Ophthalmic Antibiotics Review

07/06/2010

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to PSTCREditor@magellanhealth.com.

PROVIDER SYNERGIES L.L.C.
Together, we can do more.

Ophthalmic Antibiotics Review

FDA-Approved Indications

Drug	Manufacturer	FDA-Approved Indication(s)	Age Range
Aminoglycosides			
gentamicin[1]	generic	Superficial ocular infections involving the conjunctiva or cornea	All ages except neonates
tobramycin (Tobrex®)[2]	generic	Superficial ocular infections involving the conjunctiva or cornea	≥ 2 months
tobramycin ointment (Tobrex®)[3]	Alcon	Treatment of external infections of the eye and its adnexa	≥ 2 months
Fluoroquinolones			
besifloxacin (Besivance™)[4]	Bausch & Lomb	Bacterial conjunctivitis	≥ 1 year
ciprofloxacin solution (Ciloxan®)[5]	generic	Bacterial conjunctivitis Corneal ulcers	≥ 1 year
ciprofloxacin ointment (Ciloxan®)[6]	Alcon	Bacterial conjunctivitis	≥ 2 years
gatifloxacin (Zymar™)[7]	Allergan	Bacterial conjunctivitis	≥ 1 year
gatifloxacin (Zymaxid™)[8]	Allergan	Bacterial conjunctivitis	≥ 1 year
levofloxacin 0.5% (Quixin®)[9]	Vistakon	Bacterial conjunctivitis	≥ 1 year
levofloxacin 1.5% (Iquix®)[10]	Vistakon	Corneal ulcers	≥ 6 years
moxifloxacin (Vigamox™)[11]	Alcon	Bacterial conjunctivitis	≥ 1 year
ofloxacin (Ocuflox®)[12]	generic	Bacterial conjunctivitis Corneal ulcers	≥ 1 year
Macrolides			
azithromycin (AzaSite™)[13]	Inspire	Bacterial conjunctivitis	≥ 1 year
erythromycin (Romycin®)[14]	generic	Superficial ocular infections involving the conjunctiva or cornea For ophthalmia neonatorum due *to Chlamydia trachomatis* and prophylaxis of ophthalmia neonatorum due *to Neisseria gonorrhoeae*	newborn infants to adults

FDA-Approved Indications (continued)

Drug	Manufacturer	FDA-Approved Indication(s)	Age Range
Other			
bacitracin[15]	generic	Superficial ocular infections involving the conjunctiva or cornea	not specified
bacitracin/ polymyxin B[16,17]	generic	Superficial ocular infections involving the conjunctiva or cornea	not specified
natamycin (Natacyn®)[18]	Alcon	Fungal blepharitis, conjunctivitis, and keratitis	adults
neomycin/polymyxin B /bacitracin (Neosporin®)[19,20]	generic	Bacterial conjunctivitis Superficial ocular infections	adults
neomycin/polymyxin B /gramicidin (Neocidin®)[21,22]	generic	Bacterial conjunctivitis Superficial ocular infections	adults
polymyxin B /trimethoprim (Polytrim®)[23,24]	generic	Bacterial conjunctivitis Blepharoconjunctivitis Superficial ocular infections	≥ 2 months
sulfacetamide (Bleph®-10)[25]	generic	Bacterial conjunctivitis Superficial ocular infections Adjunctive therapy with systemic sulfonamide therapy for trachoma	≥ 2 months

Overview

Conjunctivitis can be bacterial, viral, or noninfectious (e.g., allergic or nonallergic). Viral or noninfectious conjunctivitis can be self-limiting. Therapy may reduce symptoms but does not affect the clinical course of viral conjunctivitis. Although bacterial conjunctivitis can also be a self-limiting condition, topical antibiotics may be applied as a solution, suspension, or ointment for several days, and topical antibiotics, in many cases, may shorten the clinical course as well as reduce spread of infection.[26,27] Bacterial conjunctivitis is commonly caused by *Haemophilus influenzae, Streptococcus pneumoniae, Staphylococcus aureus*, and *Moraxella catarrhalis*. These pathogens, particularly *H. influenza* and *S. pneumoniae,* are more common in children, whereas *S. aureus* and *H. influenza* are more common in adults.[28,29] A variety of antimicrobial agents are available for the treatment of conjunctivitis and other superficial ocular infections. More serious conditions such as corneal ulcers and other infections that potentially threaten vision may require broad-spectrum antibiotics.[30]

Pharmacology[31]

Aminoglycosides (gentamicin, neomycin, tobramycin) inhibit protein synthesis by binding to the 30S ribosomal subunit.

Bacitracin inhibits bacterial growth through prevention of cell wall subunits being added to the peptidoglycan chain. Bacitracin is bactericidal.

Fluoroquinolones (besifloxacin [Besivance], ciprofloxacin [Ciloxan], gatifloxacin [Zymar, Zymaxid], levofloxacin [Iquix, Quixin], moxifloxacin [Vigamox], and ofloxacin [Ocuflox]) 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.[32]

Ciprofloxacin (Ciloxan) and ofloxacin (Ocuflox) are considered second-generation fluoroquinolones, with levofloxacin (Quixin, Iquix) being a third-generation fluoroquinolone. The fourth-generation fluoroquinolones include gatifloxacin (Zymar, Zymaxid) and moxifloxacin (Vigamox). The newest fluoroquinolone, besifloxacin (Besivance) is considered a fifth generation fluoroquinolone.[33] The spectrum of activity includes gram positive bacteria such as *S. pneumoniae* and *S. aureus* and gram negative bacteria such as *H. influenzae*. Besifloxacin is not indicated for the treatment of *P. aeruginosa*.

The ophthalmic form of the macrolide azithromycin is Azasite. Azithromycin in DuraSite® (a mucoadhesive delivery system) binds to the 50S ribosomal subunit of susceptible microorganisms and interferes with microbial protein synthesis.[34] The combination of azithromycin and DuraSite showed increased bioavailability of azithromycin in rabbit ocular tissue. However, this same effect has not been demonstrated in humans. Erythromycin also binds to the 50S subunit of the ribosome, causing inhibition of protein synthesis.

Gramicidin has bactericidal action on gram-positive organisms. Gramicidin increases bacterial cell permeability to inorganic cations by forming a network of channels through the lipid bilayer of the membrane.

Natamycin (Natacyn) is a tetraene polyene antifungal antibiotic derived from *Streptomyces natalensis*. It binds to the sterol moiety of the fungal cell membrane. The polyenesterol complex alters the permeability of the membrane to produce depletion of essential cellular constituents. Natamycin is predominantly fungicidal, but its effect is dose-related.

Polymyxin B is bactericidal for a variety of gram-negative organisms. It increases the permeability of the bacterial cell membrane by interacting with the phospholipid components of the membrane.

Sulfacetamide is a synthetic sulfonamide antibiotic and inhibits bacterial dihydrofolate synthetase, an enzyme responsible for the conversion of *p*-aminobenzoic acid (PABA) into folic acid. Folic acid is essential for bacteria for the transport of one-carbon fragments from one molecule to another and is crucial during the synthesis of thymidine, purines, and certain amino acids.

Trimethoprim interferes with folate synthesis by blocking the production of tetrahydrofolic acid from dihydrofolic acid. Trimethoprim reversibly inhibits dihydrofolate reductase.

Antibacterial Activity

In a laboratory investigation, 93 bacterial endophthalmitis isolates were tested for minimum inhibitory concentrations (MICs) for ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, and ofloxacin.[35] *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* isolates 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.[36] All three fluoroquinolones had similar sensitivity patterns for gram-negative organisms. Levofloxacin demonstrated better activity against *Streptococcus* organisms than ofloxacin and ciprofloxacin.

Streptococcal isolates were collected from patients with keratitis and endophthalmitis between 1990 and 2001.[37] 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.

The MICs of 177 bacterial keratitis isolates were determined to the following ophthalmic drops: ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, and ofloxacin.[38] 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.[39] 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.

Ocular isolates from clinically symptomatic eyes (n=454) were tested for susceptibility to ciprofloxacin, norfloxacin, ofloxacin, gentamicin, neomycin, tobramycin, bacitracin, erythromycin, and chloramphenicol.[40] 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.[41] In a small report of nine cases, CA-MRSA varied in susceptibility to ciprofloxacin, whereas the nine isolates were all sensitive to gentamicin.

Isolates from bacterial conjunctivitis from a Phase III trial were examined for *in vitro* resistance to azithromycin and moxifloxacin.[42] The most common isolates collected were *Hemophilus influenzae* (40.6 percent), *Staphylococcus epidermidis* (19.3 percent), *Propionibacterium acnes* (17.3 percent), *S. pneumoniae* (16.8 percent), and *S. aureus* (0.06 percent). The MIC values for all these organisms were well below established resistance breakpoints for moxifloxacin, indicating no bacterial resistance. The MIC value for *H. influenzae* was three-fold higher than the resistance breakpoint for azithromycin, ≥128-fold higher for *S. epidermidis*, 16-fold higher for *S. pneumoniae,* and ≥128-fold higher for *S. aureus*, indicating moderate to very high bacterial resistance to azithromycin.

In an eight-year study of the patterns of bacterial resistance in bacterial keratitis isolates in southern Florida, 2,920 corneal cultures were reviewed.[43] A pathogen was isolated in half of the cultures. The number of cultures, positive cultures, isolates, and ratio of gram-positive to gram-negative isolates remained consistent from year to year during the study. *Staphylococcus aureus* and *Pseudomonas aeruginosa* were the most common isolates. *S. aureus* gradually became the most common gram-positive isolate, increasing from 29 percent in 1990 to 48 percent in 1998, whereas *P. aeruginosa* isolates decreased from 54 percent to 46 percent of gram-negative isolates during the same period. *S. aureus* isolates demonstrated increasing resistance to fluoroquinolones, from 11 percent in 1990 to 28 percent in 1998, which is similar to the trends observed for all isolates in the United States. Susceptibility to aminoglycosides for *S. aureus* remained unchanged. *P. aeruginosa* demonstrated resistance to aminoglycosides and fluoroquinolones in many cases.

The Ocular Tracking Resistance in US Today (TRUST) annually evaluates *in vitro* antimicrobial susceptibility of *S. aureus*, *S. pneumoniae*, and *H. influenzae* to ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, penicillin, azithromycin, tobramycin, trimethoprim, and polymyxin B in national samples of ocular isolates.[44] Prospectively collected ocular isolates (n=278) from 35 institutions and archived ocular isolates (n=1,116) from 34 institutions were tested. Mean minimum inhibitory concentrations that would inhibit growth of 90 percent of the tested isolates (MIC_{90}) were interpreted as susceptible, intermediate, or resistant according to standardized breakpoints for systemic treatment. Methicillin susceptible *S. aureus* (MSSA) or methicillin resistant *S. aureus* (MRSA) susceptibility patterns were virtually identical for the fluoroquinolones; MSSA susceptibility was 79.9 to 81.1 percent, and MRSA susceptibility was 15.2 percent. Trimethoprim was the only agent tested with high activity against MRSA. All *S. pneumoniae* isolates were susceptible to gatifloxacin, levofloxacin, and moxifloxacin; 89.8 percent were susceptible to ciprofloxacin. *H. influenzae* isolates were 100 percent susceptible to all tested agents except trimethoprim. Ocular TRUST 1 data were consistent with the eight-year longitudinal sample of archived ocular isolates.

Natamycin is not effective *in vitro* against gram-positive or gram-negative bacteria.[45] It has *in vitro* activity against a variety of yeast and filamentous fungi including *Candida, Aspergillus, Cephalosporium, Fusarium,* and *Penicillium*.

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. Ophthalmic ointments are useful in children, patients with poor compliance, and in patients with difficulty administering drops. However, ointments blur vision for a short period after the dose is administered. This should be taken into consideration for patients who need to perform tasks which require clear vision immediately after dosing.

Azithromycin (Azasite) and besifloxacin (Besivance) contain DuraSite® which is a mucoadhesive delivery system.[46,47]

Plasma concentrations of besifloxacin were measured in adult patients with suspected bacterial conjunctivitis who received Besivance™ bilaterally three times a day (16 doses total). Following the first and last dose, the maximum plasma besifloxacin concentration in each patient was less than 1.3 ng/mL. The mean besifloxacin Cmax was 0.37 ng/mL on day 1 and 0.43 ng/mL on day 6. The average elimination half-life of besifloxacin in plasma following multiple dosing was estimated to be 7 hours.[48]

Moxifloxacin (Vigamox) and levofloxacin 1.5% (Iquix) do not contain a preservative.[49,50] The other ophthalmic solutions may contain benzalkonium chloride (BAK) or thimerosal as a preservative.

An open-label investigation evaluated the effect of BAK on the antibiotic efficacy of gatifloxacin (Zymar) on the ocular surface.[51] 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.[52] 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.[53] 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%.[54] Patients were randomized to one of the three drugs and were to administer the 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 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 investigator-masked study, levofloxacin 0.5% and ofloxacin 0.3% were compared for concentrations in the aqueous humor in 69 patients undergoing cataract surgery.[55] Patients received four drops of either levofloxacin 0.5% or ofloxacin 0.3% eyedrops within one hour (60 minutes, 45 minutes, 30 minutes, and 15 minutes) of elective cataract surgery. The mean concentration of levofloxacin (1.1399 mcg/mL) was significantly higher than ofloxacin (0.6217 mcg/mL) at the beginning of the operation (p=0.0008).

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.[56] 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 MIC_{90} values for a wide variety of pathogens. 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%.[57] 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). Three adverse events

were reported with gatifloxacin although none were determined to be treatment-related. The study and manuscript preparation were supported by the manufacturer of levofloxacin 1.5%.

azithromycin (AzaSite) and moxifloxacin (Vigamox)

A single-dose, open-label, active-controlled trial randomized 48 adults to azithromycin or moxifloxacin and underwent conjunctival biopsy.[58] Mean concentrations of azithromycin in conjunctival tissue (lower limit of quantitation [LLOQ], 1 mcg/g for 1-mg biopsy specimen) were 131, 59, 48, and 32 mcg/g at 30 minutes and 2, 12, and 24 hours, respectively. Mean concentrations of moxifloxacin in conjunctival tissue (LLOQ, 0.05 mcg/g for 1-mg biopsy sample) were 1.92, 3.77, 0.02, and 0.01 mcg/g at 30 minutes and 2, 12, and 24 hours, respectively. Therapeutic concentrations were achieved with both agents. Both treatments were well tolerated.

Contraindications/Warnings[59,60,61,62,63,64,65,66,67,68,69,70,71,72]

Hypersensitivity is considered a contraindication for use. These agents are for topical ophthalmic use only. Patients should not wear contact lenses if they have signs and symptoms of bacterial conjunctivitis.

Bacitracin ophthalmic ointment should not be used in deep-seated ocular infections or in those that are likely to become systemic.

Fatalities have occurred, although rarely, due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias.

Drug Interactions[73,74,75,76,77,78,79,80,81,82,83]

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

Adverse Effects

Drug	Discomfort/ Pain	Eyelid edema	Foreign body sensation	Itching	Conjunctival hyperemia	Transient burning
Fluoroquinolones						
besifloxacin (Besivance)[84]	1-2	nr	nr	1-2	2	nr
ciprofloxacin solution[85]	2	<1	<10	<10	<10	reported (most common adverse effect)
ciprofloxacin ointment (Ciloxan)[86]	2	<1	<1	<1	<1	nr
gatifloxacin (Zymar)[87]	1-4	1-4	nr	1-4	1-4	1-4
gatifloxacin (Zymaxid)[88]	<1	nr	nr	nr	nr	<1
levofloxacin 0.5% (Quixin)[89]	1-3	<1	1-3	<1	nr	1-3
levofloxacin 1.5% (Iquix)[90]	1-2	<1	nr	nr	nr	1-2
moxifloxacin (Vigamox)[91]	1-6	nr	nr	1-6	1-6	1-6
ofloxacin (Ocuflox)[92]	reported	reported	reported	reported	reported	reported
Macrolides						
azithromycin (AzaSite)[93]	1-2	nr	nr	<1	nr	<1
erythromycin (Romycin)[94]	reported	nr	nr	reported	nr	reported

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

Overall, most adverse effects 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% (Iquix) and by one to four percent of patients taking gatifloxacin (Zymar). Headache was reported in 1 to 2 percent of patients

taking besifloxacin (Besivance). Taste disturbance was reported in less than ten percent and less than one percent, in patients taking ciprofloxacin solution and ointment, respectively.

Aminoglycosides (gentamicin, tobramycin) have the following adverse effects: localized ocular toxicity and hypersensitivity, lid itching, lid swelling, conjunctival erythema (less than three percent with tobramycin), bacterial/fungal corneal ulcers, nonspecific conjunctivitis, conjunctival epithelial defects, and conjunctival hyperemia.[95]

In clinical trials, tobramycin (Tobrex) ophthalmic ointment produced significantly fewer adverse reactions (3.7 percent) than did gentamicin ophthalmic ointment (10.6 percent).[96]

Ocular irritation accompanied by stinging and burning has been reported with sulfacetamide solution.[97]

The following were reported for natamycin (Natacyn): ocular irritation, change in vision, corneal opacity, eye discomfort/pain/edema, eye hyperemia, foreign body sensation, paresthesia, and tearing.[98]

Special Populations[99,100,101,102,103,104,105,106,107,108,109,110,111,112,113]

Pediatrics

Ophthalmic tobramycin ointment and solution may be used in patients two months and older. Ophthalmic gentamicin is used in pediatrics but not in neonates.

All fluoroquinolones, excluding ciprofloxacin ointment (Ciloxan) and levofloxacin 1.5% (Iquix), have been studied in children as young as one year. Ciprofloxacin ointment has been studied in children two years and older. Levofloxacin 1.5% (Iquix) has not been studied in children younger than six years of age. The macrolides, azithromycin (AzaSite) and erythromycin (Romycin), may be utilized in pediatrics at least one year of age and infants to adults, respectively.

The age for ophthalmic bacitracin and bacitracin/polymyxin B is not specified. Neomycin/polymyxin B/bacitracin (Neosporin) and neomycin/polymyxin B/gramicidin (Neocidin) are not indicated for pediatrics.

Polymyxin B/trimethoprim (Polytrim) and sulfacetamide are indicated in pediatrics two months and older.

Pregnancy

All agents in this category are Pregnancy Category C except azithromycin (AzaSite), erythromycin ophthalmic ointment, and tobramycin solution and ointment, which are Pregnancy Category B.

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[114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131]

Drug	Dosage for Blepharitis or Conjunctivitis	Dropper Dosage for Corneal Ulcers	Availability
Aminoglycosides			
gentamicin	½ inch two to three times a day	--	3 mg/g ointment 3.5 gm tube
gentamicin	One to two drops every four hours, up to two drops every hour for severe infections	--	0.3% solution 5, 15 mL
tobramycin (Tobrex)	½ inch every three to four hours up to two to three times a day dosing based on severity of infection	--	3 mg/g ointment 3.5 gm tube
tobramycin	One to two drops every four hours; in severe infections, two drops hourly until improvement then taper	--	0.3% solution 5 mL
Fluoroquinolones			
besifloxacin (Besivance)	One drop three times daily four to 12 hours apart for seven days	--	0.6% suspension 5 mL
ciprofloxacin (Ciloxan)	One to two drops every two hours while awake for two days then one to two drops every four hours while awake for five days	Day 1: Two drops every 15 minutes for six hours, then every 30 minutes Day 2: Two drops every hour Days 3-14: Two drops every four hours	0.3% solution 2.5, 5, 10 mL
ciprofloxacin (Ciloxan)	½ inch three times a day for two days then ½ inch twice daily for five days	--	3 mg/g ointment 3.5 gm tube
gatifloxacin 0.3% (Zymar)	Days 1-2: One drop every two hours (up to eight times) while awake Days 3-7: one drop up to four times a day while awake	--	0.3% solution 5 mL
gatifloxacin 0.5% (Zymaxid)	Day 1: One drop every two hours (up to eight times) while awake; Days 2-7: one drop given two to four times a day while awake	--	0.5% solution 2.5 mL
levofloxacin 0.5% (Quixin)	Days 1-2: One to two drops every two hours (up to eight times) while awake; Days 3-7: one to two drops every four hours while awake (up to four times)	--	0.5% solution 5 mL
levofloxacin 1.5% (Iquix)	--	Days 1-3: One to two drops every 30 minutes to two hours while awake and approximately four and six hours after retiring Days 4 through treatment completion: One to two drops every one to four hours while awake	1.5% solution 5 mL
moxifloxacin (Vigamox)	One drop three times a day for seven days	--	0.5% solution 3 mL
ofloxacin (Ocuflox)	One to two drops every two to four hours for two days; then one to two drops four times daily for five days	Days 1-2: One to two drops every 30 minutes, while awake. Awaken at approximately four and six hours after retiring and instill one to two drops Days 3 through 7 to 9: One to two drops hourly while awake Days 7 to 9 through treatment completion: One to two drops four times daily	0.3% solution 5, 10 mL

Dosages (continued)

Drug	Dosage for Blepharitis or Conjunctivitis	Dropper Dosage for Corneal Ulcers	Availability
Macrolides			
azithromycin (AzaSite)	One drop in the affected eye(s) twice daily for the first two days then one drop daily for the next five days	--	1% solution 2.5 mL
erythromycin (Romycin)	½ inch to affected eye(s) up to six times daily	--	0.5% ointment 3.5 gm tube
Other			
bacitracin	½ inch every 3 to 4 hours for 7 to 10 days	--	500 units/g ointment 3.5 gm tube
bacitracin/ polymyxin B	Thin film every three to four hours for seven to 10 days	--	500 units-10,000 units/g ointment 3.5 gm tube
natamycin (Natacyn)	One drop every one to two hours, reduced to every 6 to 8 times daily after the first 3 to 4 days.	--	5% suspension 15 mL
neomycin/ polymyxin B/ bacitracin (Neosporin)	½ inch every three to four hours for seven to 10 days depending on severity of infection	--	3.5 mg/gm-10,000 units/gm-400 units/gm ointment 3.5 gm tube
neomycin/ polymyxin B/ gramicidin (Neocidin)	One to two drops every four hours for 7 to 10 days, up to two drops every hour for severe infections	--	1.75 mg/mL-10,000 units/mL-0.025 mg/mL solution 10 mL
polymyxin B/ trimethoprim (Polytrim)	One drop every three hours up to six doses daily for seven to 10 days	--	10,000 units/mL-1 mg/mL solution 10 mL
sulfacetamide	½ inch four times daily and bedtime for 7-10 days. The ointment may be used adjunctively with sulfacetamide solutions.	--	10% ointment 3.5 gm tube
sulfacetamide (Bleph-10)	One to two drops to every one to three hours while awake; less frequently at night for 7-10 days. Dosing dependant on severity of infection.	--	10% solution 5, 15 mL

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed 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 seven 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.

There are currently no published, comparative trials of azithromycin ophthalmic solution (AzaSite) to any of the ophthalmic fluoroquinolones or erythromycin ophthalmic ointment (Romycin).

gatifloxacin (Zymar) and ciprofloxacin (Ciloxan)

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.[132] 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 the 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.[133] 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.

azithromycin (AzaSite) and tobramycin (Tobrex)

A prospective, randomized, active-controlled, double-masked, Phase III trial was conducted over a 14-month period at 47 sites.[134] Patients with a clinical diagnosis of bacterial conjunctivitis were randomly assigned to receive either azithromycin 1% ophthalmic solution (n=365) or tobramycin ophthalmic solution 0.3% (n=378). Both groups received masked medication four times daily for five days, but participants received an active dose of azithromycin only twice daily for the first two days then daily on days three to five. Conjunctival cultures were taken, and ocular signs and symptoms were evaluated at baseline and at two follow-up visits. A total of 743 patients were randomized; 710 completed the trial. Rates of microbial eradication and bacterial infection recurrence were the same in both groups. The most frequently observed ocular adverse events in the azithromycin group were eye irritation (1.9 percent), conjunctival hyperemia (1.1 percent), and worsening bacterial conjunctivitis (1.1 percent). These rates compared favorably with those obtained with tobramycin.

gatifloxacin (Zymar) and moxifloxacin (Vigamox)

Gatifloxacin 0.3% and moxifloxacin 0.5% were compared for ocular tolerability.[135] In this healthy volunteer study, 30 participants (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.

polymyxin B/trimethoprim (Polytrim) and moxifloxacin (Vigamox)

A multicenter study randomized 56 patients younger than 18 years with a clinical diagnosis of bacterial conjunctivitis to one drop of polymyxin B/trimethoprim four times daily for seven days or one drop of moxifloxacin 0.5% three times daily for seven days.[136] At the 48-hour visit, complete resolution of ocular signs and symptoms was observed in 81 and 44 percent of patients treated with moxifloxacin versus polymyxin B/trimethoprim, respectively (p=0.001). The majority of patients were cured and symptom-free by 48 hours. In this study, moxifloxacin was significantly more efficacious than polymyxin B/trimethoprim in the speed of clinical efficacy. No adverse events were reported. This study was sponsored by the manufacturer of moxifloxacin.

besifloxacin (Besivance) and moxifloxacin (Vigamox)

Besifloxacin ophthalmic suspension 0.6% three times daily was compared to moxifloxacin ophthalmic solution 0.5% three times daily for the treatment of bacterial conjunctivitis in a randomized, double-masked, parallel-group, active-controlled, multicenter, noninferiority study of 1,116 patients (533 with culture-confirmed bacterial conjunctivitis) ages one year and older.[137] Besifloxacin was noninferior to moxifloxacin for clinical resolution on day five (58.3 percent versus 59.4 percent, respectively; 95% CI, -9.48 to 7.29) and day eight (84.5 percent versus 84 percent, respectively, 95% CI, -5.6 to 6.75). Besifloxacin was also noninferior to moxifloxacin for microbial eradication on day five (93.3 percent versus 91.1 percent, respectively, 95% CI, -2.44 to 6.74) and day eight (87.3 percent versus 84.7 percent; 95% CI, -3.32 to 8.53). There was no

statistically significant difference between the two treatment groups for either efficacy end points on days five or eight (p>0.05). Both treatments were well tolerated. Although total ocular adverse events was similar between treatments (12 percent and 14 percent with besifloxacin and moxifloxacin, respectively), eye irritation occurred more frequently in the moxifloxacin group (0.3 percent for besifloxacin compared to 1.4 percent for moxifloxacin; p=0.0201).

Anti-Infective Efficacy Rates for Bacterial Conjunctivitis

Drug	Clinical Cure (%)	Bacterial Eradication (%)
Fluoroquinolones		
besifloxacin (Besivance)[138,139]	45-58.3	91
ciprofloxacin ointment (Ciloxan)[140]	75	80
ciprofloxacin solution (Ciloxan)[141]	52	70-80
gatifloxacin (Zymar)[142]	77	92
levofloxacin (Quixin)[143]	79	90
moxifloxacin (Vigamox)[144,145]	59.4-69	84-94
ofloxacin (Ocuflox)[146]	86	65
Macrolides		
azithromycin solution (Azasite)[147]	63	88

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

Microbiologic eradication does not always correlate with clinical outcome in anti-infective trials.

Levofloxacin 1.5% solution (Iquix) is not indicated for bacterial conjunctivitis. Efficacy data for erythromycin ophthalmic ointment (Romycin) in the treatment of bacterial conjunctivitis is not available in current literature.

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.[148,149,150,151] Topical and systemic antibiotics were included as well as combination products that included antibiotics. Six trials were identified; however, three were excluded from evaluation. In the 2005, and 2006 updates two more studies were identified. 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 but persistent.

Summary

While acute bacterial conjunctivitis is often self-limiting, empiric therapy with ophthalmic antibiotics is a common practice. Serious vision-threatening infections require the empirical use of broad-spectrum antibiotics. Treatment with antibiotics typically leads to significantly faster rates of clinical and microbiological remission.

A wide variety of ophthalmic antimicrobials are available, and many of these antibiotics exhibit a broad spectrum of activity. Many agents used to treat acute bacterial conjunctivitis are available as generic products including second generation fluoroquinolones and certain macrolides.

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

Comparative clinical data with azithromycin (AzaSite) and gatifloxacin (Zymaxid) are limited at this time.

References

[1] Available at: http://www.clinicalpharmacology.com. Accessed July 4, 2010.
[2] Tobrex [package insert]. Fort Worth, TX; Alcon; October 2003.
[3] Tobrex ointment [package insert]. Fort Worth, TX; Alcon; October 2003.
[4] Besivance [package insert]. Tampa, FL; Bausch and Lomb; April 2009.
[5] Ciloxan [package insert]. Fort Worth, TX; Alcon Labs; 2003.
[6] Ciloxan [package insert]. Fort Worth, TX; Alcon Labs; 2006.
[7] Zymar [package insert]. Irvine, CA; Allergan; August 2004.
[8] Zymaxid [package insert]. Irvine, CA; Allergan; May 2010.
[9] Quixin [package insert]. Napa, CA; Santen; April 2007.
[10] Iquix [package insert]. Jacksonville, FL; Vistakon Pharmaceuticals; April 2007.
[11] Vigamox [package insert]. Ft. Worth, TX; Alcon Labs; 2008.
[12] Ocuflox [package insert]. Irvine, CA; Allergan; May 2005.
[13] AzaSite [package insert]. Alameda, CA; Inspire Pharmaceuticals; November 2008.
[14] Available at: http://www.clinicalpharmacology.com. Accessed July 4, 2010.
[15] Available at: http://www.clinicalpharmacology.com. Accessed July 4, 2010.
[16] Available at: http://www.clinicalpharmacology.com. Accessed July 4, 2010.
[17] Bacitracin Zinc and Polymyxin B Sulfate [package insert]. Lake Forest, IL; Akorn, Inc; November 2008.
[18] Natacyn [package insert]. Forth Worth, TX; Alcon Labs; May 2008.
[19] Available at: http://www.clinicalpharmacology.com. Accessed July 5, 2010.
[20] Neosporin [package insert]. Research Triangle Park, NC; Burroughs Wellcome, Inc; October 2006.
[21] Available at: http://www.clinicalpharmacology.com. Accessed July 5, 2010.
[22] Neocidin [package insert]. Tampa, Fl; Bausch and Lomb; August 2007.
[23] Available at: http://www.clinicalpharmacology.com. Accessed July 5, 2010.
[24] Polytrim [package insert]. Irvine, CA; Allergan; August 2004.
[25] Available at: http://www.thomsonhc.com/home. Accessed July 6, 2010.
[26] Sheikh A, Hurwitz B. Antibiotics versus placebo for acute bacterial conjunctivitis. Cochrane Database Syst Rev. 2006; (2):CD001211.
[27] Everitt HA, Little PS, Smith PW. A randomized controlled trial of management strategies for acute infective conjunctivitis in general practice. BMJ. 2006; 333(7563):321.
[28] Tarabishy AB, Jeng BH. Bacterial conjunctivitis: a review for internists. Cleve Clin J Med. 2008; 75(7):507-512.
[29] Friedlander MH. A review of the causes and treatment of bacterial and allergic conjunctivitis. Clin Ther. 1995; (5):800-810.
[30] Available at: http://one.aao.org/CE/PracticeGuidelines/PPP_Content.aspx?cid=1d56d934-c309-4072-b6b5-0698559a3b47#section4. Accessed July 6, 2010.
[31] Available at: http://www.clinicalpharmacology.com. Accessed July 5, 2010.
[32] Dong Y, Xu C, Zhao X, et al. Fluoroquinolone action in mycobacteria: effects of C8 substitutions on bacterial growth, survival, and resistance. Antimicrob Agents Chemother. 1998; 42:2978-2984.
[33] Besivance [package insert]. Tampa, FL; Bausch and Lomb; April 2009.
[34] AzaSite [package insert]. Alameda, CA; Inspire Pharmaceuticals; November 2008.
[35] Mather R, Karenchak LM, Romanowski EG, et al. Fourth generation fluoroquinolones: New weapons in the arsenal of ophthalmic antibiotics. Am J Ophthalmol. 2002; 133:463-466.
[36] Graves A, Henry M, O'Brien TP, et al. In vitro susceptibilities of bacterial ocular isolates to fluoroquinolones. Cornea. 2001; 20:301-305.
[37] Miller D, Alfonso EC. Comparative in vitro activity of levofloxacin, ofloxacin, and ciprofloxacin against ocular streptococcal isolates. Cornea. 2004; 23(3):289-93.
[38] Kowalski RP, Dhaliwal DK, Karenchak LM, et al. Gatifloxacin and moxifloxacin: an in vitro susceptibility comparison to levofloxacin, ciprofloxacin, and ofloxacin using bacterial keratitis isolates Am J Ophthalmol. 2003; 136(3):500-505.
[39] Marangon FB, Miller D, Muallem MS, et al. Ciprofloxacin and levofloxacin resistance among methicillin-sensitive Staphylococcus aureus isolates from keratitis and conjunctivitis. Am J Ophthalmol. 2004; 137(3):453-8.

[40] Egger SF, Ruckhofer J, Alzner E, et al. In vitro susceptibilities to topical antibiotics of bacteria isolated from the surface of clinically symptomatic eyes. Ophthalmic Res. 2001; 33(2):117-20.
[41] Rutar R, Chambers HF, Crawford JB, et al. Ophthalmic Manifestations of Infections Caused by the USA300 Clone of Community-Associated Methicillin-Resistant *Staphylococcus aureus*. Ophthalmology. 2006; 113:1455–1462.
[42] Ohnsman C, Ritterband D, O'Brien T, et al. Comparison of azithromycin and moxifloxacin against bacterial isolates causing conjunctivitis. Curr Med Res Opin. 2007; 23(9):2241-9.
[43] Alexandrakis G, Alfonso EC, Miller D. Shifting trends in bacterial keratitis in south Florida and emerging resistance to fluoroquinolones. Ophthalmology. 2000; 107:1497-1502.
[44] Asbell PA, Colby KA, Deng S, et al. Ocular TRUST: nationwide antimicrobial susceptibility patterns in ocular isolates. Am J Ophthalmol. 2008; 145(6):951-958.
[45] Natacyn [package insert]. Forth Worth, TX; Alcon Labs; May 2008.
[46] AzaSite [package insert]. Alameda, CA; Inspire Pharmaceuticals; November 2008.
[47] Besivance [package insert]. Tampa, FL; Bausch and Lomb; April 2009.
[48]Besivance [package insert]. Tampa, FL; Bausch and Lomb; April 2009.
[49] Vigamox [package insert]. Ft. Worth, TX; Alcon Labs; 2008.
[50] Iquix [package insert]. Jacksonville, FL; Vistakon Pharmaceuticals; April 2007.
[51] Friedlaender MH, Breshears D, Amoozgar B, et al. The dilution of benzalkonium chloride (BAK) in the tear film. Adv Ther. 2006; 23(6):835-41.
[52] McCulley JP, Caudle D, Aronowicz JD, et al. Fourth-generation fluoroquinolone penetration into the aqueous humor in humans. Ophthalmology. 2006; 113(6):955-9.
[53] Kim DH, Stark WJ, O'Brien TP, et al. Aqueous penetration and biological activity of moxifloxacin 0.5% ophthalmic solution and gatifloxacin 0.3% solution in cataract surgery patients. Ophthalmology. 2005; 112(11):1992-6.
[54] Solomon R, Donnenfeld ED, Perry HD, et al. Penetration of topically applied gatifloxacin 0.3%, moxifloxacin 0.5%, and ciprofloxacin 0.3% into the aqueous humor. Ophthalmology. 2005; 112(3):466-9.
[55] Koch HR, Kulus SC, Roessler M, et al. Corneal penetration of fluoroquinolones: aqueous humor concentrations after topical application of levofloxacin 0.5% and ofloxacin 0.3% eye drops. J Cataract Refract Surg. 2005; 31(7):1377-85.
[56] Lai WW, Chu KO, Chan KP, et al. Differential aqueous and vitreous concentrations of moxifloxacin and ofloxacin after topical administration one hour before vitrectomy. Am J Ophthalmol. 2007; 144(2):315-8.
[57] Holland EJ, McCarthy M, Holland S. The ocular penetration of levofloxacin 1.5% and gatifloxacin 0.3% ophthalmic solutions in subjects undergoing corneal transplant surgery. Curr Med Res Opin. 2007; 23(12):2955-2260.
[58] Torkildsen G, O'Brien TP. Conjunctival tissue pharmacokinetic properties of topical azithromycin 1% and moxifloxacin 0.5% ophthalmic solutions: a single-dose, randomized, open-label, active-controlled trial in health adult volunteers. Clin Ther. 2008; 30(11):2005-2014.
[59] Ciloxan [package insert]. Fort Worth, TX; Alcon Labs; 2006.
[60] Zymar [package insert]. Irvine, CA; Allergan; August 2004.
[61] Quixin [package insert]. Napa, CA; Santen; April 2007.
[62] Vigamox [package insert]. Ft. Worth, TX; Alcon Labs; 2008.
[63] Ocuflox [package insert]. Irvine, CA; Allergan; May 2005.
[64] AzaSite [package insert]. Alameda, CA; Inspire Pharmaceuticals; November 2008.
[65]. Available at: http://www.clinicalpharmacology.com. Accessed July 4, 2010.
[66] Iquix [package insert]. Jacksonville, FL; Vistakon Pharmaceuticals; April 2007.
[67] Besivance [package insert]. Tampa, FL; Bausch and Lomb; April 2009.
[68] Natacyn [package insert]. Forth Worth, TX; Alcon Labs; May 2008.
[69] Tobrex [package insert]. Fort Worth, TX: Alcon; October 2003.
[70] Natacyn [package insert]. Fort Worth, TX; Alcon Labs; May 2008.
[71] Bacitracin Zinc and Polymyxin B Sulfate [package insert]. Lake Forest, IL; Akorn, Inc; November 2008.
[72] Bleph-10 [package insert]. Irvine, CA; Allergan; February 2005.
[73] Ciloxan [package insert]. Fort Worth, TX; Alcon Labs; 2006.
[74] Zymar [package insert]. Irvine, CA; Allergan; August 2004.
[75] Quixin [package insert]. Napa, CA; Santen; April 2007.
[76] Vigamox [package insert]. Ft. Worth, TX; Alcon Labs; 2008.
[77] Ocuflox [package insert]. Irvine, CA; Allergan; May 2005.
[78] AzaSite [package insert]. Alameda, CA; Inspire Pharmaceuticals; November 2008.
[79]. Available at: http://www.clinicalpharmacology.com. Accessed July 5, 2010.
[80] Iquix [package insert]. Jacksonville, FL; Vistakon Pharmaceuticals; April 2007.
[81] Besivance [package insert]. Tampa, FL; Bausch and Lomb; April 2009.
[82] Natacyn [package insert]. Forth Worth, TX; Alcon Labs; May 2008.
[83] Tobrex [package insert]. Fort Worth, TX; Alcon; October 2003.
[84] Besivance [package insert]. Tampa, FL; Bausch and Lomb; April 2009.
[85] Ciloxan [package insert]. Fort Worth, TX; Alcon Labs; 2006.
[86] Ciloxan ointment [package insert]. Fort Worth, TX; Alcon Labs; 2003.
[87] Zymar [package insert]. Irvine, CA; Allergan; August 2004.
[88] Zymaxid [package insert]. Irvine, CA; Allergan; May 2010.
[89] Quixin [package insert]. Napa, CA; Santen; April 2007.
[90] Iquix [package insert]. Jacksonville, FL; Vistakon Pharmaceuticals; April 2007.
[91] Vigamox [package insert]. Ft. Worth, TX; Alcon Labs; 2008.
[92] Ocuflox [package insert]. Irvine, CA; Allergan; May 2005.
[93] AzaSite [package insert]. Alameda, CA; Inspire Pharmaceuticals; November2008.

[94] Available at: http://www.clinicalpharmacology.com. Accessed July 4, 2010.
[95] Available at: http://www.clinicalpharmacology.com. Accessed July 4, 2010.
[96] Tobrex [package insert]. Fort Worth, TX: Alcon; October 2003.
[97] Available at: http://www.clinicalpharmacology.com. Accessed July 4, 2010.
[98] Natacyn [package insert]. Forth Worth, TX; Alcon Labs; May 2008.
[99] Ciloxan [package insert]. Fort Worth, TX; Alcon Labs; 2006.
[100] Zymar [package insert]. Irvine, CA; Allergan; August 2004.
[101] Quixin [package insert]. Napa, CA; Santen; April 2007.
[102] Vigamox [package insert]. Ft. Worth, TX; Alcon Labs; 2008.
[103] Ocuflox [package insert]. Irvine, CA; Allergan; May 2005.
[104] AzaSite [package insert]. Alameda, CA; Inspire Pharmaceuticals; November 2008.
[105] Available at: http://www.clinicalpharmacology.com. Accessed December 7, 2009.
[106] Iquix [package insert]. Jacksonville, FL; Vistakon Pharmaceuticals; April 2007.
[107] Besivance [package insert]. Tampa, FL; Bausch and Lomb; April 2009.
[108] Natacyn [package insert]. Forth Worth, TX; Alcon Labs; May 2008.
[109] Tobrex [package insert]. Fort Worth, TX: Alcon; October 2003.
[110] Bacitracin Zinc and Polymyxin B Sulfate [package insert]. Lake Forest, IL; Akorn, Inc; November 2008.
[111] Neosporin [package insert]. Research Triangle Park, NC; Burroughs Wellcome, Inc; October 2006.
[112] Neocidin [package insert]. Tampa, Fl; Bausch and Lomb; August 2007.
[113] Polytrim [package insert]. Irvine, CA; Allergan; August 2004
[114] Ciloxan [package insert]. Fort Worth, TX; Alcon Labs; 2006.
[115] Zymar [package insert]. Irvine, CA; Allergan; August 2004.
[116] Quixin [package insert]. Napa, CA; Santen; April 2007.
[117] Vigamox [package insert]. Ft. Worth, TX; Alcon Labs; 2008.
[118] Ocuflox [package insert]. Irvine, CA; Allergan; May 2005.
[119] AzaSite [package insert]. Alameda, CA; Inspire Pharmaceuticals; November 2008.
[120] Available at: http://www.clinicalpharmacology.com. Accessed July 4, 2010.
[121] Iquix [package insert]. Jacksonville, FL; Vistakon Pharmaceuticals; April 2007.
[122] Besivance [package insert]. Tampa, FL; Bausch and Lomb; April 2009.
[123] Natacyn [package insert]. Forth Worth, TX; Alcon Labs; May 2008.
[124] Tobrex [package insert]. Fort Worth, TX: Alcon; October 2003.
[125] Available at: http://www.thomsonhc.com/home. Accessed December 7, 2009.
[126] Tobrex ointment [package insert]. Fort Worth, TX; Alcon; October 2003.
[127] Zymaxid [package insert]. Irvine, CA; Allergan; May 2010.
[128] Bacitracin Zinc and Polymyxin B Sulfate [package insert]. Lake Forest, IL; Akorn, Inc; November 2008.
[129] Neosporin [package insert]. Research Triangle Park, NC; Burroughs Wellcome, Inc; October 2006.
[130] Neocidin [package insert]. Tampa, Fl; Bausch and Lomb; August 2007.
[131] Polytrim [package insert]. Irvine, CA; Allergan; August 2004.
[132] Parmar P, Salman A, Kalavathy CM, et al. Comparison of topical gatifloxacin 0.3% and ciprofloxacin 0.3% for the treatment of bacterial keratitis. Am J Ophthalmol. 2006; 141(2):282-286.
[133] Lichtenstein SJ, Rinehart M; Levofloxacin Bacterial Conjunctivitis Study Group. Efficacy and safety of 0.5% levofloxacin ophthalmic solution for the treatment of bacterial conjunctivitis in pediatric patients. J AAPOS. 2003; 7(5):3173-24.
[134] Protzko E, Bowman L, Abelson M, et al. Phase 3 safety comparisons for 1% azithromycin in polymeric mucoadhesive eye drops versus 0.3% tobramycin eye drops for bacterial conjunctivitis. Invest Ophthamol Vis Sci. 2007; 48(8):3425-9.
[135] Donnenfeld E, Perry HD, Chruscicki DA, et al. A comparison of the fourth generation fluoroquinolones gatifloxacin 0.35 and moxifloxacin 0.5% in terms of ocular tolerability. Curr Med Res Opin. 2004; 20(11):1753-58.
[136] Granet DB, Dorfman M, Stroman D, et al. A multicenter comparison of polymyxin B sulfate/trimethoprim ophthalmic solution and moxifloxacin in the speed of clinical efficacy for the treatment of bacterial conjunctivitis. J Pediatr Ophthamol Strabismus. 2008; 45(6):340-349.
[137] McDonald MB, Protzko EE, Brunner LS, et al. Efficacy and safety of besifloxacin ophthalmic suspension 0.6% compared with moxifloxacin ophthalmic solution 0.5% for treating bacterial conjunctivitis. Ophthalmology. 2009;116(9):1615-1623.e1.
[138] Besivance [package insert]. Tampa, FL; Bausch and Lomb; April 2009.
[139] McDonald MB, Protzko EE, Brunner LS, et al. Efficacy and safety of besifloxacin ophthalmic suspension 0.6% compared with moxifloxacin ophthalmic solution 0.5% for treating bacterial conjunctivitis. Ophthalmology. 2009;116(9):1615-1623.e1.
[140] Ciloxan [package insert]. Fort Worth, TX; Alcon Labs; 2006.
[141] Ciloxan [package insert]. Fort Worth, TX; Alcon Labs; 2006.
[142] Zymar [package insert]. Irvine, CA; Allergan; August 2004.
[143] Quixin [package insert]. Napa, CA; Santen; April 2007.
[144] Vigamox [package insert]. Ft. Worth, TX; Alcon Labs; 2008.
[145] McDonald MB, Protzko EE, Brunner LS, et al. Efficacy and safety of besifloxacin ophthalmic suspension 0.6% compared with moxifloxacin ophthalmic solution 0.5% for treating bacterial conjunctivitis. Ophthalmology. 2009;116(9):1615-1623.e1.
[146] Ocuflox [package insert]. Irvine, CA; Allergan; May 2005.
[147] AzaSite [package insert]. Alameda, CA; Inspire Pharmaceuticals; November 2008.
[148] Sheikh A, Hurwitz B, Cave J. Antibiotics for acute bacterial conjunctivitis. Cochrane Database Syst Rev. 2000; (2):CD001211.
[149] Sheikh A, Hurwitz B. Topical antibiotics for acute bacterial conjunctivitis: a systematic review. B r J Gen Pract. 2001; 51:473-477.
[150] Sheikh A, Hurwitz B. Topical antibiotics for acute bacterial conjunctivitis: Cochrane systematic review and meta-analysis update. Br J Gen Pract. 2005; 55(521):962-4.

[151] Sheikh A, Hurwitz B. Antibiotics versus placebo for acute bacterial conjunctivitis. Cochrane Database Syst Rev. 2006; (2):CD001211.