BESIVANCE® (besifloxacin ophthalmic suspension) 0.6%: In Vitro Potency and Broad-spectrum Activity for the Treatment of Bacterial Conjunctivitis

ABSTRACT  Bacterial conjunctivitis is a common ocular infection that, although usually self-limited, can result in severe cases and develop vision-threatening complications. Diagnosis of bacterial conjunctivitis is generally clinical, and most cases can be managed with empirical antibiotic therapy. Use of a potent, broad-spectrum topical antibiotic is important for treatment. BESIVANCE® (besifloxacin ophthalmic suspension) 0.6%, a fluoroquinolone developed specifically for topical ocular use and approved for the treatment of bacterial conjunctivitis, provides such an antibiotic choice.

As a dual-halogenated topical chlorofluoroquinolone, besifloxacin demonstrates potent in vitro activity against a range of important ocular pathogens, including strains of methicillin-resistant staphylococci, and susceptible isolates of *Pseudomonas aeruginosa*. Formulated in a mucoadhesive vehicle, BESIVANCE® also has excellent ocular surface residence time, making it a good choice for the treatment of bacterial conjunctivitis.

The clinical significance of in vitro activity has not been established.

See Important Safety Information about BESIVANCE®.

Indication
BESIVANCE® is a quinolone antimicrobial indicated for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following bacteria: *Aerococcus viridans*, *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*.

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

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.

Ron Melton, OD, FAAO

Bacterial conjunctivitis is a common ocular surface infection. In the US, the incidence of bacterial conjunctivitis is estimated at about 1.3%. Typically, bacterial conjunctivitis is acute and self-limited and can resolve spontaneously, but topical antibiotic therapy offers a number of benefits. Antibiotic treatment can shorten the course of the disease, and speed the resolution of symptoms and infections.

**Spectrum of In Vitro Activity and Potency**

The organisms that most often cause bacterial conjunctivitis include *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Staphylococcus epidermidis.* Among these, *S. aureus* is typically the most aggressive organism, and the combination of virulence and drug resistance makes methicillin-resistant *S aureus* (MRSA) an organism of great concern. Although MRSA has moved out into the community, healthcare workers remain at high risk of MRSA colonization because of its prevalence in hospital settings.

When confronted by a case of bacterial conjunctivitis, the gold standard for determining the causative pathogen is to culture the conjunctiva. Routine culture of every case of conjunctivitis is impractical in general practice settings, however, and patients with bacterial conjunctivitis diagnosed from signs and symptoms are typically treated empirically with topical ophthalmic antibiotics.

To achieve bacterial eradication with empirical therapy, it is important to choose an agent with a wide spectrum of in vitro antimicrobial activity.

**A Powerful Fluoroquinolone**

Current generation fluoroquinolones are the antimicrobial agents most often used to treat bacterial conjunctivitis, in large part because they have a broad spectrum of in vitro activity. Despite the overall effectiveness of the class, fluoroquinolone
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Please see Important Safety Information on page 1 and the prescribing information for BESIVANCE® on page 4.

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Bacterial Conjunctivitis: Differential Diagnosis

Before initiating antibiotic treatment, it is important to confirm the diagnosis of bacterial conjunctivitis. Viral conjunctivitis should not be treated with antibiotics. Bacterial conjunctivitis can occur unilaterally or bilaterally. Most often, it is isolated to one eye and characterized by a mild mucopurulent discharge that is typically worse upon awakening than later in the day.

Conjunctival hyperemia can be mild, moderate, or severe (Figure 3A). In mild cases, conjunctival hyperemia will typically be greater inferiorly than superiorly, an indication of greater bacterial activity in the inferior conjunctiva and a distinguishing factor for bacterial conjunctivitis. Mild cases of bacterial conjunctivitis are also often characterized by abundant, floating microparticulate debris in the inferior lacrimal lake, an important finding that can distinguish low-grade bacterial conjunctivitis from adenoviral infection.

Adenoviral conjunctivitis is often transient, starting in 1 eye and rapidly moving to the other. A weepy serous discharge is common. More severe cases can present with follicular conjunctivitis, which is rarely, if ever, seen in bacterial conjunctivitis (Figure 3B).

including indications to treat bacterial conjunctivitis caused by susceptible isolates of Pseudomonas aeruginosa, Aerococcus viridians, Moraxella catarrhalis, and Staphylococcus warneri.7 BESIVANCE® provides practitioners a potent topical antibiotic indicated for most of the pathogens relevant to bacterial conjunctivitis. The approval for P. aeruginosa represents an official recognition of the activity BESIVANCE® shows against this often highly virulent gram-negative organism.

P. aeruginosa is a concern not just because of its virulence but because of its ability to invade the cornea.19 BESIVANCE® offers proven activity against P. aeruginosa conjunctivitis. Indeed, a post hoc analysis of 4 clinical studies (see Figure 1 for study details) showed that treatment with BESIVANCE® provided microbial eradication in 5 days or less for all 5 cases and 40% clinical resolution at the end of treatment.16 Clinical resolution was defined as the absence of both ocular discharge and bulbar conjunctival injection.

**Figure 1:** Study details

A total of 1,317 cases of bacterial conjunctivitis caused by strains including MRSA, MRSE, and P. aeruginosa were pooled from 4 multicenter, double-masked, randomized clinical trials evaluating BESIVANCE®. Three studies (2 vehicle controlled and 1 active-controlled) administered BESIVANCE® TID for 5 days, and one vehicle-controlled study administered BESIVANCE® BID for 3 days. (P. aeruginosa n=9; MRSA n=35; MRSE n=81). Vehicle was 0.01% benzalkonium chloride.

**Conclusions**

Topical antibiotic therapy is beneficial in patients with bacterial conjunctivitis. In empirical therapy—the typical treatment for bacterial conjunctivitis—it is important to use a potent, broad-spectrum agent. BESIVANCE® has demonstrated excellent therapeutic efficacy in the treatment of bacterial conjunctivitis.14-16,19 The potent in vitro bactericidal activity of besifloxacin against a wide range of significant ocular pathogens, including resistant strains, makes it a valuable component of the ocular antibiotic armamentarium.

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**References**


17. DeCory HH, Comstock TL, Geiringer LS, Morris TW. Clinical efficacy of besifloxacin ophthalmic suspension, 0.6% against MRSA and MRSE. Poster presented at: Annual Meeting of the Association for Research in Vision and Ophthalmology; May 6-10, 2012; Fort Lauderdale, FL.


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**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use BESIVANCE safely and effectively. See full prescribing information for BESIVANCE.

**BESIVANCE** (besifloxacin ophthalmic suspension) 0.6%

**Drug Class:** Broad Spectrum Quinolone Antimicrobial

**Indications:** BESIVANCE is indicated for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following bacteria: Streptococcus pneumoniae, *S. pyogenes*, *S. anginosus*, Staphylococcus lugdunensis*, Staphylococcus hominis*, Staphylococcus epidermidis, *M. catarrhalis*, *M. lacunata*, *M. fermentans*, *Streptococcus salivarius*. 

**Contraindications:** BESIVANCE is contraindicated in patients who are hypersensitive to any of the components of BESIVANCE or any quinolone.

**Warnings and Precautions:** Patients should be advised not to wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with BESIVANCE. Adverse reactions: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals to determine the carcinogenic potential of besifloxacin have not been performed. No in vitro mutagenic activity of besifloxacin was observed in an Ames test (up to 3.3 mg/plate) on bacterial tester strains Salmonella typhimurium TA100, TA1535, TA1537 and Escherichia coli WP2uvrA. However, it was mutagenic in 5 Salmonella typhimurium strains TA102 and Ec.菌 strain WP2uvrA(G1). Positive responses in these strains have been associated with other quinolones and are likely related to topoisomerase inhibition. Besifloxacin induced chromosomal aberrations in CHO cells in vitro and it was positive in an in vivo mouse micronucleus assay at oral doses > 1,500 mg/kg. Besifloxacin did not induce unscheduled DNA synthesis in hepatocytes cultured from rat or gerbil that were treated with besifloxacin up to 2,000 mg/kg by the oral route. In a fertility and early embryonic development study in rats, besifloxacin did not impair the fertility of male or female rats at oral doses of up to 100 mg/kg/day. This is over 10,000 times higher than the recommended total daily human ophthalmic dose.

**Clinical Studies:** In a randomized, double-masked, vehicle controlled, multicenter clinical trial, in patients 1-98 years of age who were dosed 3 times a day for 5 days, BESIVANCE was superior to its vehicle in patients with bacterial conjunctivitis. Clinical response was achieved in 45% (90/191) for the treatment group versus 33% (63/191) for the vehicle treated group (difference 12%, 95% CI: -3% - 22%). Microbiological outcomes demonstrated bacterial cure or improvement rate for causative pathogens of 91% (184/191) for the BESIVANCE treated group versus 60% (119/191) for the vehicle treated group (difference 31%, 95% CI: 23% - 40%). Microbiological eradication does not always correlate with clinical outcome in anti-infective trials.

**How Supplied/Storage and Handling:** BESIVANCE is an ophthalmic suspension of besifloxacin in approximately 0.7 mL 0.6% in a white low density polyethylene (LDPE) bottle with a controlled dropper tip and a polystyrene cap. Tamper evidence is provided with a shrink band around the cap and neck area of the package.

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