BESIVANCE® (besifloxacin ophthalmic suspension) 0.6%: A Powerful Option for the Treatment of Bacterial Conjunctivitis

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ABSTRACT  Treatment of bacterial conjunctivitis can shorten the clinical course of disease, reduce symptoms, and abbreviate the period of contagion.1,2 Introduced in 2009, BESIVANCE® (besifloxacin ophthalmic suspension) 0.6% is a broad-spectrum, topical fluoroquinolone with high potency and balanced affinity for bacterial DNA gyrase and topoisomerase IV.3,5

In vitro studies have found that common bacterial conjunctivitis pathogens, including several antibiotic-resistant strains, are susceptible to besifloxacin and, in clinical trials, BESIVANCE® has an established safety profile and robust efficacy against typical bacterial conjunctivitis pathogens.6,7

BESIVANCE® is indicated for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following bacteria: *Aerococcus viridans*, CDC coryneform group G, *Corynebacterium pseudodiphtheriticum*, *Corynebacterium striatum*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Moraxella lacunata*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus hominis*, *Staphylococcus lugdunensis*, *Staphylococcus warneri*, *Streptococcus mitis* group, *Streptococcus oralis*, *Streptococcus pneumoniae*, *Streptococcus salivarius*.8

*Efficacy for this organism was studied in fewer than 10 infections.*

Use of a mucoadhesive polymer in the BESIVANCE® formulation impacts the duration of the antimicrobial on the ocular surface and contributes to its pharmacokinetic/pharmacodynamic profile.9 Formulated for use only as a topical ophthalmic antibiotic, besifloxacin has not been used in internal medicine or agriculture, which may decrease selection pressure for resistance to the drug.10

See Important Safety Information about BESIVANCE®

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Important Safety Information for BESIVANCE®

- BESIVANCE® is for topical ophthalmic use only, and should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.
- As with other anti-infectives, prolonged use of BESIVANCE® may result in overgrowth of non-susceptible organisms, including fungi. If super-infection occurs, discontinue use and institute alternative therapy.
- Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with BESIVANCE®.
- The most common adverse event reported in 2% of patients treated with BESIVANCE® was conjunctival redness. Other adverse events reported in patients receiving BESIVANCE® occurring in approximately 1–2% of patients included: blurred vision, eye pain, eye irritation, eye pruritus and headache.
- BESIVANCE® is not intended to be administered systemically. Quinolones administered systemically have been associated with hypersensitivity reactions, even following a single dose. Patients should be advised to discontinue use immediately and contact their physician at the first sign of a rash or allergic reaction.
- Safety and effectiveness in infants below one year of age have not been established.

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Introduction

Approximately 4 million cases of bacterial conjunctivitis are estimated to occur in the US annually, and many of them seek medical attention.11 An estimated 1% to 4% of primary care consultations are for acute red eye, and there is evidence that the majority of those cases are caused by bacterial conjunctivitis.1,11,12

In a published review of clinical studies, it was found that most cases of acute conjunctivitis in children were bacterial in origin.1,13 Interestingly, physicians have been found to underestimate the prevalence of bacterial conjunctivitis.1

Patients with acute bacterial conjunctivitis characteristically experience tearing, ocular surface irritation, marked redness, and the presence of mucopurulent discharge that can be copious and lead to matting of the lash cilia. To prevent spreading the infection to others, patients are frequently required to stay home from work or school. While the prognosis is generally favorable—60% of cases resolve spontaneously within 2 weeks—bacterial conjunctivitis carries a small (but not zero) risk of progressing to keratitis, particularly in patients carrying large numbers of bacteria and/or an epithelial defect.13 Furthermore, infection with a difficult-to-treat pathogen such as *Pseudomonas aeruginosa* (Figure 1) carries a higher risk for adverse outcomes.2

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1 In vitro studies demonstrated cross-resistance between besifloxacin and some fluoroquinolones.
Microbiology

Since bacterial conjunctivitis is typically treated without culturing the eye, selection of an appropriate treatment requires knowledge of the most likely etiologic agents and their susceptibilities. Pathogens commonly implicated in bacterial conjunctivitis include the following typical commensal flora of the skin and nasopharynx: gram-positive organisms Staphylococcus aureus, Staphylococcus epidermidis, and Streptococcus pneumoniae; and gram negatives Moraxella catarrhalis and Haemophilus influenzae.10 P aeruginosa is of special concern, especially for contact lens wearers.2

An important challenge in the management of bacterial conjunctivitis is antimicrobial resistance.

Resistance

Clinicians who treat external ocular disease have been somewhat protected from problems associated with antibiotic resistance due to the unique pharmacokinetics of topically administered ophthalmic drugs—which can typically achieve concentrations at the site of infection greater than systemic drugs. However, even among ocular infections, rates of in vitro resistance to commonly used antibiotics are increasing rapidly; and resistant pathogens have been identified as a potential cause of treatment failure.10 It is therefore important that ophthalmologists keep abreast of the changing status of antibiotic resistance.

The study-designated Ocular TRUST (for Tracking Resistance in the US Today) reported nationwide antibiotic susceptibility patterns of three key ocular pathogens—S aureus, S pneumoniae, and H influenzae—to multiple classes of ophthalmic antibiotics.15 Ocular TRUST found that, despite widespread use of fluoroquinolones in medicine and veterinary settings, and consequently high resistance selection pressure, the three large clinical studies of BESIVANCE® for the treatment of bacterial conjunctivitis demonstrated low MICs among ocular MRSE isolates, and concerning levels of multidrug resistance among other staphylococci and Pseudomonas strains.15

Potency

Antibiotic potency is typically quantified in terms of the minimum inhibitory concentration (MIC), the lowest concentration of a drug able to inhibit the growth of a bacterial isolate.16 To describe the potency of a drug against a bacterial species, we use the MIC50 and MIC90, the concentrations of antibiotic necessary to inhibit the growth of 50% and 90%, respectively, of different bacterial isolates of the same species. While low MIC values indicate that low concentrations of drug will be required to effect bacterial inhibition, the clinical significance of in vitro data has not been established.16

Three large clinical studies of BESIVANCE® for the treatment of bacterial conjunctivitis demonstrated low MICs against the 1324 bacterial pathogens collected (MIC50 = 0.06 and MIC90 = 0.25 µg/mL).16 The clinical significance of in vitro data has not been established. A randomized, double-masked, vehicle controlled parallel-

A 42-year-old man requested an emergency ophthalmology visit due to symptoms of “pink eye.” The patient reported a 2-day history of redness, irritation, and a thickened discharge from his right eye. Upon awakening, his eyelid was matted shut. His left eye felt normal and seemed to be unaffected. He reported no contact with anyone who had pink eye at home or work. He wore glasses for distance; otherwise he had no significant ocular or medical history.

Examination of his right eye revealed a best corrected visual acuity of 20/30. Slit lamp examination showed trace lid swelling, 2+ conjunctival injection, and mucopurulent discharge. The eye tested negative for the presence of adenovirus. The cornea and anterior segment appeared normal. The left eye was correctable to 20/20, and slit lamp exam was normal.

The patient was diagnosed with acute bacterial conjunctivitis in the right eye. BESIVANCE® (befsloxacin ophthalmic solution) 0.6% was prescribed and the patient instructed to instill one drop in the affected eye 3 times a day (4 to 12 hours apart) for 7 days. Seen 3 days later, the patient was significantly improved. He was instructed to continue BESIVANCE® to the end of the initial 7-day period and then discontinue.

Figure 1 (a) Eye with confirmed bacterial conjunctivitis due to P aeruginosa. (b) The same eye after 1 week of therapy with BESIVANCE® TID.
The Besifloxacin Molecule

The besifloxacin molecule is part of the topical ocular fluoroquinolone family. Fluoroquinolones work by binding 2 enzymes critical for DNA bacterial replication: DNA gyrase (topoisomerase II) and topoisomerase IV. The original quinolones predominantly targeted DNA gyrase, which gave them good activity against replication of gram-negative organisms. Subsequent generations have had better activity against topoisomerase IV, which expanded the spectrum of coverage against gram-positive organisms.

Besifloxacin has 2 halogen atoms on the quinoline backbone: a fluorine (common to all fluoroquinolones) and a chlorine at carbon 8. This contributes to a balanced and increased affinity for both DNA gyrase and topoisomerase IV, enhancing besifloxacin’s overall in vitro potency. Targeting both enzymes relatively equally also means that 2 mutations would be required for the development of substantial resistance. The clinical significance of in vitro data has not been established. In vitro studies demonstrated cross-resistance between besifloxacin and some fluoroquinolones.

Treating Bacterial Conjunctivitis

Since suspected bacterial conjunctivitis cases are not routinely cultured, empirical therapy should be broad-spectrum, covering as many as possible of the common gram-positive and gram-negative pathogens known to cause bacterial conjunctivitis.

BESIVANCE® has a broad spectrum of coverage that commonly cause bacterial conjunctivitis. BESIVANCE® has demonstrated potency against worrisome pathogens such as MRSA, MRSE, and P. aeruginosa. BESIVANCE® is also formulated with a mucoadhesive polymer.

Finally, BESIVANCE® has an established safety profile and is a potent agent for the treatment of bacterial conjunctivitis.

References


Please see indication and important safety information on page 1 and the prescribing information for BESIVANCE® on page 4.
8.4 Pediatric Use

Pediatric use of Besivance in infants below one year of age has not been established. The safety and effectiveness of Besivance in treating bacterial conjunctivitis in pediatric patients one year or older has been demonstrated in clinical trials.

5.3 Avoidance of Contact Lenses

Avoidance of Contact Lenses. Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with Besivance.

6 ADVERSE REACTIONS

The most frequently reported ocular adverse reactions in clinical trials were conjunctival redness, burning, and irritation, reported in approximately 2% of patients.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Since Besivance has been shown to be excreted in human milk, with the aid of magnification, such as slit-lamp staining. There is no evidence that the topically administered concentration of besifloxacin has any effect on weight bearing joints, even though systemic administration of some quinolones has been found to cause arthropathy in immature animals.

5.2 Growth of Resistant Organisms with Prolonged Use

Avoidance of Contact Lenses. Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with Besivance. (3.5)

8.2 Nursing Mothers

Besivance has not been measured in human milk although it can be presumed to be excreted in human milk. Caution should be exercised when Besivance is administered to a nursing mother.

8.4 Pediatric Use

Pediatric use of Besivance in infants below one year of age has not been established. The safety and effectiveness of Besivance in treating bacterial conjunctivitis in pediatric patients one year or older has been demonstrated in clinical trials. (1.5)

6 ADVERSE REACTIONS

The most common adverse reaction reported in 2% of patients treated with Besivance was conjunctival redness. (6)

9 CLINICAL STUDIES

The most frequently reported ocular adverse reactions in clinical trials were conjunctival redness, burning, and irritation, reported in approximately 2% of patients.

2 DESCRIPTION

Besivance is for topical ophthalmic use only, and is a sterile ophthalmic suspension, 0.6%, to treat bacterial conjunctivitis caused by susceptible isolates of the following bacteria:

Streptococcus pneumoniae
Streptococcus salivarius* (S. salivarius)
Streptococcus oralis
Streptococcus mitis*
Staphylococcus hominis*
Moraxella catarrhalis*
Moraxella lacunata*
Moraxella osloensis#
Moraxella osloensis
Staphylococcus aureus
Staphylococcus epidermidis
Staphylococcus haemolyticus
Erysipelothrix rhusiopathiae
Streptococcus agalactiae
Streptococcus anginosus
Streptococcus gordonii
Streptococcus intermedius
Streptococcus anginosus
Streptococcus intermedius
Streptococcus anginosus
Streptococcus equi
Staphylococcus capitis
Staphylococcus epidermidis
Staphylococcus haemolyticus
Staphylococcus aureus
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Staphylococcus epidermidis
Staphylococcus aureus
Erysipelothrix rhusiopathiae
Streptococcus spp.
Streptococcus anginosus
Streptococcus gordonii
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Streptococcus anginosus
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