mg/rabbit/day -30 days	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. 6) Fluorescein Angiography: once before start of administration, on the first day of administration, and once weekly thereafter.	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.

Species/ Strain	Number per Group/Sex/ Age/Initial Body Weight	Treatment Groups	Dosing Regimen	Evaluated Parameters	Results
				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 12 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 1 month recovery period	Placebo ophthalmic solution 0.5% Gatifloxacin	2 drops (80 mcL) 10 times/day, right eye, 1 month 2 drops (80 mcL) 10 times/day, right eye, 4 mg/dog/day for 1 month	1) Mortality checks: twice daily during pre-treatment, treatment and recovery phases. 2) Clinical observations: once daily during pre-treatment, treatment and recovery period. 3) Gross ocular observations including:	1) Mortality no mortality 2) Clinical observations: -no drug-related clinical observations. 3) Gross ocular observations: -After the first three weeks of treatment, there was a slight increase in the frequency of mild

Species/ Strain	Number per Group/Sex/Age/Body Weight	Treatment Groups	Dosing Regimen/Duration	Evaluated Parameters	Results
	13-14 months old at start of treatment 7.5-11.7 kg during treatment	Placebo ophthalmic solution, 0.5% Gatifloxacin	2 drops (80 mcL) 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 mcL) 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	-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 pretreatment; 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	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,

Species/ Strain	Number per Group/Sex/Age/Body Weight	Treatment Groups	Dosing Regimen/Duration	Evaluated Parameters	Results
				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. 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	Coagulation, Urinalysis: -No drug-related changes 8) 1 month study: C_{max} (ng/mL) = 73.7 (day 7); 65 (day 28) AUC_{0-t}(ng•h/mL) =581 (day 7); 616 (day 28) 3 month study: C_{max} (ng/mL) = 162 (day 1); 18 (day 90) AUC_{0-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 mcg/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 to 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 hours 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 at 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 β 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 β 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 β 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.

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.

Genotoxicity: 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.

Reproductive and Developmental Toxicology: 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 Toxicology:

- 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 β cells

Gatifloxacin produced reversible changes in glucose tolerance, serum insulin levels, and

morphology of pancreatic β 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 β cells were seen in dogs (6 months at 24 mg/kg/day) and monkeys (5 months at 60 mg/kg/day) given gatifloxacin orally.

17 SUPPORTING PRODUCT MONOGRAPHS

1. ZYMAR® (gatifloxacin Ophthalmic Solution, 0.3% w/v), submission control 266066, Product Monograph, AbbVie Corporation (AUG 15, 2022).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]APO-GATIFLOXACIN

Gatifloxacin Ophthalmic Solution

Read this carefully before you start taking **APO-GATIFLOXACIN** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APO-GATIFLOXACIN**.

What is APO-GATIFLOXACIN used for?

APO-GATIFLOXACIN is used to treat the signs and symptoms of bacterial conjunctivitis (pink eye).

Antibacterial drugs like APO-GATIFLOXACIN treat only bacterial infections. They do not treat viral infections.

How does APO-GATIFLOXACIN work?

APO-GATIFLOXACIN is an antibiotic that kills and stops the growth of bacteria in the eye.

What are the ingredients in APO-GATIFLOXACIN?

Medicinal ingredient: gatifloxacin, which is a member of the group of antibiotics known as "quinolones".

Non-medicinal ingredients: benzalkonium chloride, as preservative, edetate disodium, sodium chloride and water for injection. It may also contain hydrochloric acid and or sodium hydroxide.

APO-GATIFLOXACIN comes in the following dosage forms:

Ophthalmic solution, 0.3% w/v

Do not use APO-GATIFLOXACIN if:

- 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 APO-GATIFLOXACIN (**See section What are the ingredients in APO-GATIFLOXACIN**).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-GATIFLOXACIN. Talk about any health conditions or problems you may have, including if you:

- wear soft contact lenses.
- have allergies to any medications.
- are pregnant or intend to become pregnant.
- are breast-feeding or intend to breast-feed.

Other warnings you should know about:

Do not use any other eye (ophthalmic) medicines without talking to your healthcare professional.

If you develop pain or swelling in your tendons, stop using APO-GATIFLOXACIN and get immediate medical help. This is more likely to happen if you are elderly or taking corticosteroids at the same time as APO-GATIFLOXACIN.

Contact Lenses

You should not wear contact lenses when you are suffering bacterial conjunctivitis (pink eye). APO-GATIFLOXACIN contains a preservative called benzalkonium chloride. It may discolour your soft contact lenses. If you must wear contact lenses, remove them before using APO-GATIFLOXACIN. Wait 15 minutes after using the drops before you put your lenses back in.

Driving and using machines

Your vision may be temporarily blurred after using APO-GATIFLOXACIN. Wait until you can see clearly before driving or using machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

There are no known relevant interactions at this time.

How to take APO-GATIFLOXACIN:

- Use APO-GATIFLOXACIN as directed by your healthcare professional. Do not change the dosage of the drug without consulting your healthcare professional. If you stop treatment contact your healthcare professional immediately.

- Although you may feel better early in the treatment, APO-GATIFLOXACIN should be used exactly as directed.

- Misuse or overuse of APO-GATIFLOXACIN could lead to the growth of bacteria that will not be killed by APO-GATIFLOXACIN (resistance). This means that APO-GATIFLOXACIN may not work for you in the future.

- Do not share your medicine.

- To help prevent infections and eye injury, 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.

Follow these steps to use APO-GATIFLOXACIN properly for each eye that needs treatment:

1. Wash your hands. Tilt your head back and look at the ceiling. (See Illustration 1)

2. Gently pull down your lower eyelid down to create a small pocket. (See Illustration 2)

3. Turn the bottle upside down and squeeze it gently to release one drop into the eyelid pocket. If a drop misses your eye, try again. (See Illustration 3)

4. Let go of your lower eyelid, and close your eye for 30 seconds. (See Illustration 4)

5. Repeat steps 1 to 4 in the other eye if both eyes need treatment.

Usual dose:

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 in the affected eye(s) while awake. Doses should be evenly spaced throughout the day.

Overdose:

If APO-GATIFLOXACIN is swallowed, contact your healthcare professional or poison control centre.

If you accidentally add too many drops to your eye, APO-GATIFLOXACIN may be flushed from your eye(s) with warm water.

If you think you, or a person you are caring for, have taken too much APO-GATIFLOXACIN, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

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

What are possible side effects from using APO-GATIFLOXACIN?

These are not all the possible side effects you may have when taking APO-GATIFLOXACIN. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- altered sense of taste
- blurred vision
- dizziness
- light sensitivity
- nausea
- runny nose
- sneezing
- sore throat
- spots on the cornea
- swelling or other disorders of the area around the cornea

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNKNOWN			
Allergic reaction: difficulty breathing, difficulty swallowing, fever, hives, itchy skin, rash, swelling of your tongue or throat, swelling or redness of the skin			✓
Corneal melts and perforation (damage to a part of your eye): vision loss, eye pain and leakage that may be mistaken as tears			✓
Eye irritation or any new eye problems such as: dryness of the eye, swelling or redness of the eyelid, tearing or eye discharge, decreased vision, or eye pain		✓	
Stevens-Johnson syndrome (life-threatening skin condition): blisters, rash, skin peeling, especially in mouth and eyes, skin pain			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep the dispensing container tightly closed when not in use. Store at room temperature 15°C to 30°C, protect from freezing.

Discard container 28 days after opening.

Do not use APO-GATIFLOXACIN after the expiration date (marked "EXP") on the bottle and the box.
Keep out of reach and sight of children.

If you want more information about APO-GATIFLOXACIN:

- Talk to your healthcare professional.

- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (http://www.apotex.ca/products), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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