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.[1,2] 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 drug activity, and BESIVANCE® has two halogen atoms on its molecule.[3] Because bacterial conjunctivitis is often treated empirically—without knowledge of the causative organism or its susceptibility—the chances of success can be maximized when a potent, broad-spectrum antibiotic is used. Balanced activity, low MICs against organisms of greater concern, and the ability to remain on the eye in effective concentrations: all argue strongly for the use of BESIVANCE® in the treatment of bacterial conjunctivitis.

See Important Risk Information about BESIVANCE®.

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

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.[1]

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.[4]

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.[5] The classic metrics of potency are the MIC_{50} and MIC_{90}, 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.

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 bewteen 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).[1,6]

Table 1 Minimum inhibitory concentrations of besifloxacin against ciprofloxacin-resistant *S. aureus* and *S. epidermidis*. (Source: Adapted from Reference 6.) Clinical significance of in vitro data has not been established.

Organism	MIC (µg/mL)		
	Range	MIC_{50}	MIC_{90}
MSSA–CR (n = 14)	0.5–2	0.5	1
MRSA–CR (n = 15)	0.5–16	1	4
MSSE–CR (n = 9)[a]	0.5	0.5	
MRSE–CR (n = 13)	0.5–8	0.5	4

[a]Due to the limited isolates, only the MIC_{50} value is given.

Abbreviations:
MSSA-CR = methicillin-susceptible ciprofloxacin-resistant *Staphylococcus aureus*; MRSA-CR = methicillin-resistant ciprofloxacin-resistant *S. aureus*; MSSE-CR = methicillin-susceptible ciprofloxacin-resistant *Staphylococcus epidermidis*; MRSE-CR = methicillin-resistant ciprofloxacin-resistant *S. 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 MIC_{90} values. As can be seen from the low MIC_{90} 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.[8] 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.[3] The strong affinity of BESIVANCE® for topoisomerase IV has been demonstrated to result in low MIC_{90} 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.[3,9]

In vitro resistance to BESIVANCE® occurs at a general frequency of $< 3.3 \times 10^{-10}$ for *S. aureus* and $< 7 \times 10^{-10}$ 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.[3,9] 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 chlorofluoroquinolones 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 MIC_{90}s of the most significant ocular pathogens (Figure 1).[2,6,12] 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

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

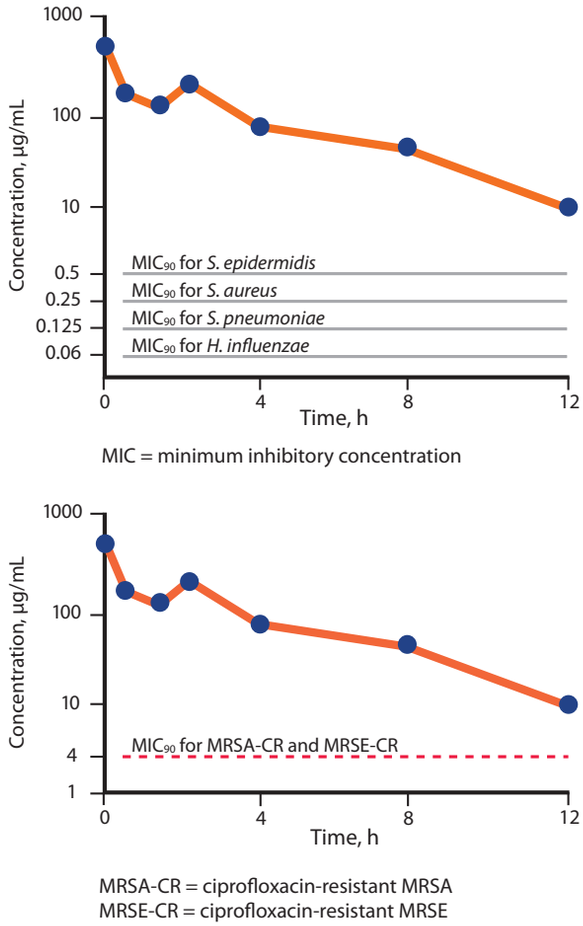

Figure 1 Human tear concentrations after one drop of BESIVANCE®. Note that after 12 hours, the concentration remains above the drug's MIC_{90} values—even for resistant strains. Clinical significance of in vitro data has not been established. (Source: References 2 and 6.)

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

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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

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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)]*.

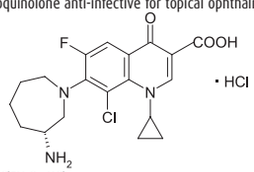
There is no evidence that the ophthalmic administration of quinolones has any effect on weight bearing joints, even though systemic administration of some quinolones has been shown to cause arthropathy in immature animals.

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.



$C_{19}H_{21}ClFN_3O_3$•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

Besivance® is a registered trademark of Bausch & Lomb Incorporated.

U.S. Patent Nos. 6,685,958; 6,699,492; 5,447,926

†DuraSite is a trademark of InSite Vision Incorporated

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