Therapeutic Class Overview
Ophthalmic Fluoroquinolones

Therapeutic Class

- **Overview/Summary:** This review will focus on the ophthalmic fluoroquinolone antibiotics. These agents are used for the treatment of bacterial conjunctivitis and corneal ulcers caused by susceptible isolates.[1-8] Conjunctivitis occurs worldwide and affects all ages, social strata, and both genders. This infection rarely causes permanent visual loss or structural damage and mild cases may be self-limited, as many cases will resolve without treatment in immunocompetent individuals. The most common causative pathogens seen with bacterial conjunctivitis include *Staphylococcus* aureus, *Streptococcus pneumonia*, *Haemophilus influenza*, and *Moraxella catarrhalis*.[9] Major clinical features of bacterial conjunctivitis include redness and discharge in one eye, although it can be bilateral. Patients eye(s) will often be "stuck shut" in the morning. Purulent discharge continues throughout the day and is thick, globular and may be yellow, white or green in color, which may help distinguish between viral and allergic conjunctivitis which usually has watery discharge.[9] Fluoroquinolone antibiotics act via direct inhibition of bacterial DNA synthesis, preventing the action of DNA gyrase and topoisomerase IV, which blocks DNA replication and eventually leads to damage to bacterial DNA and cell death.[10] Currently, ofloxacin, levofloxacin, gatifloxacin and ciprofloxacin hydrochloride (solution) are available generically.

  These ophthalmiac quinolones include besifloxacin, ciprofloxacin hydrochloride, gatifloxacin, levofloxacin, moxifloxacin hydrochloride, and ofloxacin. They are all indicated for the treatment of bacterial conjunctivitis.[1-8] In addition, ciprofloxacin solution and ofloxacin have the indication to treat corneal ulcers caused by susceptible isolates.[2,8] All medications are formulated as drops (either solution or suspension) with only ciprofloxacin hydrochloride being formulated as an ointment (Ciloxan®).[3] Although generally considered equally effective, differences in resistance exist, with fewer gram-positive cocci being resistant to gatifloxacin and moxifloxacin hydrochloride than other fluoroquinolones.[13] Frequency and duration of therapy varies depending on specific agents. Treatment for bacterial conjunctivitis with besifloxacin and moxifloxacin hydrochloride is usually dosed twice or three times daily, while the others are generally prescribed every two to four hours.[1-8] Most ophthalmic quinolones are indicated for use in patients one year of age or older, however, moxifloxacin hydrochloride (Moxeza®) is indicated for use in children four months of age and older and ciprofloxacin hydrochloride ointment is only indicated for use in children two years of age or older.[1-8]

Table 1. Current Medications Available in Therapeutic Class[1-8]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Besifloxacin ophthalmic (Besivance®)	Treatment of bacterial conjunctivitis	Ophthalmic suspension: 0.6% (5 mL)	-
Ciprofloxacin hydrochloride ophthalmic (Ciloxan®*)	Treatment of bacterial conjunctivitis; treatment of corneal ulcers (solution)	Ophthalmic ointment: 0.3% (3.5 g) Ophthalmic solution: 0.3% (2.5, 5, 10 mL)	✔
Gatifloxacin ophthalmic (Zymaxid®*)	Treatment of bacterial conjunctivitis	Ophthalmic solution: 0.5% (2.5 mL)	✔
Levofloxacin ophthalmic	Treatment of bacterial conjunctivitis; treatment of corneal ulcers	Ophthalmic solution: 0.5% (5 mL)	✔
Moxifloxacin hydrochloride ophthalmic (Moxeza®, Vigamox®)	Treatment of bacterial conjunctivitis	Ophthalmic solution: 0.5% (3 mL)	-

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Ofloxacin ophthalmic (Ocuflox®*)	Treatment of bacterial conjunctivitis; treatment of corneal ulcers	Ophthalmic solution: 0.3% (5, 10 mL)	✔

*Generic available in at least one dosage form or strength.

Evidence-based Medicine

- Clinical trials have demonstrated that ophthalmic fluoroquinolones are effective in treating and providing relief of conjunctivitis and corneal ulcers in pediatric and adult patients.[15-40]
- Several studies comparing ophthalmic fluoroquinolones to either placebo or vehicle have concluded that these medications resulted in significantly higher clinical resolution rates at days one through five.[15-20]
- Head-to-head trials evaluating the efficacy of ophthalmic antibiotics for the treatment of bacterial conjunctivitis have found that no one medication was inferior to another.[21-30]
- In one trial, significantly more patients in the ophthalmic moxifloxacin group had complete resolution of ocular signs and symptoms at 48 hours when compared to patients treated with ophthalmic polymyxin B sulfate/trimethoprim (P=0.001).[22] One study found levofloxacin 0.5% to have statistically greater microbial eradication in pediatric patients two to 11 years of age with bacterial conjunctivitis (P≤0.032) compared to ofloxacin 0.3% in, but not in any other pediatric age group..[26] In a seven day trial, a higher percentage of patients receiving levofloxacin had microbial eradication at the final visit compared to patients receiving ofloxacin (P=0.034);however, clinical cure rates were similar between the two treatments (P value not reported).[27] In a small meta-analysis, moxifloxacin was found to be associated with fewer drop-outs for treatment failure (P=0.002) compared to ofloxacin.[28]
- In patients with a diagnosis of corneal ulcer, ophthalmic ciprofloxacin hydrochloride was shown to be efficacious treatment options.[31,32] Specifically, in one trial of patients with a diagnosis of infectious keratitis ophthalmic ciprofloxacin had a shorter average time to healing as compared to ophthalmic cefazolin sodium fortified with gentamicin sulfate, although this was not found to be significant (P value not reported).[32]
- A number of studies consisted of patients with multiple diagnoses such as blepharitis, blepharoconjunctivitis, bacterial conjunctivitis and blepharitis, keratoconjunctivitis, or symptoms of surface ocular infections. These studies found that the ophthalmic formulations of ciprofloxacin, gentamicin sulfate, ofloxacin, tobramycin solution, and polymyxin B sulfate/trimethoprim were efficacious in resolving or curing multiple ocular infections. No significant differences were observed in any study with regard to cure rates, decline in bacterial counts, bacterial eradication or reduction of bacteria, microbial improvement or overall improvement. [34-39]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Use of ophthalmic antibiotics is associated with earlier clinical and microbiological remission when compared to placebo. Therapy for severe conjunctivitis disease be based on culture and sensitivity, but if that is not available or if mild disease is present, empiric therapy is considered appropriate.[9,11-13]
    - The selection of an ophthalmic antibiotics for bacterial conjunctivitis is typically empirical, and the most convenient or least expensive ophthalmic antibiotic is typically effective for most cases of conjunctivitis.[11]
    - Although effective, ophthalmic quinolones are generally regarded as second-line agents for routine bacterial conjunctivitis because of resistance and cost concerns.[9,11,12]
    - Ophthalmic quinolones are the considered the treatment of choice for corneal ulcers and for infections caused by pseudomonas.[9,13]
    - The recommended ophthalmic antibiotics for treatment of keratitis vary depending on organism identified. Empiric therapy is often utilized and includes ophthalmic quinolones[13]
    - Fewer gram-positive cocci are resistant to gatifloxacin and moxifloxacin hydrochloride than other fluoroquinolones[13]

  - Single-drug therapy using an ophthalmic fluoroquinolone has been shown to be as effective as combination therapy with ophthalmic antibiotics that are fortified by increasing their concentration over commercially available topical antibiotics.[13]
- Other Key Facts:
  - Ofloxacin, levofloxacin, gatifloxacin and ciprofloxacin hydrochloride (solution) are available generically.
  - Only ciprofloxacin hydrochloride is formulated as an ointment.[3]
  - Moxeza® (moxifloxacin) is dosed twice daily while besifloxacin and Vigamox® (moxifloxacin) are dosed three times a day. The remaining agents are dosed every two or every four hours while awake.[1-8]
  - Most ophthalmic quinolones are indicated for use in patients one year of age or older; however, moxifloxacin hydrochloride (Moxeza®) is indicated for use in children four months of age and older and ciprofloxacin hydrochloride ointment is only indicated for use in children two years of age or older.[1-8]

References

1. Besivance® [package insert]. Tampa, FL: Bausch & Lomb Inc.; 2012 Sep.
2. Ciloxan® solution [package insert]. Fort Worth, TX: Alcon Laboratories, Inc.; 2006 Mar.
3. Ciloxan® ointment [package insert]. Fort Worth, TX: Alcon Laboratories, Inc.; 2011 Jul.
4. Zymaxid® [package insert]. Irvine, CA: Allergan, Inc.; 2012 Jan.
5. Levofloxacin solution [package insert]. Amityville, NY: Hi-Tech Pharmacal Co., Inc.; 2012 Sep.
6. Moxeza® [package insert]. Fort Worth, TX: Alcon Laboratories Inc.; 2012 Sep.
7. Vigamox® [package insert]. Fort Worth, TX: Alcon Laboratories Inc.; 2011 Jul.
8. Ocuflox® [package insert]. Irvine, CA: Allergan, Inc.; 2007 Aug.
9. Jacobs DS. Conjunctivitis. In: Trobe S (Ed). UpToDate [database on the internet. Waltham (MA): UpToDate; 2014 May [cited 2014 Sep 5]. Available from http://www.uptodate.com/contents/search.
10. Hooper DC. Fluoroquinolones. In: Calderwood SB (Ed). UpToDate [database on the internet. Waltham (MA): UpToDate; 2014 Jun [cited 2014 Sep 5]. Available from http://www.uptodate.com/contents/search.
11. American Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Pattern® Guidelines. Conjunctivitis. San Francisco, CA: American Academy of Ophthalmology; 2013. Available at: www.aao.org/ppp.
12. American Optometric Association Consensus Panel on Care of the Patient with Conjunctivitis. Care of the Patient with Conjunctivitis. St. Louis, MO: American Optometric Association; 2007. Available at: http://www.aoa.org.
13. American Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Pattern® Guidelines. Bacterial Keratitis. San Francisco, CA: American Academy of Ophthalmology; 2013. Available at: www.aao.org/ppp.
14. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Healthcare; Updated periodically [cited 2014 Sep 5]. Available from: http://www.thomsonhc.com/.
15. Karpecki P, Depaolis M, Hunter JA, White EM, Rigel L, Brunner LS, et al. Besifloxacin ophthalmic suspension 0.6% in patients with bacterial conjunctivitis: A multicenter, prospective, randomized, double-masked, vehicle-controlled, five-day efficacy and safety study. Clin Ther. 2009;31:514-26.
16. Hwang DG, Schanzlin DJ, Rotberg MH, Foulks G, Raizman MB; Levofloxacin Bacterial Conjunctivitis Place-controlled Study Group. A phase III, placebo controlled clinical trial of 0.5% levofloxacin ophthalmic solution for the treatment of bacterial conjunctivitis. Br J Ophthalmol. 2003;87:1004-9.
17. Tepedino ME, Heller WH, Usner DW, Brunner LS, Morris TW, Haas W, et al. Phase III efficacy and safety study of besifloxacin ophthalmic suspension 0.6% in the treatment of bacterial conjunctivitis. Curr Med Res Opin. 2009 May;25(5):1159-69.
18. Silverstein BE, Allaire C, Bateman KM, Gearinger LS, Morris TW, Comstock TL. Efficacy and tolerability of besifloxacin ophthalmic suspension 0.6% administered twice daily for three days in the treatment of bacterial conjunctivitis: a multicenter, randomized, double-masked, vehicle-controlled, parallel-group study in adults and children. Clin Ther. 2011 Jan;33(1):13-26.
19. DeLeon J, Silverstein BE, Allaire C, Gearinger LS, Bateman KM, Morris TW, et al. Besifloxacin ophthalmic suspension 0.6% administered twice daily for 3 days in the treatment of bacterial conjunctivitis in adults and children. Clin Drug Investig. 2012 May 1;32(5):303-17.
20. Tauber S, Cupp G, Garber R, Bartell J, Vohra F, Stroman D. Microbiological efficacy of a new ophthalmic formulation of moxifloxacin dosed twice-daily for bacterial conjunctivitis. Adv Ther. 2011 Jul;28(7):566-74.
21. Gross RD, Hoffman RO, Lindsay RN. A comparison of ciprofloxacin and tobramycin in bacterial conjunctivitis in children. Clin Pediatr. (Phil) 1997;36:435-44.
22. Granet B, Dorfman M, Stroman D, Cockrun P. A multicenter comparison of polymyxin B sulfate/trimethoprim ophthalmic solution and moxifloxacin in the speed of clinical efficacy for the treatment of bacterial conjunctivitis [abstract]. J Pediatr Ophthalmol Strabismus. 2008;45:340-9.
23. Leibowitz HM. Antibacterial effectiveness of ciprofloxacin 0.3% ophthalmic solution in the treatment of conjunctivitis [abstract]. Am J Ophthalmol. 1991 Oct;112(Suppl 4):29S-33S.
24. Williams L, Malhotra Y, Murante B, Laverty S, Cook S, Topa D, et al. A single-blinded randomized clinical trial comparing polymyxin B-trimethoprim and moxifloxacin for treatment of acute conjunctivitis in children. J Pediatr. 2013 Apr;162(4):857-61. doi: 10.1016/j.jpeds.2012.09.013. Epub 2012 Oct 23.
25. McDonald MB, Protzko EE, Brunner LS, Morris TW, Haas W, Paterno MR, et al. Efficacy and safety of besifloxacin ophthalmic suspension 0.6% compared to moxifloxacin ophthalmic solution 0.5% for treating bacterial conjunctivitis. Ophthalmology. 2009 Sep;116(9):1615-23.

26. Lichtenstein S, Rinehart M. Efficacy and safety of 0.5% levofloxacin ophthalmic solution for the treatment of bacterial conjunctivitis in pediatric patients [abstract]. J AAPOS. 2003;7:317-24.
27. Schwab IR, Friedlaender M, McCulley J, Lichtenstein SJ, Moran CT; Levofloxacin Bacterial Conjunctivitis Active Control Study Group. A phase III clinical trial of 0.5% levofloxacin ophthalmic solution vs 0.3% ofloxacin ophthalmic solution for the treatment of bacterial conjunctivitis. Ophthalmology. 2003 Mar;110(3):457-65.
28. Kodjikian L, Lafuma A, Khoshnood B, Laurendeau C, Berdeaux G. Efficacy of moxifloxacin in treating bacterial conjunctivitis: a meta-analysis. J Fr Ophtalmol. 2010 Apr;33(4):227-33.
29. Silver LH, Woodside AM, Montgomery DB. Clinical safety of moxifloxacin ophthalmic solution 0.5% (Vigamox®) in pediatric and nonpediatric patients with bacterial conjunctivitis. Surv Ophthalmol. 2005;50:S55-S63.
30. Sheikh A, Hurwitz B, van Schayck CP, McLean S, Nurmatov U. Antibiotics vs placebo for acute bacterial conjunctivitis. Cochrane Database Syst Rev. 2012 Sep 12;(9):CD001211.
31. Booranapong W, Kosrirukvongs P, Prabhasawat P, Srivannaboon S, Suttiprakarn P. Comparison of topical lomefloxacin 0.3 per cent vs topical ciprofloxacin 0.3 percent for the treatment of presumed bacterial corneal ulcers [abstract]. J Med Assoc Thai. 2004 Mar;87(3):246-54.
32. Kosrirukvongs P. Buranapongs W. Topical ciprofloxacin for bacterial corneal ulcer [abstract]. J Med Assoc Thai. 2000 Jul;83(7):776-82.
33. Sharma N, Goel M, Bansal S, Agarwal P, Titiyal JS, Upadhyaya AD, et al. Evaluation of moxifloxacin 0.5% in treatment of nonperforated bacterial corneal ulcers: a randomized controlled trial. Ophthalmology. 2013 Jun;120(6):1173-8. doi: 10.1016/j.ophtha.2012.11.013. Epub 2013 Feb 15.
34. Parks DJ, Abrams DA, Sarfarazi FA, Katz HR. Comparison of topical ciprofloxacin to conventional antibiotic therapy in the treatment of ulcerative keratitis [abstract]. Am J Ophthalmol. 1993 Apr 15;115(4):471-7.
35. Bloom PA, Leeming JP, Power W, Laidlaw DA, Collum LM, Easty DL. Topical ciprofloxacin in the treatment of blepharitis and blepharoconjunctivitis [abstract]. Eur J Ophthalmol. 1994 Jan-Mar;4(1):6-12.
36. Adenis JP, Colin J, Verin P, Riss I, Saint-Blancat P. Ciprofloxacin ophthalmic solution in the treatment of conjunctivitis and blepharitis: a comparison with fusidic acid [abstract]. Eur J Ophthalmol. 1996 Oct-Dec;6(4):368-74.
37. Adenis JP, Colin J, Verin P, Saint-Blancat P, Malet F. Ciprofloxacin ophthalmic solution vs rifamycin ophthalmic solution for the treatment of conjunctivitis and blepharitis [abstract]. Eur J Ophthalmol. 1995 Apr-Jun;5(2):82-7.
38. Bron AJ, Leber G, Rizk S, Baig H, Elkingont AR, Kirk GR, et al. Ofloxacin compared to chloramphenicol in the management of external ocular infection. Br J Ophthalmol. 1991;75:675-9.
39. Gwon A. Topical ofloxacin compared to gentamicin in the treatment of external ocular infection. Br J Ophthalmol. 1992 Dec;76(12):714-8.
40. Gwon A. Ofloxacin vs tobramycin for the treatment of external ocular infection. Arch Ophthalmol. 1992 Sep;110(9);1234-7.