



Besivance[®]

besifloxacin ophthalmic suspension, 0.6%

MEDICARE PART D COUPON PROGRAM

BAUSCH + LOMB

PAY NO MORE THAN \$60*


If your Medicare out-of-pocket cost for BESIVANCE[®] exceeds \$60, Bausch + Lomb may be able to help.

To obtain your BESIVANCE[®] PART D Coupon Program Card, please visit www.besivancepartdcoupon.com

Most eligible patients pay \$60 out-of-pocket for your prescription fill of BESIVANCE[®] and receive up to \$100 off your remaining expenses

The BESIVANCE[®] Part D Coupon Program is sponsored by Bausch + Lomb and designed to reduce your out-of-pocket cost for BESIVANCE[®] if your Medicare Part D plan does not cover the product or you opt out of using your prescription benefit in conjunction with this offer. If you have questions related to this program, please call **1-800-511-0260**.

*Offer varies at cash-only pharmacies, terms and conditions apply, see reverse for details



Besivance[®]
besifloxacin ophthalmic
suspension, 0.6%

POWERED BY
 **COMP**SM

BESIVANCE® Part D Coupon Program

To obtain your card, go to

www.besivancepartdcoupon.com

BESIVANCE® Part D Coupon Program card can only be used by eligible patients up to 6 times for BESIVANCE® (besifloxacin ophthalmic suspension, 0.6%) before the end of the calendar year, and reduces the patient's out-of-pocket costs for BESIVANCE® to no more than \$60 for each qualifying prescription, subject to Bausch + Lomb's maximum contribution. Maximum Bausch + Lomb contribution is \$100 per prescription. This card is not insurance.

PLEASE NOTE: Regardless of how many BESIVANCE® Part D Coupon Program cards you receive or print, you may only use the card on or before December 31, 2015. Maximum Bausch + Lomb contribution is \$100 per prescription.

Terms and Conditions

- ▶ BESIVANCE® Part D Coupon Program card is valid for a reduction in an eligible patient's out-of-pocket cost to no more than \$60 on each qualifying prescription for BESIVANCE®, subject to Bausch + Lomb's maximum contribution.
- ▶ Maximum Bausch + Lomb contribution is \$100 per prescription.
- ▶ You will be responsible for all costs and expenses of each BESIVANCE® prescription after application of Bausch & Lomb's maximum contribution, if any.
- ▶ At cash-only pharmacies (i.e., those pharmacies not accepting insurance) all patients are responsible for the first \$75 of out-of-pocket expense for each BESIVANCE® prescription and then, Bausch + Lomb will be responsible for the remaining out-of-pocket expenses up to \$100 per eligible prescription fill of BESIVANCE®. Patient will be responsible for all additional costs and expenses for BESIVANCE® after application of this offer including any applicable taxes.
- ▶ You must have prescription drug insurance through a Medicare Part D or Medicare Advantage prescription drug plan.
- ▶ You must agree to not seek reimbursement from your Medicare or Medicare Advantage prescription plan for your out-of-pocket costs for BESIVANCE® purchased with the card.
- ▶ You must also agree to not count the cost of BESIVANCE® toward your deductible or true out-of-pocket cost (TrOOP).
- ▶ You must notify your prescription plan that you have purchased BESIVANCE® outside of your benefit by sending the form letter provided by Bausch + Lomb at www.besivancepartdcoupon.com
- ▶ You must purchase all prescriptions for BESIVANCE® during the calendar year with the card and you must not use your Medicare Part D benefit for BESIVANCE®, if your benefits were to change during the calendar year.
- ▶ Program is not valid for any patients with commercial / private insurance, uninsured / cash paying patients, or patients with prescription coverage under any other federal or state health program such as Medicaid or TRICARE.
- ▶ No other purchase necessary.
- ▶ BESIVANCE® Part D Coupon Program card is not transferable. No substitutions are permitted. Cannot be combined with any other coupon, free trial, discount, prescription savings card, or other offer not already associated with this offer.
- ▶ BESIVANCE® Part D Coupon Program card is not insurance.
- ▶ BESIVANCE® Part D Coupon Program card can be used only by eligible United States residents at participating eligible retail pharmacies in the United States. Product must originate from the United States.
- ▶ BESIVANCE® Part D Coupon Program card is the property of Bausch + Lomb and must be turned in on request.
- ▶ It is illegal to sell, purchase, trade, or counterfeit, or offer to sell, purchase trade, or counterfeit the BESIVANCE® Part D Coupon Program card. Void if reproduced. Void where prohibited by law, taxed, or restricted.
- ▶ Bausch + Lomb reserves the right to rescind, revoke, or amend this offer at any time without notice.
- ▶ Data related to your redemption of the BESIVANCE® Part D Coupon Program card may be collected, analyzed, and shared with Bausch + Lomb, for market research and other purposes related to assessing patient savings programs. Data shared with Bausch + Lomb will be aggregated and de-identified, meaning it will be combined with data related to other card redemptions and will not identify you.
- ▶ Expiration Date: 12/31/2015

BAUSCH + LOMB

BESIVANCE is a registered trademark of Bausch & Lomb Incorporated or its affiliates.

All other products/brand names are trademarks of their respective owners.

©2015 Bausch + Lomb Incorporated. US/BES/15/0016

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*

- 1 INDICATIONS AND USAGE**
- 2 DOSAGE AND ADMINISTRATION**
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
 - 5.1 Topical Ophthalmic Use Only
 - 5.2 Growth of Resistant Organisms with Prolonged Use
 - 5.3 Avoidance of Contact Lenses
- 6 ADVERSE REACTIONS**
- 8 USE IN SPECIFIC POPULATIONS**
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers
 - 8.4 Pediatric Use

- 8.5 Geriatric Use
 - 11 DESCRIPTION**
 - 12 CLINICAL PHARMACOLOGY**
 - 12.1 Mechanism of Action
 - 12.3 Pharmacokinetics
 - 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**
 - PACKAGE/LABEL PRINCIPAL DISPLAY PANEL**
- *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:

- I *Aerococcus viridans**
CDC coryneform group G
*Corynebacterium pseudodiphtheriticum**
*Corynebacterium striatum**
- I *Haemophilus influenzae*
- I *Moraxella catarrhalis**
*Moraxella lacunata**
- I *Pseudomonas aeruginosa**
Staphylococcus aureus
Staphylococcus epidermidis
*Staphylococcus hominis**
- I *Staphylococcus lugdunensis**
- I *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 occurring 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 (NOEL) 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 NOELs 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)].

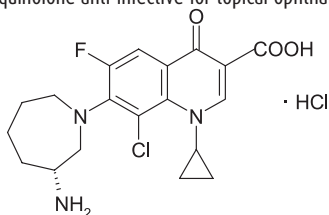
There is no evidence that the ophthalmic administration of quinolones has any effect on weight bearing joints, even though systemic administration of some quinolones has been shown to cause arthropathy in immature animals.

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 $< 3.3 \times 10^{-10}$ 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 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.

©Bausch & Lomb Incorporated

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

†DuraSite is a trademark of InSite Vision Incorporated

9142605 (flat)
9142705 (folded)