Ophthalmic Fluoroquinolones Review

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FDA-Approved Indications

Drug	Manufacturer	FDA-Approved Indication(s)	Age Range
ciprofloxacin 0.3% solution (Ciloxan®)	generic	Conjunctivitis Corneal ulcers	> 1 year
ciprofloxacin 3 mg/g ointment (Ciloxan®)	Alcon	Conjunctivitis	> 2 years
gatifloxacin 0.3% solution (Zymar™)	Allergan	Conjunctivitis	> 1 year
levofloxacin 0.5% solution (Quixin®)	Vistakon (J&J)	Conjunctivitis	> 1 year
levofloxacin 1.5% solution (Iquix®)	Vistakon (J&J)	Corneal ulcers	> 6 years
moxifloxacin 0.5% solution (Vigamox™)	Alcon	Conjunctivitis	> 1 year
ofloxacin 0.3% solution (Ocuflox®)	generic	Conjunctivitis Corneal ulcers	> 1 year

Overview

A variety of antimicrobial agents are available for the treatment of conjunctivitis and other superficial ocular infections. Although bacterial conjunctivitis can be a self-limiting condition, topical antibiotics are applied as a solution or ointment for several days in many cases. More serious infections including those that may threaten vision may require broad-spectrum antibiotics.

Pharmacology

Fluoroquinolones (ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, and ofloxacin) inhibit DNA gyrase (topoisomerase II) and topoisomerase IV. DNA gyrase is an essential enzyme 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. Fluoroquinolones with an 8-methoxy substitution, such as gatifloxacin and moxifloxacin, have enhanced antimicrobial activities that may limit the selection of resistant mutants in pathogens.[1]

Antibacterial Activity

In a laboratory investigation, 93 bacterial endophthalmitis isolates were tested for minimum inhibitory concentrations (MICs) for ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, and ofloxacin.[2] *In vitro* tests showed that *Staphylococcus aureus* isolates resistant to ciprofloxacin and ofloxacin were most susceptible (p=0.01) to moxifloxacin. *Coagulase-negative Staphylococci* resistant to ciprofloxacin and ofloxacin were most susceptible (p=0.02) to moxifloxacin and gatifloxacin. *Streptococcus viridans* were more susceptible (p=0.02) to moxifloxacin, gatifloxacin, and levofloxacin than ciprofloxacin and ofloxacin. *Streptococcus*

pneumoniae was least susceptible (p=0.01) to ofloxacin compared with the other fluoroquinolones. Susceptibilities were equivalent (p=0.11) for all other bacterial groups. In general, moxifloxacin was the most potent fluoroquinolone for gram-positive bacteria (p=0.05) while ciprofloxacin, moxifloxacin, gatifloxacin, and levofloxacin demonstrated equivalent potencies to gram-negative bacteria.

In a study of *in vitro* susceptibilities of fluoroquinolones, ciprofloxacin, levofloxacin, and ofloxacin were compared in 101 bacterial conjunctivitis isolates.[3] All three fluoroquinolones had similar sensitivity patterns for gram-negative organisms. Levofloxacin demonstrated better activity against *Streptococcus* organisms than ofloxacin and ciprofloxacin. A similar study published in 2004 with data from isolates from 1999 and 2000 found that levofloxacin had better activity than ciprofloxacin and ofloxacin against *S. pneumoniae* and *S. viridans* including those organisms with intermediate- or high-level penicillin resistance.[4]

The MICs of 177 bacterial keratitis isolates were determined to the following ophthalmic drops: ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, and ofloxacin.[5] Both gatifloxacin and moxifloxacin demonstrated increased activity for *S. aureus* resistant to ciprofloxacin, levofloxacin, and ofloxacin. Generally, ciprofloxacin demonstrated the lowest MICs for gram-negative bacteria. Comparing the two fourth-generation fluoroquinolones, moxifloxacin demonstrated lower MICs for most gram-positive bacteria, whereas gatifloxacin demonstrated lower MICs for most gram-negative bacteria.

Ciprofloxacin and levofloxacin MICs were compared in 1,230 *S. aureus* isolates from patients with keratitis and conjunctivitis from two time periods – 1990 to 1995 and 1996 to 2001.[6] MICs were evaluated in the methicillin-sensitive and methicillin-resistant *S. aureus* strains. The resistance rate of *S. aureus* among the methicillin-resistant *S. aureus* (MRSA) isolates to ciprofloxacin rose from 55.8 percent to 83.7 percent; the resistance rate for methicillin-sensitive *S. aureus* (MSSA) isolates to ciprofloxacin increased from two percent to five percent. In data from January 2000 to December 2001, the resistance rate for MSSA was 4.7 percent versus 11.9 percent for levofloxacin and ciprofloxacin, respectively (p=0.05). For MRSA isolates, the resistance rate most recently was 82.1 percent versus 95.7 percent for levofloxacin and ciprofloxacin, respectively (p=0.04). Vancomycin resistance was not identified in this collection of *S. aureus* isolates.

Streptococcal isolates were collected from patients with keratitis and endophthalmitis between 1990 and 2001.[7] Levofloxacin, ofloxacin, and ciprofloxacin were compared for the *in vitro* MICs against the 65 isolates using E-test methodology. Levofloxacin was more active than ofloxacin and ciprofloxacin against the *S. pneumoniae* isolates with MIC values of 1.5, 6, and 3 mcg/mL, respectively. Levofloxacin was also the most active against the *S. viridans* isolates compared to ofloxacin and ciprofloxacin. Of the penicillin-intermediate or –resistant strains of *S. pneumoniae* (63 percent of isolates), levofloxacin covered 100 percent of the isolates compared to only 33.8 and 29.2 percent for ofloxacin and ciprofloxacin, respectively.

Ocular isolates from clinically symptomatic eyes (n=454) were tested for susceptibility to ciprofloxacin, norfloxacin, ofloxacin, gentamicin, neomycin, tobramycin, bacitracin, erythromycin, and chloramphenicol.[8] The fluoroquinolones were very effective against the gram-negative organisms but were not reliable against the gram-positive organisms including coagulase-negative *Staphylococcus* and *S. viridans*. Bacitracin and chloramphenicol demonstrated good *in vitro* activity against gram-positive organisms. The overall relative *in vitro* efficacy is as follows (descending order): chloramphenicol, ciprofloxacin, ofloxacin, norfloxacin, bacitracin, tetracycline, neomycin, erythromycin, tobramycin, and gentamicin. No antibiotic demonstrated 100 percent coverage.

Community-acquired methicillin-resistant *S. aureus* (CA-MRSA) has been the presumed infectious agent for a variety of ophthalmic infections.[9] In a small report of nine cases, CA-MRSA varied in susceptibility to ciprofloxacin whereas the nine isolates were all sensitive to gentamicin.

Pharmacokinetics

Ophthalmic ointments have the longest contact time between the drug and the ocular tissues; however, ointments can impede delivery of other ophthalmic drugs by serving as a physical barrier. Ointments are useful in children as they decrease the loss of drug by tears. Ophthalmic suspensions mix with tears less rapidly and remain in the cul-de-sac longer than solutions.

Moxifloxacin (Vigamox) solution does not contain a preservative.[10] The other ophthalmic solutions may contain benzalkonium chloride or thimerosal as a preservative.

An open-label investigation evaluated the effect of benzalkonium chloride (BAK) on the antibiotic efficacy of gatifloxacin (Zymar) on the ocular surface.[11] Ten patients received five separate instillations of a 35 microliter drop of gatifloxacin 0.3% in each eye. Tear samples were collected at five time points over 20 minutes, then BAK concentration was measured by high-performance liquid chromatography. The BAK concentrations were 6.4 mcg/mL at 30 seconds, 3.2 mcg/mL at one minute, 1.4 mcg/mL at three minutes, and below the level of detection at five and 20 minutes after instillation of a single drop. Based on the rapid dilution of BAK, it is not expected that BAK contributes any antimicrobial activity to the gatifloxacin 0.3% ophthalmic solution on the ocular surface.

Ocular Penetration

Several studies have been published regarding the corneal penetration of fluoroquinolone products as measured in the aqueous humor during surgery. The dosing regimens used to determine ocular penetration are not those approved by FDA. While comparative penetrations and resultant antibiotic concentrations are important, the study endpoints do not represent clinical outcomes nor do these studies provide insight into aqueous humor concentrations achieved with FDA-approved regimens.

gatifloxacin (Zymar) and moxifloxacin (Vigamox)

In a prospective, randomized, double-blind trial, moxifloxacin 0.5% solution and gatifloxacin 0.3% solution were compared for penetration into the aqueous humor after topical application.[12] Patients (n=46) were undergoing a cataract extraction. Patients received either moxifloxacin 0.5% (n=22) or gatifloxacin 0.3% (n=24) solutions four times daily the day prior to surgery, then one drop one hour before surgical entry. The mean peak aqueous humor concentration of moxifloxacin (1.86 mcg/mL) was significantly greater than gatifloxacin (0.94 mcg/mL; p=0.001).

A randomized, double-blind trial compared the aqueous concentration of moxifloxacin 0.5% and gatifloxacin 0.3% in 50 patients scheduled for cataract surgery.[13] Patients administered one drop of the assigned antibiotic every 10 minutes for four doses beginning one hour before surgery. Moxifloxacin and gatifloxacin aqueous humor concentrations were 1.8 mcg/mL and 0.48 mcg/mL at time of surgery, respectively, as assayed by HPLC analysis. This was a significant difference (p=0.00003).

ciprofloxacin (Ciloxan), gatifloxacin (Zymar), and moxifloxacin (Vigamox)

Fifty-two patients scheduled to undergo cataract extraction were enrolled in a double-blind study to compare the aqueous humor penetration of gatifloxacin 0.3%, moxifloxacin 0.5%, and ciprofloxacin 0.3%.[14] Patients were randomized to one of the three drugs and were to administer that drug four times daily for three days prior to surgery. Just prior to surgery, each patient received the randomized antibiotic every 15 minutes for three doses ending one hour pre-operatively. Mean aqueous concentrations were 0.63 mcg/mL for gatifloxacin, 1.31 mcg/mL for moxifloxacin, and 0.15 mcg/mL for ciprofloxacin at the time of surgery. Moxifloxacin and gatifloxacin achieved significantly greater levels in the aqueous humor than ciprofloxacin ($p<0.001$, $p<0.005$, respectively), and additionally, mean moxifloxacin levels were significantly greater than mean gatifloxacin levels ($p<0.05$).

levofloxacin 0.5% solution (Quixin) and ofloxacin (Ocuflox)

In a similarly designed double-blind study, levofloxacin 0.5% and ofloxacin 0.3% were compared for concentrations in the aqueous humor in 69 patients undergoing cataract surgery.[15] The mean concentration of levofloxacin (1.1399 mcg/mL) was significantly higher than ofloxacin (0.6217 mcg/mL) at the beginning of the operation.

moxifloxacin (Vigamox) and ofloxacin (Ocuflox)

A randomized, double-blind study enrolled 27 patients undergoing vitrectomy. Patients were randomized to ofloxacin 0.3% or moxifloxacin 0.5% given every 10 minutes for one hour prior to surgery.[16] Aqueous and vitreous samples were obtained and analyzed by HPLC. Moxifloxacin aqueous (1.576 mcg/mL) and vitreous (0.225 mcg/mL) levels were significantly higher than ofloxacin aqueous (0.816 mcg/mL, $p=0.0009$) and vitreous levels (0.184 mcg/mL, $p=0.0054$). Moxifloxacin concentrations exceeded the MICs for 90 percent of isolates for a wide variety of pathogens. This study used doses exceeding those approved by the FDA and also used the ophthalmic antibiotics for an unapproved indication. This study was supported by manufacturer of moxifloxacin.

levofloxacin 1.5% (Iquix) and gatifloxacin (Zymar)

A total of 59 patients were undergoing penetrating keratoplasty and participated in an observer-masked, randomized evaluation of the ocular penetration of levofloxacin 1.5% and gatifloxacin 0.3%. Prior to surgery, one drop of either levofloxacin 1.5% or gatifloxacin 0.3% at 15 and 10 minutes prior to surgery was instilled. Corneal tissue and aqueous humor concentrations were evaluated. Levofloxacin 1.5% achieved significantly higher mean concentrations than gatifloxacin in corneal tissue ($p<0.0001$) and aqueous humor ($p=0.0002$). Indication for use and dosing of the ophthalmic fluoroquinolones in the study are inconsistent with the FDA approval.

Contraindications/Warnings[17,18,19,20,21,22]

All the fluoroquinolone agents in this category are contraindicated in hypersensitivity to fluoroquinolones or any of the components of the ophthalmic products.

Drug Interactions[23,24,25,26,27,28]

Specific drug interaction studies have not been performed with the ophthalmic preparations of the fluoroquinolones.

Adverse Effects

Drug	Discomfort/ Pain	Edema	Foreign body sensation	Itching	Conjunctival hyperemia	Transient burning
ciprofloxacin (Ciloxan)[29]	2	<1	<10	<10	<10	reported
gatifloxacin 0.3% solution (Zymar)[30]	1-4	1-4	nr	1-4	1-4	1-4
levofloxacin 0.5% solution (Quixin)[31]	1-3	<1	1-3	<1	nr	1-3
levofloxacin 1.5% solution (Iquix)[32]	1-2	<1	nr	nr	nr	1-2
moxifloxacin 0.5% solution (Vigamox)[33]	1-6	nr	nr	1-6	1-6	1-6
ofloxacin 0.3% solution (Ocuflox)[34]	reported	reported	reported	reported	reported	reported

Adverse effects data are reported from product information as percentage occurrence and therefore cannot be considered comparative. nr = not reported.

Overall, most adverse reactions are related to local irritation upon instillation. Occasionally, allergic sensitization reactions such as itching, swelling, and conjunctival erythema occur. Serious hypersensitivity reactions, including anaphylaxis, have rarely been reported. Secondary fungal and viral infections have been reported. Headache and taste disturbance were reported by eight to ten percent of patients receiving levofloxacin 1.5%.

Gatifloxacin 0.3% and moxifloxacin 0.5% were compared for ocular tolerability.[35] Thirty healthy volunteers (mean age 34.4 years) underwent baseline examination of ocular tissues for conjunctival hyperemia, conjunctival vascularity, and pupil size. Patients then received, in a double-blind fashion, drops to both eyes – one eye receiving gatifloxacin and the other moxifloxacin in a random order. After five minutes, moxifloxacin was associated with a mean increase in conjunctival hyperemia and conjunctival vascularity compared to gatifloxacin (both p=0.0005). Patients reported less pain and irritation with gatifloxacin after five minutes (both p=0.001). Pupil size was significantly smaller with moxifloxacin.

Special Populations[36,37,38,39,40,41]

Pediatrics

All products, excluding ciprofloxacin ointment and levofloxacin 1.5% solution, have been studied in children as young as one year. Ciprofloxacin ointment has been studied in children two years and older. Levofloxacin 1.5% solution has not been studied in children younger than six years of age.

Pregnancy

All agents in this category are Pregnancy Category C.

Renal and Hepatic Impairment

Due to the topical application of these agents, it is not expected that any dosage adjustments are required for renal or hepatic impairment.

Dosages

Drug	Dosage for Blepharitis or Conjunctivitis	Dropper Dosage for Corneal Ulcers	Availability
ciprofloxacin 0.3% solution (Ciloxan)	One to two drops every two hours while awake for two days then one to two drops every four hours while awake for seven days	Day 1: Two drops every 15 minutes x six hours, then every 30 minutes; Day 2: Two drops every hour; Days 3-14: Two drops every four hours	2.5, 5, and 10 mL
ciprofloxacin 3 mg/g ointment (Ciloxan)	½ inch three times a day for two days then ½ inch twice daily for five days	--	3.5 gm tube
gatifloxacin 0.3% solution (Zymar)	One drop every two hours (up to eight times) while awake for two days; then one drop four times a day for five days	--	5 mL
levofloxacin 0.5% solution (Quixin)	One to two drops every two hours (up to eight times) while awake for two days; then one to two drops every four hours (up to four times) while awake for five days	--	5 mL
levofloxacin 1.5% solution (Iquix)	--	Days 1-3: One to two drops in the affected eye(s) every 30 minutes to two hours while awake and every 4 to 6 hours after retiring. Days 4 through treatment completion: Instill one to two drops in the affected eye(s) every one to four hours while awake.	5 mL
moxifloxacin 0.5% solution (Vigamox)	One drop three times a day for seven days	--	3 mL
ofloxacin 0.3% solution (Ocuflox)	One to two drops every two to four hours for two days then one to two drops four times a day for five days	One to two drops every 30 minutes while awake (sleep for four to six hours) for two days then one to two drops every hour for an additional five to seven days; may taper to one to two drops four times a day after day 7-9	5 and 10 mL

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed, www.ifpma.org/clinicaltrials, and review of information sent by manufacturers. Search strategy included the ophthalmic use

of all drugs in this class. Due to changing susceptibility patterns, only trials from the last five years are included. Randomized controlled comparative trials for ophthalmic FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance. In studies evaluating minor infections such as acute bacterial conjunctivitis, a large portion of patients are lost to follow-up. Very little comparative data of good quality from the United States have been published.

gatifloxacin (Zymar) and ciprofloxacin

A randomized, double-masked trial compared gatifloxacin 0.3% and ciprofloxacin 0.3% in 104 eyes of 104 patients with bacterial keratitis for bacteriological and clinical efficacy.[42] The study was performed in India. The majority of pathogens identified were gram-positive bacteria. Significantly more patients with mild or moderate ulcers in the gatifloxacin group (n=39; 95.1 percent) had complete healing compared to those in the ciprofloxacin group (n=38; 80.9 percent; p=0.042). There were too few patients with severe ulcers to make a conclusion. *In vitro* results demonstrated gatifloxacin was significantly more effective against gram-positive cocci (p<0.001). A greater healing rate was achieved with gatifloxacin against gram-positive pathogens (p=0.009). For patients with positive cultures, gatifloxacin (26/28 eyes, 92.9 percent) and ciprofloxacin (26/33 eyes, 78 percent) had similar rates of healing (p=0.165). The mean time to healing of ulcer in gatifloxacin group was 13.9 days, which was similar to that reported for the ciprofloxacin group (16.8 days; p=0.43). For gram-negative bacteria, the mean healing time and efficacy were similar in both treatment groups.

levofloxacin (Quixin) and ofloxacin (Ocuflox)

In an analysis of 167 patients (ages one to 16 years), either levofloxacin 0.5% or ofloxacin 0.3% were instilled every two hours on days one and two and every four hours on days three through five for the treatment of bacterial conjunctivitis.[43] There was also a placebo comparison group in this study. This analysis was taken from two randomized, double-blind, multicenter studies in patients with bacterial conjunctivitis. Signs and symptoms were collected as well as conjunctival cultures. At endpoint (mean of 6.5 days), levofloxacin demonstrated greater microbial eradication than ofloxacin in children ages two to 11 years – 87 percent for levofloxacin versus 62 percent for ofloxacin (p≤0.032) and 88 percent for levofloxacin versus 24 percent for placebo (p<0.001). No differences in microbial eradication rates were observed in other age subgroups.

Anti-Infective Efficacy Rates for Bacterial Conjunctivitis

Drug	Clinical Cure (%)	Bacterial Eradication (%)
ciprofloxacin (Ciloxan) ointment	75	80
ciprofloxacin (Ciloxan) solution[44]	52	70-80
gatifloxacin (Zymar)[45]	77	92
levofloxacin (Quixin)[46]	79	90
moxifloxacin (Vigamox)[47]	66-69	84-94
ofloxacin (Ocuflox)[48]	86	65

Data are collected from product information and therefore cannot be considered comparative.

Levofloxacin 1.5% solution (Iquix) is not indicated for bacterial conjunctivitis.

Meta-analysis

For acute bacterial conjunctivitis, there appears to be a lack of good quality literature comparing antibiotics of any type compared to placebo. The Cochrane Eyes and Vision Group did a systematic review of all randomized controlled trials of any type of antibiotic treatment versus placebo for acute bacterial conjunctivitis.[49,50,51] Topical and systemic antibiotics were included as well as combination products that included antibiotics. Only six trials were identified; however, three were excluded from evaluation. Two more studies were identified in the recent update. The meta-analysis found that antibiotics are associated with beneficial effects on early (days two through five) clinical and microbiological remission rates; however, after day six, the benefit of antibiotics is reduced. Acute bacterial conjunctivitis cases are often self-limiting.

Summary

A wide variety of ophthalmic antimicrobials are available; many of the antibiotics have a broad spectrum of activity. Many agents used to treat acute conjunctivitis are available as generic products. Serious vision-threatening infections require the empirical use of broad-spectrum antibiotics.

In *in vitro* studies, the two fourth-generation fluoroquinolones, gatifloxacin (Zymar) and moxifloxacin (Vigamox), appear to provide better coverage for gram-positive and resistant organisms than the third-generation fluoroquinolone, levofloxacin (Quixin, Iquix), and the second-generation fluoroquinolones, ciprofloxacin (Ciloxan) and ofloxacin (Ocuflox).[52] Comparative clinical studies will need to be conducted to demonstrate this claim.

Moxifloxacin (Vigamox) does not contain a preservative, unlike all of the other ophthalmic fluoroquinolones. Moxifloxacin (Vigamox) is administered three times daily for conjunctivitis whereas the other ophthalmic fluoroquinolones require more frequent dosing.

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