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. (1)

DOSAGE AND ADMINISTRATION
Invert closed bottle and shake once before use. Instill one drop in the affected eye(s) 3 times a day, 4 to 12 hours apart for 7 days. (2)

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 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

DESCRIPTION
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 clinical 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 occurring in approximately 1–2% of patients included: blurred vision, eye pain, eye irritation, eye pruritus and headache.

ADVERSE REACTIONS

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. (1)

2 DOSAGE AND ADMINISTRATION
Invert closed bottle and shake once before use. Instill one drop in the affected eye(s) 3 times a day, 4 to 12 hours apart for 7 days.

3 DOSAGE FORMS AND STRENGTHS
Ophthalmic suspension: besifloxacin 6 mg/mL (0.6%) (3)

4 CONTRAINDICATIONS
None. (4)

5 WARNINGS AND PRECAUTIONS
5.1 Not for Injection into 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

11 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacokinetics
12.3 Pharmacodynamics
12.4 Microbiology

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

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

CLINICAL STABILITY
Invert closed bottle and shake once before use. Instill one drop in the affected eye(s) 3 times a day, 4 to 12 hours apart for 7 days.

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

ANIMAL DATA

6 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 clinical 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 occurring in approximately 1–2% of patients included: blurred vision, eye pain, eye irritation, eye pruritus and headache.

ADVERSE REACTIONS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

RISK SUMMARY
There are no available human data for the use of BESIVANCE during pregnancy to inform any drug-associated risks; however, systemic exposure to besifloxacin from ocular administration is low [see Clinical Pharmacology (12.3)]. Oral administration of besifloxacin to pregnant rats during organogenesis or during the prenatal and postnatal period did not produce adverse embryofetal or offspring effects at clinically relevant systemic exposures [see Data].

DATA

ANIMAL DATA

In an embryofetal development study in rats, the administration of besifloxacin at oral doses up to 1,000 mg/kg/day during organogenesis was not associated with visceral or skeletal malformations in rat fetuses, 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 Cmax in the rat dams was approximately 20 mcg/mL, approximately 46,500 times the mean plasma concentrations measured in humans at the recommended human ophthalmic dose (RHOD). The No Observed Adverse Effect Level (NOAEL) for this embryofetal development study was 100 mg/kg/day (Cmax, 5 mcg/mL, approximately 11,600 times the mean plasma concentrations measured in humans at the RHOD).

In a prenatal and postnatal development study in rats, the NOAELs for both fetal/ neonatal and maternal toxicity were 100 mg/kg/day. At 1,000 mg/kg/day, pups weighed significantly less than controls and had a reduced neonatal survival rate. Attainment of developmental landmarks and sexual maturation was 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.
Besifloxacin is an 8-chloro fluoroquinolone with an N-1 cyclopropyl group. The compound has activity against Gram-positive and Gram-negative bacteria due to the inhibition of an essential enzyme required for partitioning of the chromosomal DNA during bacterial cell division. Besifloxacin is bactericidal with minimum bactericidal concentrations (MBCs) 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 $<3.3 \times 10^{-10}$ for Staphylococcus aureus and $<7 \times 10^{-10}$ 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 (see Indications and Usage (1)):

- Aerococcus viridans*
- CDC corneal 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.

8.2 Lactation

**Risk Summary**

There are no data on the presence of BESIVANCE in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to besifloxacin following topical ocular administration is low (see Clinical Pharmacology (12.3)), and it is not known whether measurable levels of besifloxacin would be present in maternal milk following topical ocular administration.

The developmental and health benefits of breastfeeding should be considered, along with the mother’s clinical need for BESIVANCE, and any potential adverse effects on the breastfed infant from BESIVANCE.

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 0.63 mg besifloxacin hydrochloride equivalent to 6 mg besifloxacin base. It is an 8-chloro fluoroquinolone anti-infective for topical ophthalmic use.

- 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.
- Molecular Weight: 430.30
- C$_{21}$H$_{24}$ClF$_{2}$N$_{2}$O$_{4}$·HCl
- Each mL contains:
  - Active: besifloxacin 0.6% (6 mg/mL);
  - Inactives: polycarbophil, mannitol, poloxamer 407, sodium chloride, edetate disodium dihydrate, sodium hydroxide and water for injection.
- Preservative: benzalkonium chloride 0.01%

**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 Microbiology (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 an 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 aminoglycosides, macrolides, 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 $<3.3 \times 10^{-10}$ for Staphylococcus aureus and $<7 \times 10^{-10}$ 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 (see Indications and Usage (1)):