BESIVANCE® (besifloxacin ophthalmic suspension) 0.6%: A Potent Broad-spectrum Fluoroquinolone for the Treatment of Bacterial Conjunctivitis

Francis S. Mah, MD

ABSTRACT As bacteria develop resistance to the drugs we use to treat infection, we need increasingly potent antibiotics to keep them in check. BESIVANCE® (besifloxacin ophthalmic suspension) 0.6% is a fluoroquinolone with a number of very appealing features. BESIVANCE® is a quinolone antimicrobial 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*.

*Efficacy for this organism was studied in fewer than 10 infections. Among the things that distinguish BESIVANCE® are its low minimum inhibitory concentrations (MICs) against many of the bacteria of concern to ophthalmologists, including methicillin-resistant staphylococci, and its ability to remain on the eye at effective (ie, greater-than-MIC) concentrations for up to 12 hours. These combine to make BESIVANCE® an excellent agent for the treatment of bacterial conjunctivitis. Several factors account for the potency of BESIVANCE®. Its balanced activity against DNA gyrase and topoisomerase IV makes it effective against indicated gram-negative and gram-positive organisms. In addition, halogenation has long been used to impact gyrase and topoisomerase IV makes it effective against indicated gram-negative and gram-positive organisms. In addition, halogenation has long been used to impact

The rise of methicillin-resistant *Staphylococcus aureus* (MRSA) and other resistant organisms is a serious concern for all physicians who deal with bacterial conjunctivitis. Bacteria would not have survived for billions of years were they not brilliantly able to adapt to changed environments. Their ability to develop resistance against the agents we use to control them is something we must respect and contend with.

For physicians, MRSA may be the single most concerning resistant organism, because of its ubiquity and virulence. Within ophthalmology we also have to be cognizant of methicillin-resistant *Staphylococcus epidermidis* (MRSE), another common cause of bacterial conjunctivitis. Among the gram-negative species, *Pseudomonas aeruginosa* is a special concern because of its virulence and its frequent association with infection in contact lens abusers.

The Importance of Potency

Antibiotic potency is an important key to dealing with both actual and potential resistance. The commonly accepted measure of potency is a drug’s minimum inhibitory concentration (MIC), the concentration at which that drug can inhibit the in vitro growth of a specific isolate. The classic metrics of potency are the MIC90 and MIC50, which represent the lowest concentration at which a drug inhibits 50% and 90%, respectively, of tested isolates of a given species.

All other things being equal, the lower a drug’s MIC, the more bacteria that can be eliminated with exposure to the drug.

See Important Risk Information about BESIVANCE®.

Please see the full prescribing information for BESIVANCE® on page 4.

Important Risk Information about 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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This might be important for clinical efficacy and to possibly lower the opportunity for development of resistant strains: The greater the number of bacteria killed or inhibited, the smaller the risk that there will be survivors left with a mutation leading to the development of resistance. So potency—as demonstrated by low MICs—is a highly desirable trait in an antibiotic. That said, the true clinical significance of in vitro data is not known, and in vitro studies have demonstrated cross-resistance between BESIVANCE® and other fluoroquinolones.

**BESIVANCE®**

Taking a close look at BESIVANCE® (besifloxacin ophthalmic suspension) 0.6%, it demonstrates very low MICs against relevant ocular pathogens (Table 1).³,⁶

![Table 1](image)

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC (µg/mL)</th>
<th>Range</th>
<th>MIC₅₀</th>
<th>MIC₉₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSA–CR (n = 14)</td>
<td>0.5–2</td>
<td>0.5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>MRSA–CR (n = 15)</td>
<td>0.5–16</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>MSSE–CR (n = 9)³</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRSE–CR (n = 13)</td>
<td>0.5–8</td>
<td>0.5</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

³Due to the limited isolates, only the MIC₅₀ value is given.

Abbreviations:

- MSSA–CR = methicillin-susceptible ciprofloxacin-resistant
- MSSA–CR = methicillin-resistant ciprofloxacin-resistant
- Staphylococcus aureus
- MRSA–CR = methicillin-resistant ciprofloxacin-resistant
- Staphylococcus epidermidis
- MSSE–CR = methicillin-susceptible ciprofloxacin-resistant
- Staphylococcus epidermidis
- MRSE–CR = methicillin-resistant ciprofloxacin-resistant
- Staphylococcus epidermidis

The MIC values shown in Table 1 are particularly important because today, most cases of bacterial conjunctivitis are treated empirically—we initiate treatment without knowing the causative organism or its susceptibility. The drug with the greatest ability to eradicate organisms of interest is found by looking at MIC₉₀ values. As can be seen from the low MIC₉₀ values in Table 1, BESIVANCE® is potent against resistant staphylococci—important gram-positive pathogens in ophthalmology.

In addition, BESIVANCE® is indicated for the treatment of bacterial conjunctivitis caused by *P. aeruginosa*. While all members of the quinolone family have been successfully used to treat gram-negative infections, the FDA label recognizes the ability of BESIVANCE® to address this major pathogen capable of causing serious damage to the eye.⁷ A specific indication from the FDA may be important for the many physicians outside ophthalmology who treat bacterial conjunctivitis but may be less familiar with ophthalmic pharmaceuticals.

**Sources of Potency: Balanced Action**

Fluoroquinolones work by inhibiting two enzymes that are critical for bacterial replication: DNA gyrase and topoisomerase IV.³ The original quinolones bound DNA gyrase, with relatively little effect on topoisomerase IV.⁶ Since DNA gyrase inhibition has a disproportionately greater effect on gram-negative bacteria, the early quinolone antibiotics had relatively less efficacy against gram-positive organisms.⁸

Succeeding generations of quinolones have had greater affinity for topoisomerase IV; indeed, BESIVANCE® has well balanced activity against both DNA gyrase and topoisomerase IV.¹ The strong affinity of BESIVANCE® for topoisomerase IV has been demonstrated to result in low MIC₉₀ values against resistant gram-positive *S. aureus* and *S. pneumoniae* (Table 1).³ A balanced targeting of both enzymes may also slow the emergence of resistance to BESIVANCE®, since this would require two separate bacterial mutations.⁹

In vitro resistance to BESIVANCE® occurs at a general frequency of < 3.3 × 10⁻¹⁰ for *S. aureus* and < 7 × 10⁻¹⁰ for *S. pneumoniae*.¹⁰

**Sources of Potency: Dual Halogenation**

In addition to the fluorine atom common to all fluoroquinolones, besifloxacin has a second halogen substitution, a chlorine, on its molecule. Halogenation has long been used to modulate the activity of drugs, and in the case of BESIVANCE® that halogenation appears to contribute to its increased affinity for topoisomerase IV, increasing its potency.¹⁰ Additionally, the drug’s 7-azepinyl ring distinguishes it from other fluoroquinolones. This functional group also contributes to its potency.¹¹

Before the development of BESIVANCE®, other chloro-fluoroquinolones had been formulated, some of which were extremely potent, but most of which were deemed too toxic for systemic medical application.⁷ A topical ophthalmic agent, BESIVANCE® emerged as a broad-spectrum bactericidal antibiotic that has high potency and an established safety profile in topical application. Topical ophthalmic use of besifloxacin was carefully evaluated for years prior to its release; and the safety seen in those years of testing has been borne out in clinical practice.

**On-eye Staying Power**

Not just its potency but its formulation contributes to the ability of BESIVANCE® to eradicate organisms on the surface of the eye. BESIVANCE® is prepared with a mucoadhesive polymer vehicle designed to extend the drug’s residence time on the ocular surface. The effect is significant: besifloxacin remains on the eye for close to 24 hours.¹² At 12 hours, the concentration is above the MIC₉₀ of the most significant ocular pathogens (Figure 1).²,¹² Recommended dosing for BESIVANCE® is TID, with 4 to 12 hours between each dose.¹⁰

In my clinical experience, BESIVANCE® is extremely effective in the treatment of bacterial conjunctivitis, and I believe that the increased contact time contributes significantly to the ability of BESIVANCE® to bring about rapid resolution of bacterial conjunctivitis.

**Clinical Significance**

Although it does not often cause severe morbidity, there are good reasons to treat bacterial conjunctivitis. Because it is highly contagious, it keeps patients out of school or work. Often, healthy parents have to stay home from work to be with a child.
who has bacterial conjunctivitis. A 2005 study estimated that 4 million cases of bacterial conjunctivitis occur per year in the US, with the total cost to households of lost wages, and to society of lost work reaching over 500 million dollars.13

It is also important to treat bacterial conjunctivitis because some conjunctivitis is caused by bacteria that are capable of producing significant damage to the eye. Since conjunctivitis is rarely cultured, we typically do not know which bacterial species we are dealing with. An infection caused by *P. aeruginosa*, for example, can be limited to the conjunctiva upon initial presentation, but can progress to far more serious disease.

**Why Potency Matters**

What do we need in a medication to treat bacterial conjunctivitis? First, to cover a range of possible pathogens, it must have broad-spectrum activity. The fluoroquinolones—especially BESIVANCE® (besifloxacin ophthalmic suspension) 0.6%, with its activity against indicated gram-negative and gram-positive organisms—meet this criterion. Again, because it is not routine to culture in cases of conjunctivitis, any given case may be caused by a highly susceptible, highly resistant, or intermittently susceptible organism—we simply don’t know. But a potent, broad-spectrum antibiotic like BESIVANCE® can be effective in many of these scenarios.

We also want a potent medication because we want to help patients recover and return to work or school as soon as possible. In a clinical trial of patients with culture-proven bacterial conjunctivitis, after 5 days of treatment with either BESIVANCE® or vehicle (TID), more BESIVANCE™-treated patients had resolution of infection.14

**Conclusion**

It is important to treat bacterial conjunctivitis with a potent and broad-spectrum antibiotic. BESIVANCE®, an ophthalmic chlorofluoroquinolone, is both highly potent and has balanced activity against bacterial DNA gyrase and topoisomerase IV. It has been shown to be effective against resistant bacteria, including MRSA and MRSE. Formulated in a vehicle for prolonged residence time on the eye, BESIVANCE® is a potent agent for the treatment of bacterial conjunctivitis.

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**References**


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**BESIVANCE TECHNICAL PAPER**

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

**5.3 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**

Because clinical trials are conducted under widely varied conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

For the data described below reflect exposure to BESIVANCE in approximately 1,000 patients between 6 and 96 years old with clinical signs and symptoms of bacterial conjunctivitis.

The most frequently reported scale adverse reactions was conjunctival redness, reported in approximately 10% of patients.

Other adverse reactions reported in patients receiving BESIVANCE including eye pain, eye irritation, and eye discharge.

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

The relationship of besifloxacin to human pregnancy is unknown.

**8.2 Pediatric Use**

Studies in pediatric patients one year or older has not been established. The safety and effectiveness of Besivance® in infants below one year of age have not been established. The efﬁcacy and safety in treating bacterial conjunctivitis in pediatric patients one year or older has been demonstrated in controlled clinical trials. (See CLINICAL STUDIES (14).)

**9 NONCLINICAL TOXICOLOGY**

**13.1 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. (See 13.1.)

**14 CLINICAL STUDIES**

In a randomized, double-masked, vehicle controlled, multicerteral clinical trial, in which patients 6-99 years of age were dosed three times a day for 5 days, BESIVANCE® was superior to vehicle in patients with bacterial conjunctivitis. Clinical resolution was achieved in 45% (90/191) of cases for the BESIVANCE® treated group versus 33% (63/191) for the vehicle treated group (difference 12%, 95% CI 3% - 22%). Microbiological resolution was achieved in 78% (148/191) of the BESIVANCE® treated group versus 44% (84/191) for the vehicle treated group (difference 34%, 95% CI 21% - 46%). Microbiological eradication was achieved in 71% (136/191) of the BESIVANCE® treated group versus 37% (71/191) for the vehicle treated group (difference 34%, 95% CI 24% - 44%). BESIVANCE® may improve the clinical outcome in anti-infective trials.

**16 HOW SUPPLIED/STORAGE AND HANDLING**

BESIVANCE® (besifloxacin ophthalmic suspension) 0.6% is a sterile ophthalmic suspension of besifloxacin formulated with Dextrose 5% and Hydrogen Peroxide 1.5% in a white low density polyethylene (LDPE) bottle with a controlled dropper tip and polyethylene cap. H展开内容...