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

Ron Melton, OD, FAAO

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 signficance 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**, 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.*

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.

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

Bacterial conjunctivitis is a common ocular surface infection. In the US, the incidence of bacterial conjunctivitis is estimated at about 1.3%.[1] Typically, bacterial conjunctivitis is acute and self-limited and can resolve spontaneously, but topical antibiotic therapy offers a number of benefits.[2,3] Antibiotic treatment can shorten the course of the disease, and speed the resolution of symptoms and infections.[2]

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*.[4] 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.[5]

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

resistance is a growing problem, and there has been a concerning rise in the prevalence of MRSA-caused ocular infections.[6] To meet the long-term threat of bacterial resistance, a continuous stream of novel agents will be necessary. Until that time, clinicians usually treat bacterial conjunctivitis empirically with currently available agents.

BESIVANCE® was developed specifically for ophthalmic use and approved for the treatment of bacterial conjunctivitis in 2009.[7] Like other fluoroquinolones, its bactericidal activity is a result of inhibitory effects on topoisomerase II (DNA gyrase) and topoisomerase IV, 2 bacterial enzymes that are essential for DNA replication.[7] While older fluoroquinolones targeted primarily topoisomerase IV, later generation fluoroquinolones have increased affinity for topoisomerase II.[8]

The besifloxacin molecule contains an N-cyclopropyl group that confers broad-spectrum antimicrobial activity.[9] It acts against gram-positive and gram-negative organisms commonly associated with bacterial conjunctivitis.[4] Besifloxacin also has a chlorine atom at the C-8 position, which makes besifloxacin an 8-chlorofluoroquinolone. It is the first and only double-halogenated ocular fluoroquinolone available in the US. The chlorine addition provides potency against both bacterial topoisomerases.[9,10] This balanced dual-binding mechanism may also increase its in vitro potency across the bacterial spectrum.[10] Additionally, besifloxacin has no systemic equivalent, eliminating the risk of resistance from systemic use.[9] In vitro studies have demonstrated cross-resistance between besifloxacin and some fluoroquinolones. In vitro resistance to besifloxacin occurs at a general frequency of $< 3.3 \times 10^{-10}$ for *S aureus* and $< 7 \times 10^{-10}$ for *S pneumoniae*.[7]

In Vitro Potency

Besifloxacin demonstrates efficient killing of the common isolates in bacterial conjunctivitis.[11] A review of minimum inhibitory concentration (MIC) values indicates that besifloxacin has excellent in vitro potency against both gram-positive and gram-negative bacteria.[4]

In vitro studies find besifloxacin also has significant potency against MRSA and ciprofloxacin-resistant staphylococci.[4,12] Besifloxacin demonstrates low MIC_{50} and MIC_{90} values against MRSA (0.5 µg/mL and 4 µg/mL, respectively), which are comparable to those of vancomycin (MIC_{50} = 1 µg/mL; MIC_{90} = 4 µg/mL), a glycopeptide antibiotic regularly used for the treatment of MRSA infections because of its potency against the highly resistant organism.[6]

Clinical Information

Bacterial conjunctivitis clinical trials have shown excellent microbial eradication rates and therapeutic efficacy of BESIVANCE® in adults and children of at least 1 year of age.[13-16] In one analysis (see Figure 1 for study details), treatment with besifloxacin brought about microbial eradication in cases of bacterial conjunctivitis culture-positive for MRSA and methicillin-resistant *S epidermidis* (MRSE)—even where isolates were also ciprofloxacin-resistant.[17] At day 5, microbial eradication rates for MRSA or MRSE was 81.2% for BESIVANCE® vs 57.1% for vehicle, while the clinical resolution rate at day 5 was 49.0% BESIVANCE® vs 51.4% for vehicle. Clinical resolution was defined as the absence of both ocular discharge and bulbar conjunctival injection. Microbial eradication does not always correlate with clinical resolution in an anti-infective trial.

In vitro reports from this study found the MIC_{90} values for besifloxacin to be 2 µg/mL against ciprofloxacin-resistant MRSA isolates, and 4 µg/mL against ciprofloxacin-resistant MRSE isolates.[17] The clinical significance of in vitro data has not been established.

In my experience, BESIVANCE® is highly effective in treating bacterial conjunctivitis (see Case Study boxes).

Formulation Attributes

BESIVANCE® is formulated in a mucoadhesive polymer that is designed to adhere to the ocular surface.[18] Extended residence time may result in increased drug concentration on the surface of the eye. Measurement of human tear concentration after a single instillation of BESIVANCE® has shown that besifloxacin remains on the ocular surface through 24 hours.[8] BESIVANCE® is approved for instillation of 1 drop in the affected eye(s) 3 times a day, 4 to 12 hours apart, for 7 days.

Expanded Label

In 2012, the US Food and Drug Administration approved additional microorganisms for BESIVANCE®

Bacterial Conjunctivitis: Case Study

A 57-year-old female nurse at a local hospital presented with a 3-day history of occasional watering, with significant discharge from both eyes on the morning of the office visit (Figure 2). On examination, her best corrected vision was 20/30 OU. She had 3+ bulbar conjunctival injection (with injection somewhat more intense on the inferior bulbar conjunctiva). Both corneas were clear, and there was no preauricular node swelling on either side. The patient was tested for the presence of adenovirus (using the 10-minute AdenoPlus test [Nicox]), and specimens were taken for culture.

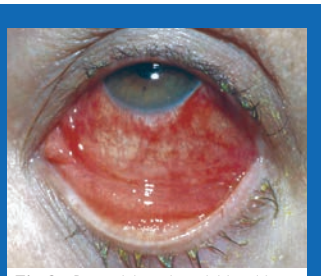

Fig 2 Bacterial conjunctivitis with a MRSA-positive culture. *(All images courtesy of Ron Melton, OD, FAAO.)*

The adenovirus test was negative, and the patient was started on BESIVANCE® and followed up in 3 days. On follow-up, there was a 75% improvement in the bulbar conjunctival injection. The culture came back positive for scant MRSA. The patient was sent home and told to continue BESIVANCE® 3 times a day for 4 more days.

Indication

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.*

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

Please see Important Safety Information on page 1 and the prescribing information for BESIVANCE® on page 4.

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.

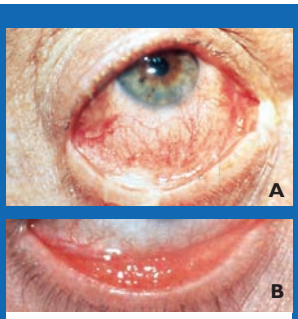

Fig 3 **A** Bacterial conjunctivitis with grade 2 hyperemia, more pronounced toward the inferior fornices, and less so near the limbus, and moderate mucopurulent discharge. **B** Conjunctival follicles.

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.[19] 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

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BAUSCH+LOMB

Besivance®

besifloxacin ophthalmic suspension, 0.6%

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%
Sterile topical ophthalmic drops
Initial U.S. Approval: 2009

---------- RECENT MAJOR CHANGES ----------
Indications and Usage (1) 09/2012
---------- INDICATIONS AND USAGE ----------

Besivance® (besifloxacin ophthalmic suspension) 0.6%, 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. (1)

---------- DOSAGE AND ADMINISTRATION----------

Instill one drop in the affected eye(s) 3 times a day, four to twelve hours apart for 7 days. (2)

---------- DOSAGE FORMS AND STRENGTHS----------

7.5 mL size bottle filled with 5 mL of besifloxacin ophthalmic suspension, 0.6% (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS ----------

Topical Ophthalmic Use Only. (5.1)

Growth of Resistant Organisms with Prolonged Use. (5.2)

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. (5.3)

---------- ADVERSE REACTIONS ----------

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

To report SUSPECTED ADVERSE REACTIONS, contact Bausch & Lomb Incorporated at 1-800-323-0000 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION
Revised: 09/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Besivance® (besifloxacin ophthalmic suspension) 0.6%, 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**
*Efficacy for this organism was studied in fewer than 10 infections.

2 DOSAGE AND ADMINISTRATION

Invert closed bottle and shake once before use.

Instill one drop in the affected eye(s) 3 times a day, four to twelve hours apart for 7 days.

3 DOSAGE FORMS AND STRENGTHS

7.5 mL bottle filled with 5 mL of besifloxacin ophthalmic suspension, 0.6%.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Topical Ophthalmic Use Only

NOT FOR INJECTION INTO THE EYE.

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.

5.2 Growth of Resistant Organisms with Prolonged Use

As with other anti-infectives, prolonged use of Besivance (besifloxacin ophthalmic suspension) 0.6% may result in overgrowth of non-susceptible organisms, including fungi. If super-infection occurs, discontinue use and institute alternative therapy. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy, and, where appropriate, fluorescein staining.

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 varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly compared with the rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to Besivance in approximately 1,000 patients between 1 and 98 years old with clinical signs and symptoms of bacterial conjunctivitis.

The most frequently reported ocular adverse reaction was conjunctival redness, reported in approximately 2% of patients.

Other adverse reactions reported in patients receiving Besivance occuring in approximately 1-2% of patients included: blurred vision, eye pain, eye irritation, eye pruritus and headache.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

Oral doses of besifloxacin up to 1000 mg/kg/day were not associated with visceral or skeletal malformations in rat pups in a study of embryo-fetal development, although this dose was associated with maternal toxicity (reduced body weight gain and food consumption) and maternal mortality. Increased post-implantation loss, decreased fetal body weights, and decreased fetal ossification were also observed. At this dose, the mean C_{max} in the rat dams was approximately 20 mcg/mL, >45,000 times the mean plasma concentrations measured in humans. The No Observed Adverse Effect Level (NOAEL) for this embryo-fetal development study was 100 mg/kg/day (C_{max}, 5 mcg/mL, >11,000 times the mean plasma concentrations measured in humans).

In a prenatal and postnatal development study in rats, the NOAELs for both fetal and maternal toxicity were also 100 mg/kg/day. At 1000 mg/kg/day, the pups weighed significantly less than controls and had a reduced neonatal survival rate. Attainment of developmental landmarks and sexual maturation were delayed, although surviving pups from this dose group that were reared to maturity did not demonstrate deficits in behavior, including activity, learning and memory, and their reproductive capacity appeared normal.

Since there are no adequate and well-controlled studies in pregnant women, Besivance should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

Besifloxacin 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

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

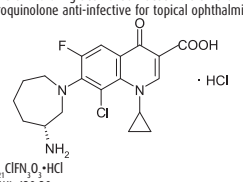
There is no evidence that the ophthalmic administration of quinolones has any effect on weight bearing joints, even though systemic administration of some quinolones has been shown to cause arthropathy in immature animals.

8.5 Geriatric Use

No overall differences in safety and effectiveness have been observed between elderly and younger patients.

11 DESCRIPTION

Besivance (besifloxacin ophthalmic suspension) 0.6%, is a sterile ophthalmic suspension of besifloxacin formulated with DuraSite®† (polycarbophil, edetate disodium dihydrate and sodium chloride). Each mL of Besivance contains 6.63 mg besifloxacin hydrochloride equivalent to 6 mg besifloxacin base. It is an 8-chloro fluoroquinolone anti-infective for topical ophthalmic use.



$C_{19}H_{21}ClFN_3O_3 \cdot HCl$
Mol Wt 430.30

Chemical Name: (+)-7-[(3R)-3-aminohexahydro-1H-azepin-1-yl]-8-chloro-1- cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride.

Besifloxacin hydrochloride is a white to pale yellowish-white powder.

Each mL Contains:
Active: besifloxacin 0.6% (6 mg/mL);
Preservative: benzalkonium chloride 0.01%
Inactives: polycarbophil, mannitol, poloxamer 407, sodium chloride, edetate disodium dihydrate, sodium hydroxide and water for injection.

Besivance is an isotonic suspension with an osmolality of approximately 290 mOsm/kg.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Besifloxacin is a fluoroquinolone antibacterial *[see CLINICAL PHARMACOLOGY (12.4)]*.

12.3 Pharmacokinetics

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 C_{max} 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.

12.4 Microbiology

Besifloxacin is an 8-chloro fluoroquinolone with a N-1 cyclopropyl group. The compound has activity against Gram-positive and Gram-negative bacteria due to the inhibition of both bacterial DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme required for replication, transcription and repair of bacterial DNA. Topoisomerase IV is an essential enzyme required for partitioning of the chromosomal DNA during bacterial cell division. Besifloxacin is bactericidal with minimum bactericidal concentrations (MBCs) generally within one dilution of the minimum inhibitory concentrations (MICs).

The mechanism of action of fluoroquinolones, including besifloxacin, is different from that of aminoglycoside, macrolide, and β-lactam antibiotics. Therefore, besifloxacin may be active against pathogens that are resistant to these antibiotics and these antibiotics may be active against pathogens that are resistant to besifloxacin. *In vitro* studies demonstrated cross-resistance between besifloxacin and some fluoroquinolones.

In vitro resistance to besifloxacin develops via multiple-step mutations and occurs at a general frequency of < 3.3×10^{-10} for *Staphylococcus aureus* and < 7×10^{-10} for *Streptococcus pneumoniae*.

Besifloxacin has been shown to be active against most isolates of the following bacteria both *in vitro* and in conjunctival infections treated in clinical trials as described in the INDICATIONS AND USAGE section:

*Aerococcus viridans**, CDC coryneform group G, *Corynebacterium pseudodiphtheriticum**, *C. striatum**, *Haemophilus influenzae*, *Moraxella catarrhalis**, *M. lacunata**, *Pseudomonas aeruginosa**, *Staphylococcus aureus*, *S. epidermidis*, *S. hominis**, *S. lugdunensis**, *S. warneri**, *Streptococcus mitis* group, *S. oralis*, *S. pneumoniae*, *S. salivarius**

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

13 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 in an Ames test (up to 3.33 mcg/plate) on bacterial tester strains *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2uvrA. However, it was mutagenic in *S. typhimurium* strain TA102 and *E. coli* strain WP2(pKM101). Positive responses in these strains have been observed 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 ≥ 1500 mg/kg. Besifloxacin did not induce unscheduled DNA synthesis in hepatocytes cultured from rats given the test compound 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 500 mg/kg/day. This is over 10,000 times higher than the recommended total daily human ophthalmic dose.

14 CLINICAL STUDIES

In a randomized, double-masked, vehicle controlled, multicenter clinical trial, in which patients 1-98 years of age were dosed 3 times a day for 5 days, Besivance was superior to its vehicle in patients with bacterial conjunctivitis. Clinical resolution was achieved in 45% (90/198) for the Besivance treated group versus 33% (63/191) for the vehicle treated group (difference 12%, 95% CI 3% - 22%). Microbiological outcomes demonstrated a statistically significant eradication rate for causative pathogens of 91% (181/198) for the Besivance treated group versus 60% (114/191) for the vehicle treated group (difference 31%, 95% CI 23% - 40%). Microbiologic eradication does not always correlate with clinical outcome in anti-infective trials.

16 HOW SUPPLIED/STORAGE AND HANDLING

Besivance® (besifloxacin ophthalmic suspension) 0.6%, is supplied as a sterile ophthalmic suspension in a white low density polyethylene (LDPE) bottle with a controlled dropper tip and tan polypropylene cap. Tamper evidence is provided with a shrink band around the cap and neck area of the package.

5 mL in 7.5 mL bottle
NDC 24208-446-05

Storage:

Store at 15°-25°C (59°-77°F). Protect from Light. Invert closed bottle and shake once before use.

17 PATIENT COUNSELING INFORMATION

Patients should be advised to avoid contaminating the applicator tip with material from the eye, fingers or other source.

Although 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.

Patients should be told that although it is common to feel better early in the course of the therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Besivance or other antibacterial drugs in the future.

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.

Patients should be advised to thoroughly wash hands prior to using Besivance.

Patients should be instructed to invert closed bottle (upside down) and shake once before each use. Remove cap with bottle still in the inverted position. Tilt head back, and with bottle inverted, gently squeeze bottle to instill one drop into the affected eye(s).

Manufactured by: Bausch & Lomb Incorporated
Tampa, Florida 33637

9142605(flat)
9142705(folded)