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 parahaemolyticum®, Corynebacterium striatum®, Haemophilus influenzae, Moraxella catarrhalis®, Moraxella lacunata®, Pseudomonas aeruginosa®, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus hominis®, Staphylococcus lugdunensis, Staphylococcus warneri®, Streptococcus mitis group, Streptococcus viridans, Streptococcus pneumoniae, Strepococcus salivarius®. Efficacy for this organism was studied in fewer than 10 isolates. (1)

CONTRAINDICATIONS
None. (4)

WARNINGS AND PRECAUTIONS
• Not for Injection into the Eye (5.1)
• Growth of Resistant Organisms with Prolonged Use (5.2)
• Avoidance of Contact Lenses (5.3)

ADVERSE REACTIONS
The most common adverse reaction reported in ≥2% of patients treated with BESIVANCE was conjunctival redness, reported in approximately 2% of patients: blurred vision, eye pain, eye irritation, eye pruritus and headache.

Other adverse reactions reported in patients receiving BESIVANCE occurring in approximately 1-2% of patients included: erythema, photophobia, tearing, conjunctival redness, reported in approximately 2% of patients.

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.

The most common adverse reaction reported in ≥2% of patients treated with BESIVANCE was conjunctival redness, reported in approximately 2% of patients: blurred vision, eye pain, eye irritation, eye pruritus and headache.

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.

Efficacy for this organism was studied in fewer than 10 isolates. (1)

PHARMACOLOGY
[see Clinical Pharmacology (12.3)].

MICROBIOLOGY
[see Clinical Pharmacology (12.3)].

11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
• 12.1 Mechanism of Action
• 12.2 Pharmacokinetics
• 12.4 Microbiology
13 NONCLINICAL TOXICITY
• 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.

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.

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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 hearing joints, even though systemic administration of some quinolones has been shown to cause arthropathy in immature animals.

11. DESCRIPTION

BESIVANCE® (besifloxacin ophthalmic suspension) 0.6%, is a sterile suspension of besifloxacin formulated with Durisol® (polyacarbophil, edetate disodium 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.

C₂₁H₂₃ClFN₂O₇.HCl Molecular Weight 430.30

Chemical Name: (+)-7-[(3R, 3S)-aminobenzylxymethyl]-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% (5 mg/mL).
Inactives: polyacarbophil, mannitol, polysorben 304, sodium chloride, edetate disodium dihydrate and sodium hydroxide.
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). Besifloxacin is a synthetic quinolone with DuraSite® ophthalmic vehicle.

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 13.9 ng/mL. The mean besifloxacin C₀ 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 active in vitro against fluoroquinolone with an N-1 cyclopropyl group. The compound has activity against Gram-positive and Gram-negative bacteria due to the inhibition of DNA gyrase and topoisomerase IV. Topoisomerase IV is an essential enzyme required for replication, transcription and repair of bacterial DNA. Topoisomerase IV is an essential enzyme required for replication 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, 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 (1) besifloxacin and some fluoroquinolones.

In vitro resistance to besifloxacin develops via multiple-step mutations and occurs at a general frequency of < 3.3 x 10⁻¹⁰ for Staphylococcus aureus and < 7 x 10⁻¹⁰ for Staphylococcus pneumoniae.

Besifloxacin has been shown to be active against most isolates of bacteria following both in vitro and in conjunctival infections treated in clinical trials [see Indications and Usage (14)].

Aerococcus niavoris
CoC coryneform group 6
Corynebacterium pseudodiphtheriticum
Eikenella corrodens
Hemophilus influenzae
Maximaella catarrhalis
Mersella lacunata
Pseudomonas aeruginosa
Staphylococcus aureus
Staphylococcus epidermidis
Staphylococcus hominis
Staphylococcus lugdunensis
Staphylococcus warneri

Streptococcus mitis group
Streptococcus pneumoniae
Streptococcus pyogenes

Besifloxacin may be active against pathogens that are resistant to besifloxacin.

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 WP2uvrB. However, it was mutagenic in S. typhimurium strain TA102 and E. coli strain WP2 (pM101). Positive responses in these strains have been observed with other quinolones and are likely related to toposiomerase 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 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 dose is approximately 25,600 times higher than the mean plasma concentration measured in humans at the recommended human ophthalmic dose.

14. CLINICAL STUDIES

In a randomized, double-masked, vehicle-controlled, multicenter clinical trial, in which patients 5-6 years of age were dosed three times a day for 5 days, BESIVANCE was superior to its vehicle in patients with bacterial conjunctivitis. Clinical resolution was achieved in 45% (217/478) for the BESIVANCE-treated group versus 33% (63/191) for the vehicle-treated group (difference 31%, 95% CI 23% - 40%).

Microbiological outcomes demonstrated a statistically significant reduction in the number of Giardia (183/198) for the BESIVANCE-treated group versus 60% (114/191) for the vehicle-treated group (difference 34%, 95% CI 22% - 46%).

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.

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


Use with Contact Lenses

Advise patients not to wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with BESIVANCE.

Dosing Instructions

Patients should be instructed to insert closed bottle (upside down) and shake once before each use.

Distributed by:
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Bridgewater, NJ 08807 USA

U.S. Patent Numbers: 6,458,955, 6,699,492, 8,145,342, 8,481,526, 8,604,020 and 9,373,062

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