PRODUCT MONOGRAPH

Pr® BESIVANCE™

Besifloxacin ophthalmic suspension, 0.6% w/v

Antibacterial (ophthalmic)

Sponsor:
Bausch & Lomb Incorporated
1400 North Goodman Street
Rochester, NY 14609

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Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION ..............................................................3
  SUMMARY PRODUCT INFORMATION ................................................................3
  INDICATIONS AND CLINICAL USE ..................................................................3
  CONTRAINDICATIONS .......................................................................................4
  WARNINGS AND PRECAUTIONS ......................................................................4
  ADVERSE REACTIONS .......................................................................................6
  DRUG INTERACTIONS .........................................................................................7
  DOSAGE AND ADMINISTRATION .....................................................................8
  OVERDOSAGE .....................................................................................................9
  ACTION AND CLINICAL PHARMACOLOGY ...................................................9
  STORAGE AND STABILITY .............................................................................10
  SPECIAL HANDLING INSTRUCTIONS .............................................................10
  DOSAGE FORMS, COMPOSITION AND PACKAGING ......................................10

PART II: SCIENTIFIC INFORMATION ........................................................................11
  PHARMACEUTICAL INFORMATION .................................................................11
  CLINICAL TRIALS ............................................................................................12
  DETAILED PHARMACOLOGY ..........................................................................15
  MICROBIOLOGY ...............................................................................................17
  TOXICOLOGY ....................................................................................................20
  REFERENCES .....................................................................................................25

PART III: CONSUMER INFORMATION ......................................................................26
BESIVANCE™
besifloxacin ophthalmic suspension, 0.6% w/v

PART 1: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Dosage Form / Strength</th>
<th>Clinically Relevant Nonmedicinal Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ophthalmic Topical</td>
<td>7.5 mL bottle containing 5 mL of 0.6% w/v sterile ophthalmic suspension</td>
<td>Contains poloxamer 407, polycarbophil, benzalkonium chloride. For a complete listing see Dosage Forms, Composition and Packaging section.</td>
</tr>
</tbody>
</table>

INDICATIONS AND CLINICAL USE

BESIVANCE™ (besifloxacin ophthalmic suspension) 0.6% w/v is indicated for the treatment of patients one year of age and older with bacterial conjunctivitis caused by susceptible strains of the following organisms:

**Aerobic, Gram-Positive**
- CDC coryneform group G
- Staphylococcus aureus
- Staphylococcus epidermidis
- Streptococcus mitis
- Streptococcus oralis
- Streptococcus pneumoniae

**Aerobic, Gram-Negative**
- Haemophilus influenzae

To reduce the development of drug-resistant bacteria and maintain the effectiveness of BESIVANCE™ and other antibacterial drugs, BESIVANCE™ should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.

**Geriatrics (> 60 years of age):**
No overall differences in safety and effectiveness have been observed between elderly and younger patients.
Pediatrics (<1 years old):
The safety and efficacy of BESIVANCE™ in patients less than one year of age have not been established.

CONTRAINDICATIONS

BESIVANCE™ is contraindicated in patients with known hypersensitivity to this drug, to other quinolones, or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

General
NOT FOR INJECTION INTO THE EYE. FOR TOPICAL OPHTHALMIC USE ONLY.

BESIVANCE™ is a sterile suspension for topical ophthalmic use only, and should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye. There are no data to support use of BESIVANCE™ in patients with concomitant corneal injury/damage.

Contact Lenses:
Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis or during the course of therapy with BESIVANCE™.

Carcinogenesis and Mutagenesis
Long-term studies in animals to determine the carcinogenic potential of besifloxacin have not been performed (see TOXICOLOGY).

Immune
Anaphylaxis and Hypersensitivity:
Besifloxacin is only commercially available for topical ophthalmic administration. While anaphylaxis or other hypersensitivity reactions have not been observed with topical ophthalmic use of besifloxacin in humans, the potential for such reactions should be considered since patients with known hypersensitivity to fluoroquinolones were excluded from clinical trials.

In patients receiving systemically administered quinolones, serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported, some following the first dose. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial edema), airway obstruction, dyspnea, urticaria, and itching.

If any allergic reaction occurs, BESIVANCE™ should be discontinued and appropriate therapy should be administered as clinically indicated.
Susceptibility/Resistance

Development of Drug Resistant Bacteria:
Prescribing BESIVANCE™ in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of resistant organisms.

Potential for Microbial Overgrowth:
The use of BESIVANCE™ may promote the selection on non-susceptible organisms. Should superinfection occur during the therapy, appropriate measures should be taken.

Special Populations

Pregnant Women:
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.

In an oral embryofetal development study in rats, the No Observable Adverse Effect Level (NOAEL) for besifloxacin was 100 mg/kg/day for both parental and reproductive toxicity based on maternal mortality, decreased uterine weight, increased resorptions and post-implantation loss, and reduced fetal bodyweight together with a delay in fetal ossification at the highest dose of 1000 mg/kg/day. This NOAEL is approximately 3333 times the highest recommended total daily human ophthalmic dose (based on a three times daily dosing regimen with 50 µL eye drops in both eyes of a 60 kg patient). In a similar study in rabbits, the fetal and maternal NOAEL was 2 mg/kg/day based on abortions and early deliveries, decreased uterine weight, increased resorptions and post-implantation loss and reduced fetal bodyweight at the highest dose of 20 mg/kg/day. This NOAEL is approximately 67 times the highest recommended total daily human ophthalmic dose. In a prenatal and postnatal development study in rats, the NOAEL for parental toxicity was 10 mg/kg/day (approximately 333 times the highest recommended total daily human ophthalmic dose), based on decreased body weight and food intake at 100 mg/kg/day, and the NOAEL for reproductive performance of parental females and development of their pups was 100 mg/kg/day (approximately 3333 times the highest recommended total daily human ophthalmic dose), based on litter size reduction, decreased survival, developmental retardation, and delayed sexual maturation of the pups at 1000 mg/kg/day. The exposure-based safety factors for embryofetal and prenatal/postnatal development, calculated using the lowest NOAEL dose of 2 mg/kg in the rabbit compared to human exposure following ocular administration is greater than 150-fold.

Nursing Women:
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.

Pediatrics (<1 year of age):
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 TRIALS).

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.

Geriatrics (> 60 years of age):
No overall differences in safety and effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
A total of 2377 patients were enrolled in three safety and efficacy trials, 1187 into the BESIVANCE™ group, 614 into a vehicle group, and 576 into an active control group. BESIVANCE™ was administered three times daily for five days. The population treated with BESIVANCE™ was between 1 and 98 years old with clinical signs and symptoms of bacterial conjunctivitis.

No serious adverse reactions related to BESIVANCE™ were reported.

Overall, 75/1187 (6.3%) subjects treated with BESIVANCE™ had a treatment-emergent non-ocular adverse event.

Similarly, 139/1187 (11.7%) study eyes treated with BESIVANCE™ had a treatment-emergent ocular adverse event.

15/1187 (1.3%) of subjects treated with BESIVANCE™ discontinued treatment due to an AE.

The most frequently reported treatment-emergent ocular adverse events in the study eye were blurred vision (2.1%), eye pain (1.9%), and eye irritation (1.4%).

Clinical Trial Adverse Drug Reactions
Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Bacterial Conjunctivitis Trials
The rates of the most common treatment-emergent ocular adverse events irrespective of causality observed in eyes treated with BESIVANCE™ during the three bacterial conjunctivitis clinical trials are displayed in Table 1.
Table 1 - Incidence (%) of Treatment-Emergent Adverse Events Irrespective of Causality that Occurred in ≥ 1% of Study Eyes/Patients Treated with BESIVANCE™ or Vehicle in Bacterial Conjunctivitis Studies
(Population: Safety¹)

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Besifloxacin n= 1187 (%)</th>
<th>Vehicle n= 614 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vision Blurred</td>
<td>25 (2.1%)</td>
<td>24 (3.9%)</td>
</tr>
<tr>
<td>Eye Irritation</td>
<td>17 (1.4%)</td>
<td>18 (2.9%)</td>
</tr>
<tr>
<td>Eye Pain</td>
<td>22 (1.9%)</td>
<td>11 (1.8%)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>14 (1.2%)</td>
<td>15 (2.4%)</td>
</tr>
<tr>
<td>Eye Pruritus</td>
<td>13 (1.1%)</td>
<td>10 (1.6%)</td>
</tr>
<tr>
<td>Conjunctivitis Bacterial</td>
<td>7 (0.6%)</td>
<td>9 (1.5%)</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>21 (1.8%)</td>
<td>11 (1.8%)</td>
</tr>
</tbody>
</table>

¹ Safety population includes subjects treated for bacterial conjunctivitis that were randomized and received at least one dose of the study drug in the three safety and efficacy studies. **BESIVANCE™** was tested in all three studies, while the vehicle was tested in only two of the studies.

The most frequently reported treatment-related ocular adverse events (possibly, probably or definitely related) in the study eye were blurred vision (1.9%), eye irritation (1.3%), and eye pain (1.2%).

**Less Common Clinical Trial Adverse Drug Reactions (<1%)**
Treatment-related adverse events (possibly, probably or definitely related) reported in 0.1 to 1.0% of eyes receiving **BESIVANCE™** included:

**Eye Disorders:** eye pruritus, dry eye, conjunctivitis, conjunctivitis bacterial, punctate keratitis, conjunctival oedema, eye discharge, corneal infiltrates, corneal staining, eyelid margin crusting, keratoconjunctivitis sicca, foreign body sensation in eyes, conjunctival follicles, dry skin, eye disorder, instillation site pain, photophobia, visual disturbance.

**Nervous System Disorders:** headache

**DRUG INTERACTIONS**

**Overview**
No specific interaction studies have been performed. Results from *in vitro* and *in vivo* metabolism studies demonstrated that the overall extent of besifloxacin metabolism was very
low. Topical ophthalmic use of besifloxacin is not expected to elicit any potential systemic PK drug interactions because systemic exposure to besifloxacin is low following topical administration to humans (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

**Drug-Drug Interactions**
No specific drug-drug interaction studies were conducted.

**Drug-Food Interactions**
Interactions of BESIVANCE™ with food have not been established.

**Drug-Herb Interactions**
Interactions of BESIVANCE™ with herbal products have not been established.

**Drug-Laboratory Interactions**
Interactions of BESIVANCE™ with laboratory tests have not been established.

**DOSAGE AND ADMINISTRATION**

**Dosing Considerations**
BESIVANCE™ (besifloxacin ophthalmic suspension) 0.6% is administered by instillation into the affected eye(s). It is indicated for topical ophthalmic use only, and should not be administered systemically, injected subconjunctivally, or introduced directly into the anterior chamber of the eye. BESIVANCE™ is NOT FOR INJECTION.

**Recommended Dose and Dosage Adjustment**
The recommended dosage regimen for BESIVANCE™ in the treatment of patients one year of age and older with bacterial conjunctivitis is to instill one drop in the affected eye(s) 3 times a day for 7 days.

**Missed Dose**
If a dose of this medication has been missed, it should be taken as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped and return to the regular dosing schedule. Do not double doses.

**Administration**
Patients should be advised to thoroughly wash hands prior to using BESIVANCE™.

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

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).
OVERDOSAGE

For management of suspected drug overdose, contact your regional Poison Control Centre.

No information is available on overdosage of BESIVANCE™. A topical overdose of BESIVANCE™ may be flushed from the eye(s) with warm tap water.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Besifloxacin is an 8-chloro fluoroquinolone with a N-1 cyclopropyl group that has activity against Gram-positive and Gram-negative bacteria.

The antibacterial action of besifloxacin results from dual inhibition of 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 (see MICROBIOLOGY).

Pharmacodynamics
Due to low systemic exposure of besifloxacin, QT prolongation in patients is unlikely (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Pharmacokinetics

Table 2: Summary of Besifloxacin Pharmacokinetic Parameters Following Topical Ocular Administration in Humans

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Dose Regimen/Study Day</th>
<th>C&lt;sub&gt;max&lt;/sub&gt;</th>
<th>t&lt;sub&gt;½ (h)&lt;/t&gt;</th>
<th>AUC&lt;sub&gt;(0-12)&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.6% TID Day 1</td>
<td>0.37 ± 0.27 ng/mL</td>
<td>4.3 ± 2.2</td>
<td>AUC&lt;sub&gt;(0-6)&lt;/sub&gt; 1.45 ± 0.87 ng*h/mL</td>
</tr>
<tr>
<td></td>
<td>0.6% TID Day 6&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.43 ± 0.30 ng/mL</td>
<td>6.8 ± 2.1</td>
<td>AUC&lt;sub&gt;(0-6)&lt;/sub&gt; 1.95 ± 1.31 ng*h/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AUC&lt;sub&gt;(0-12)&lt;/sub&gt; 3.21 ± 2.50 ng*h/mL</td>
</tr>
<tr>
<td>Tears&lt;sup&gt;3&lt;/sup&gt;</td>
<td>0.6% Single Dose Day 1</td>
<td>610 ± 540 μg/g</td>
<td>3.4</td>
<td>AUC&lt;sub&gt;(0-24)&lt;/sub&gt; 1232 μg*h/g</td>
</tr>
</tbody>
</table>

<sup>1</sup>Data from human subjects with clinically diagnosed bilateral bacterial conjunctivitis.

<sup>2</sup>Subjects received 3 doses per day for 5 days and a single dose on Day 6 (16 doses total).

<sup>3</sup>Data from healthy human volunteers; values represent data from Full Analysis Set (FAS) population.

Absorption: 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, variability in plasma besifloxacin concentrations between subjects was large, and the maximum plasma besifloxacin concentration in each patient was less than 1.3 ng/mL.
**Distribution:** The concentration of besifloxacin in tear fluid was measured in healthy adult subjects who received a single drop of **BESIVANCE™**. Following a single administration, the mean besifloxacin concentration observed in samples collected 24 hours after a single administration was 1.6 µg/g. *In vitro*, besifloxacin was approximately 39-44% bound to proteins in human plasma and was approximately evenly distributed between plasma and the cellular components of human blood.

**Metabolism:** Results from *in vitro* studies with human hepatocytes and nonclinical *in vivo* studies demonstrate that besifloxacin is metabolically stable, with little or no chiral interconversion to the (-) enantiomer. Following *in vitro* incubation with hepatocytes from multiple species, a total of eight metabolites were observed; however, the relative amount of each metabolite was small and the overall extent of metabolism was very low.

**Excretion:** Following repeated topical ocular administration to humans, besifloxacin was eliminated from the systemic circulation with an apparent half-life of 6.8 hours. Excretion of besifloxacin has not been studied in humans. Results from excretion studies in animals are summarized in the **DETAILED PHARMACOLOGY** section.

**Special Populations and Conditions**

The pharmacokinetics of besifloxacin have not been studied specifically in special populations (e.g., pediatrics, geriatrics, gender, race, genetic polymorphism) or certain conditions (e.g., hepatic insufficiency, renal insufficiency).

**STORAGE AND STABILITY**


**SPECIAL HANDLING INSTRUCTIONS**

There are no special handling instructions for **BESIVANCE™**.

**DOSAGE FORMS, COMPOSITION AND PACKAGING**

**BESIVANCE™** (besifloxacin ophthalmic suspension) 0.6% 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 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
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name: besifloxacin hydrochloride

Chemical name: \(7-[(3R)-3-Aminohexahydro-1H-azepin-1-yl]-8-chloro-1-cyclopropyl-6\text{-}fluoro-1,4\text{-}dihydro-4\text{-}oxo-3\text{-}quinolinecarboxylic\text{ acid monohydrochloride}}\)

Molecular formula: \(C_{19}H_{21}ClFN_{3}O_{3}\cdot HCl\)

Molecular mass: 430.30 as hydrochloride salt and 393.84 as free base.

Structural formula:

\[
\begin{array}{c}
\text{Cl} \\
\text{N} \\
\text{NH}_{2} \\
\text{F} \\
\text{N} \\
\text{O} \\
\text{COOH} \\
\cdot \text{HCl}
\end{array}
\]

Physicochemical properties:

Besifloxacin hydrochloride is a white to pale yellowish-white powder. Each mL of **BESIVANCE™** contains 6 mg besifloxacin base, derived from 6.63 mg besifloxacin hydrochloride.

STERILE

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.
CLINICAL TRIALS

Study demographics and trial design

The patient demographics and basic trial design for the three bacterial conjunctivitis safety and efficacy studies are summarized in Table 3. A total of 2377 patients were enrolled in the 3 safety and efficacy trials, 1187 into the BESIVANCE™ group, 614 into a vehicle group, and 576 into an active control group. All patients were treated with the assigned study drug three times daily (TID) for five days. There was a follow-up visit at Day 8 (+1). Overall, the 3 groups had similar characteristics and similar rates of culture-confirmed bacterial conjunctivitis.
Table 3: Summary of Patient Demographics for Clinical Trials in Bacterial Conjunctivitis

<table>
<thead>
<tr>
<th>Study #</th>
<th>Trial design</th>
<th>Efficacy Parameters</th>
<th>Dosage, route of administration and duration</th>
<th>Study subjects mITT1 (n=number)</th>
<th>Mean age (Range)</th>
<th>Gender (%M/F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL-433</td>
<td>Multicenter, randomized, parallel-group, double masked, placebo (vehicle) controlled</td>
<td>Clinical Resolution and Microbial Eradication in mITT1 Day 5 ±1 day</td>
<td>Topical Ocular 0.6% besifloxacin suspension (5 days, TID)2 versus Topical Ocular vehicle (5 days, TID)</td>
<td>198</td>
<td>22.2 (1-98)</td>
<td>37.9/62.1</td>
</tr>
<tr>
<td>US</td>
<td></td>
<td></td>
<td></td>
<td>191</td>
<td>24.4 (1-87)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL-373</td>
<td>Multicenter, randomized, parallel-group, double masked, placebo (vehicle) controlled</td>
<td>Clinical Resolution and Microbial Eradication in ITT3 Day 4 ±1 day</td>
<td>Topical Ocular 0.6% besifloxacin suspension (5 days, TID) versus Topical Ocular vehicle (5 days, TID)</td>
<td>60</td>
<td>28.7 (1-89)</td>
<td>41.7/58.3</td>
</tr>
<tr>
<td>US</td>
<td></td>
<td></td>
<td></td>
<td>58</td>
<td>34.7 (1-81)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL-434</td>
<td>Multicenter, randomized, parallel-group, double masked, active controlled</td>
<td>Clinical Resolution and Microbial Eradication in mITT1 Day 5 ±1 day</td>
<td>Topical Ocular 0.6% besifloxacin suspension (5 days, TID) versus Topical Ocular moxifloxacin HCl ophthalmic solution 0.5% (5 days, TID)</td>
<td>255</td>
<td>31.2 (1-92)</td>
<td>43.5/56.5</td>
</tr>
<tr>
<td>US</td>
<td></td>
<td></td>
<td></td>
<td>278</td>
<td>38.7 (05^2-100)</td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

1 The modified Intent-to-Treat (mITT) population includes subjects who were randomized to treatment and received at least 1 drop of study medication, and who had baseline cultures in at least 1 eye indicating bacteria levels at or above threshold for any accepted ocular species.
2 TID = Three times a day.
3 ITT population in Study 373 is similar to the modified Intent-to-Treat (mITT) populations used in Studies 433 and 434.
4 Subject was 11 months of age.

**Study results**
Overall clinical efficacy results are provided in Table 4 for the sponsor-defined primary clinical and microbial efficacy parameters at Visit 2 for population with baseline cultures in at least 1 eye indicating bacteria levels at or above threshold for any accepted ocular species (mITT).
Table 4: Results of Safety and Efficacy Studies in Bacterial Conjunctivitis at Visit 2<sup>1</sup> (mITT Population)

<table>
<thead>
<tr>
<th>Outcome&lt;sup&gt;2&lt;/sup&gt;</th>
<th>BL-433 Besifloxacin</th>
<th>Vehicle (N=191)</th>
<th>BL-373 Besifloxacin</th>
<th>Vehicle (N=58)</th>
<th>BL-434 Besifloxacin</th>
<th>Comparator (N=278)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Resolution (%)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>90 (45.5)</td>
<td>63 (33.0)</td>
<td>20 (33.3)</td>
<td>10 (17.2)</td>
<td>149 (58.4)</td>
<td>165 (59.4)</td>
</tr>
<tr>
<td>p-value&lt;sup&gt;5&lt;/sup&gt;</td>
<td>0.0084 / 0.0129</td>
<td>0.0691/ 0.0574</td>
<td>0.21% / 31.97%</td>
<td>0.6838/ 0.8603</td>
<td>0.0183 / 0.0544</td>
<td>0.01%/ 9.17%</td>
</tr>
<tr>
<td>95% CI&lt;sup&gt;6&lt;/sup&gt;</td>
<td>2.73% / 22.21%</td>
<td>0.21% / 31.97%</td>
<td>0.21% / 31.97%</td>
<td>0.21% / 31.97%</td>
<td>23.19% / 40.26%</td>
<td>23.19% / 40.26%</td>
</tr>
<tr>
<td>Microbial Eradication (%)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>181 (91.4)</td>
<td>114 (59.7)</td>
<td>54 (90.0)</td>
<td>27 (46.6)</td>
<td>241 (94.5)</td>
<td>250 (89.9)</td>
</tr>
<tr>
<td>p-value&lt;sup&gt;5&lt;/sup&gt;</td>
<td>&lt;0.0001 / &lt;0.0001</td>
<td>&lt;0.0001 / &lt;0.0001</td>
<td>26.53%/ 60.37%</td>
<td>0.0183 / 0.0544</td>
<td>0.01%/ 9.17%</td>
<td></td>
</tr>
<tr>
<td>95% CI&lt;sup&gt;6&lt;/sup&gt;</td>
<td>&lt;0.0001 / &lt;0.0001</td>
<td>26.53%/ 60.37%</td>
<td>26.53%/ 60.37%</td>
<td>26.53%/ 60.37%</td>
<td>26.53%/ 60.37%</td>
<td></td>
</tr>
</tbody>
</table>

1 Visit 2: Day 4 ± 1 day for Study 373 and Day 5 ± 1 day for Studies 433 and 434.
2 Missing or discontinued subjects imputed as failures.
3 Clinical resolution is defined as the absence of ocular discharge and bulbar conjunctival injection.
4 Microbial eradication was defined as the absence of all accepted ocular bacterial species that were present at or above threshold at baseline.
5 p-values from Cochran Mantel Haenszel (CMH) test stratified by center/exact Pearson chi-squared test, respectively.
6 95% CI = 95% Confidence Interval.

Table 5 presents the results for microbial eradication against the most common conjunctival pathogens across clinical trials at Visit 2 using the Per Protocol (PP) Population.

Table 5: Besifloxacin Microbial Eradication<sup>1</sup> Results Across Safety and Efficacy Studies at Visit 2<sup>2</sup> (PP Population<sup>3</sup>)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Study 433</th>
<th>Study 373</th>
<th>Study 434</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC coryneform group G</td>
<td>6/6 (100.0%)</td>
<td>1/1 (100.0%)</td>
<td>3/3 (100.0%)</td>
<td>10/10 (100.0%)</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>37/41 (90.2%)</td>
<td>15/17 (88.2%)</td>
<td>45/45 (100.0%)</td>
<td>97/103 (94.2%)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>18/19 (94.7%)</td>
<td>6/8 (75.0%)</td>
<td>31/33 (93.9%)</td>
<td>55/60 (91.7%)</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>13/13 (100.0%)</td>
<td>3/3 (100.0%)</td>
<td>18/19 (94.7%)</td>
<td>34/35 (97.1%)</td>
</tr>
<tr>
<td>Streptococcus mitis</td>
<td>3/5 (60.0%)</td>
<td>1/1 (100.0%)</td>
<td>2/2 (100.0%)</td>
<td>6/8 (75.0%)&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Streptococcus oralis</td>
<td>2/2 (100.0%)</td>
<td>2/2 (100.0%)</td>
<td>4/4 (100.0%)</td>
<td>8/8 (100.0%)</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>52/58 (89.7%)</td>
<td>15/16 (93.8%)</td>
<td>35/35 (100.0%)</td>
<td>102/109 (93.6%)</td>
</tr>
</tbody>
</table>

1 Microbiologic eradication does not always correlate with clinical outcome in anti-infective trials.
Visit 2: Day 4 ± 1 day for Study 373 and Day 5 ± 1 day for Studies 433 and 434.

The Per Protocol (PP) population includes subjects who were randomized to treatment and received at least 1 drop of study medication, and who had baseline cultures in at least 1 eye indicating bacteria levels at or above threshold for any accepted ocular species, and who completed the study with no major protocol violations noted.

Microbiological eradication was 8/8 (100.0%) at Visit 3 (Day 8 ± 1 day).

DETAILED PHARMACOLOGY

Animal Pharmacology

Pharmacodynamics

Safety pharmacology

Safety pharmacology studies evaluating the effects of besifloxacin on the cardiovascular and respiratory systems and renal function were conducted. The NOAEL for an increase in ECG QT interval duration was 10 mg/kg after a single oral dose in dogs. In vitro cardiovascular testing showed that $10^{-5}$ M (~ 4 μg/mL) of besifloxacin was necessary to induce a very slight in vitro HERG current inhibition. Besifloxacin induced no respiratory parameter abnormalities following single oral administration to rats at dose levels up to 1000 mg/kg. Besifloxacin showed slight anti-diuretic and kaliuretic effects at single oral doses above 100 mg/kg in rats. The effects observed in the safety pharmacology program were observed at doses at least 300 times the intended human daily dose (30 μg/kg).

Pharmacokinetics

In vitro studies

Plasma protein binding and distribution into red blood cells of radiolabeled besifloxacin was investigated in vitro in rat and human blood. The binding of besifloxacin to plasma proteins was independent of besifloxacin concentration in rat and human plasma, with estimates of 30-33% and 39-44% bound in rats and humans, respectively. The relative distribution of besifloxacin into red blood cells was 48-49% in rat blood and 48-51% in human blood.

Besifloxacin was metabolically stable in all of the species tested, with only dog hepatocytes showing a measurable decrease of (+)besifloxacin concentrations by 16% after 2 h of incubation. All of the metabolites observed in incubations of human hepatocytes were also observed in mouse, rat, rabbit, and/or dog incubations, indicating that no unique human metabolites were observed.

In Vivo studies

Absorption:

The systemic PK of besifloxacin in plasma was evaluated in rats following a single oral administration at dose levels of 20, 100, and 1000 mg/kg. Besifloxacin was rapidly absorbed following a single oral administration with maximal concentrations in plasma of approximately 1700, 6700, and 21000 ng/mL, respectively, observed within 2 h after dosing. Systemic exposure to besifloxacin, based on Cmax and AUC estimates, was dose-proportional for the 20- and 100-mg/kg dose groups, with a less-than proportional increase observed in the 1000-mg/kg dose group.
Distribution:
Following a single instillation of [14C]besifloxacin ophthalmic suspension to pigmented rabbits, radioactivity was rapidly absorbed and detected in all ocular structures of the treated eyes at all timepoints, up to 16 h after instillation. Maximum concentrations were observed in most of the ocular tissues within 0.5-2 h. The mean maximal amount of radioactivity was found in bulbar and palpebral conjunctivae (Cmax = 15.9 μg-Eq/g), followed by extraocular muscles (Cmax = 9.29 μg-Eq/g), cornea (Cmax = 6.57 μg-Eq/g), and sclera (Cmax = 3.89 μg-Eq/g). For non-ocular tissues, measurable levels of radioactivity were observed in all of the tissues collected, with the highest levels of radioactivity observed in urinary bladder (Cmax = 0.044 μg-Eq/g), ileum (Cmax = 0.021 μg-Eq/g), jejunum (Cmax = 0.021 μg-Eq/g), duodenum (Cmax = 0.020 μg-Eq/g), and kidney (Cmax = 0.020 μg-Eq/g). Concentration versus time profiles for these tissues are shown in Figure 1.

Figure 1 Levels of total radioactivity in tissues measured following topical ocular administration of [14C]besifloxacin to pigmented rabbits

Following repeated topical administration of besifloxacin (BID and TID for 4 days) to pigmented rabbits, ocular and systemic exposure to besifloxacin was similar following the last daily dose on day 1 and day 4. Repeated (QID) administration of [14C]besifloxacin was associated with low systemic exposure (Cmax <0.025 μg/g in all non-excretory organs), though exposure in most tissues was higher following QID dosing compared with a single administration.

The effect of DuraSite on the penetration of besifloxacin into the cornea was assessed following a single instillation of 0.6% besifloxacin, either in the DuraSite vehicle or in a DuraSite-free formulation, in rabbits. At predetermined time intervals from 0.25-4 h after dosing, cornea samples were collected for the purpose of determining besifloxacin levels. The DuraSite formulation was associated with higher besifloxacin concentrations in the cornea compared with the DuraSite-free formulation. Besifloxacin exposure was 3.7-fold (based on AUC) and 8.4-fold.
Metabolism:
The *in vivo* metabolism of besifloxacin was evaluated following oral administration of \([^{14}C]\)besifloxacin to rats at a dose level of 40 mg (11.1 MBq)/kg. In plasma, urine, and feces, unchanged besifloxacin accounted for the majority of radioactivity in each sample. In plasma samples, three metabolites were observed and each accounted for <10% of the total radioactivity. In urine, a single metabolite was observed, which accounted for <6% of the total radioactivity in each sample. In feces, a single metabolite was observed, which accounted for <3% of total radioactivity in each sample.

Excretion:
Results from ocular and systemic PK studies suggest that besifloxacin is excreted via multiple routes of elimination. Following oral administration of \([^{14}C]\)besifloxacin to rats, 96% of the radioactive dose was recovered within 120 h after dosing, with more than 80% of the dose excreted within 24 h after dosing. About 73% of the administered dose was recovered in feces, and 23% of the dose was recovered in the urine. Following single or repeated topical ocular administration of \([^{14}C]\)besifloxacin, the highest levels of radioactivity in non ocular tissues were observed in excretory organs, including the gastrointestinal tract, kidney, and urinary bladder, consistent with the presence of multiple routes of excretion following ocular administration.

**MICROBIOLOGY**
Besifloxacin is a synthetic fluoroquinolone antibacterial agent active in vitro against a broad spectrum of Gram-positive and Gram-negative pathogens.

**Mechanism of Action**
The antibacterial action of besifloxacin is 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.

**Development of Resistance**
*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*.

**Cross-Resistance**
*In vitro* studies demonstrated cross-resistance between besifloxacin and some fluoroquinolones.
Spectrum of Activity
Besifloxacin has been shown to be active against most isolates of the following microorganisms (Table 6), both in vitro and in conjunctival infections treated in clinical trials, as described in the INDICATIONS AND CLINICAL USE section.

Table 6:  In vitro Activities of Besifloxacin Against Organisms For Which Besifloxacin Has Demonstrated Efficacy in Clinical Trials

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>N</th>
<th>MIC Range µg/mL</th>
<th>MIC50 µg/mL</th>
<th>MIC90 µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobic, Gram-Positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDC coryneform group G</td>
<td>29</td>
<td>0.008-2</td>
<td>0.015</td>
<td>0.125</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>190</td>
<td>0.008-8</td>
<td>0.03</td>
<td>0.5</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>111</td>
<td>0.03-4</td>
<td>0.06</td>
<td>0.5</td>
</tr>
<tr>
<td>Streptococcus mitis</td>
<td>20</td>
<td>0.06-0.25</td>
<td>0.125</td>
<td>0.125</td>
</tr>
<tr>
<td>Streptococcus oralis</td>
<td>18</td>
<td>0.015-0.25</td>
<td>0.125</td>
<td>0.25</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>302</td>
<td>0.03-0.25</td>
<td>0.06</td>
<td>0.125</td>
</tr>
<tr>
<td>Aerobic, Gram-Negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>344</td>
<td>0.008-0.5</td>
<td>0.03</td>
<td>0.06</td>
</tr>
</tbody>
</table>

The besifloxacin MIC values presented in this table are from all baseline (Visit 1) isolates for each corresponding species from besifloxacin clinical trials, regardless of treatment group.

The following in vitro data (Table 7) are also available, but their clinical significance in ophthalmic infections is unknown. The safety and effectiveness of BESIVANCE<sup>TM</sup> in treating ophthalmic infections due to these organisms have not been established in adequate and well-controlled trials. The following organisms are considered susceptible when evaluated using a 2 µg/mL threshold, the systemic breakpoint of other fluoroquinolones indicated for bacterial conjunctivitis. However, a correlation between in vitro systemic breakpoints and ophthalmic efficacy has not been established. The list of organisms (Table 7) is provided as guidance only in assessing the potential treatment of conjunctival infections.

Table 7: In vitro Activities of Besifloxacin Against Clinical Isolates For Which Clinical Efficacy of Besifloxacin Has Not Been Tested

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>N</th>
<th>MIC Range µg/mL</th>
<th>MIC50 µg/mL</th>
<th>MIC90 µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobic, Gram-Positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus haemolyticus</td>
<td>101</td>
<td>0.015-4</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Staphylococcus hominis</td>
<td>50</td>
<td>0.015-2</td>
<td>0.25</td>
<td>1</td>
</tr>
<tr>
<td>Staphylococcus lugdunensis</td>
<td>15</td>
<td>0.015-2</td>
<td>0.06</td>
<td>0.5</td>
</tr>
<tr>
<td>Staphylococcus saprophyticus</td>
<td>101</td>
<td>0.015 – 0.25</td>
<td>0.06</td>
<td>0.12</td>
</tr>
<tr>
<td>Staphylococcus warneri</td>
<td>50</td>
<td>0.015 - 2</td>
<td>0.06</td>
<td>1</td>
</tr>
<tr>
<td>Streptococcus agalactiae</td>
<td>100</td>
<td>0.03 – 0.12</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>Streptococcus Group C, F, G</td>
<td>50</td>
<td>0.015 – 0.25</td>
<td>0.03</td>
<td>0.06</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>101</td>
<td>0.03 – 0.06</td>
<td>0.03</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>viridans streptococci</td>
<td>156</td>
<td>0.015 – 2</td>
<td>0.06</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Aerobic, Gram-Negative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Citrobacter koseri</em></td>
<td>100</td>
<td>0.03 - &gt;8</td>
<td>0.06</td>
<td>0.25</td>
</tr>
<tr>
<td><em>Klebsiella oxytoca</em></td>
<td>50</td>
<td>0.06 - 8</td>
<td>0.12</td>
<td>1</td>
</tr>
<tr>
<td><em>Legionella pneumophilia</em></td>
<td>50</td>
<td>0.015 – 0.06</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>101</td>
<td>0.015 – 0.12</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td>103</td>
<td>0.004 - 2</td>
<td>0.015</td>
<td>0.015</td>
</tr>
<tr>
<td><strong>Anaerobic, Gram-Positive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Clostridium perfringens</em></td>
<td>21</td>
<td>0.12 – 0.25</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td><em>Propionibacterium acnes</em></td>
<td>21</td>
<td>0.12 – 0.25</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Anaerobic, Gram-Negative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Bacteroides fragilis</em></td>
<td>20</td>
<td>0.25 - 2</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td><em>Fusobacterium species</em></td>
<td>21</td>
<td>0.12 – 8</td>
<td>0.25</td>
<td>1</td>
</tr>
</tbody>
</table>

**Susceptibility Tests:** There are currently no CLSI (Clinical Laboratory Standards Institute) approved standards for assessing *in vitro* susceptibility of conjunctival isolates to topical antibiotics, including besifloxacin. Standardized systemic susceptibility tests may not be appropriate to predict clinical effectiveness in treating conjunctivitis.
TOXICOLOGY

Tabular summaries of the key toxicology studies can be found in Tables 8-12.

Along with other excipients, Besifloxacin ophthalmic suspension contains poloxamer 407 (0.1%) used in ophthalmic solutions as a non-ionic surfactant and benzalkonium chloride (BAC, 0.01%), a commonly used preservative in ophthalmic products.

Studies on the ocular toxicity of poloxamer 407 in rabbits demonstrated that when poloxamer 407 concentrations ranging from 15% to 20% were applied on the cornea, in the anterior chamber, and within the vitreous, no untoward reactions to the material were found. However, when the vitreous was totally replaced by 20% poloxamer 407, significant retinal effects were observed suggesting that poloxamer 407 is safe for topical use, but not as a vitreous substitute after total vitrectomy. While BAC has shown cytotoxicity potential in some in vitro systems, no adverse ocular effects have been seen in human or animal species following administration of the besifloxacin formulation containing 0.01% BAC.

Carcinogenicity

Long-term studies in animals to determine the carcinogenic potential of besifloxacin have not been performed.

Table 8. Repeat Dose Oral Toxicity

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Species/Strain/Sex/No per group</th>
<th>Route/Duration</th>
<th>Doses</th>
<th>Key Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-dose/7-day repeated dose intravenous injection/oral gavage toxicity and toxicokinetic study</td>
<td>Rat/Sprague-Dawley IV: 1-2/sex Oral single dose: 1/sex Oral 7d: 5/sex</td>
<td>IV then oral Single dose then up to 7d (oral)</td>
<td>5 to 400 mg/kg, IV then 40 to 2000 mg/kg/d, oral</td>
<td>IV: Death at 200 and 400 mg/kg attributed to large volume injected Oral NOAEL: 100mg/kg BID (avg Cmax at NOAEL = 3430 ng/mL) Oral: BW loss; BW gain decrease; food consumption decrease; bone marrow decreased proportion of lymphoid cells and increased proportion of granulocytic cells; femoral and humeral bone marrow depletion; for both males and females Cmax and AUC increased with increasing doses with no obvious differences between Day 1 and 7 Safety margin = 8575-fold when NOAEL Cmax compared to avg plasma levels in humans</td>
</tr>
<tr>
<td>Study Type</td>
<td>Species/Strain/Sex/No per group</td>
<td>Route/Duration</td>
<td>Doses</td>
<td>Key Results</td>
</tr>
<tr>
<td>------------</td>
<td>--------------------------------</td>
<td>----------------</td>
<td>-------</td>
<td>-------------</td>
</tr>
<tr>
<td>Escalating dose range-finding toxicokinetic study</td>
<td>Dog/Beagle 4d: 2/sex 14d: 1/sex</td>
<td>IV and oral 4d (dose-escalation) then up to 14d</td>
<td>5 to 50 mg/kg/d for 4d + 3d washout, IV (dose escalation) then 1 to 1000 mg/kg/d for 4d + 3d washout, oral (dose escalation) then 100 mg/kg/d for 14d</td>
<td>Oral MTD: 1000 mg/kg/d  No NOAEL  IV/Oral: Decreased activity; emesis; soft feces; skin discoloration; tremors  Oral only: increased salivation; lacrimation; panting; slow breathing; increased urine specific gravity, protein, glucose and bilirubin concentration; occult blood</td>
</tr>
<tr>
<td>28-day oral gavage toxicity study</td>
<td>Rat/Sprague-Dawley 10/sex (control group) 19/sex (drug-treated groups - includes satellite animals)</td>
<td>Oral 4wk</td>
<td>10, 100, and 500 mg/kg/d</td>
<td>NOAEL: 500 mg/kg/d (avg Cmax at NOAEL = 10670 ng/mL)  Decreased urinary pH and increased urinary proteins in males; absolute and relative heart weights decrease in males; Tmax at 0.5-1 h, dose-proportional Cmax and AUC for 100- and 500-mg/kg groups with greater-than proportional Cmax and AUC in 10-mg/kg group and no consistent gender differences  Safety margin = 26675-fold when NOAEL Cmax compared to avg plasma levels in humans†</td>
</tr>
<tr>
<td>28-day oral gavage toxicity study followed by a 2-week recovery</td>
<td>Dog/Beagle 6/sex/group</td>
<td>Oral 4wk</td>
<td>0.5, 5, and 50 mg/kg/d</td>
<td>NOAEL: 5 mg/kg/d (avg Cmax at NOAEL = 1145 ng/mL)  Emesis; increased salivation; transient facial swelling; transient pupillary dilation; Tmax between 0.5 and 1h; dose proportionality, no accumulation, and no gender difference for plasma AUCs  Safety margin = 2863-fold when NOAEL Cmax compared to avg plasma levels in humans†</td>
</tr>
</tbody>
</table>

† Systemic exposure after topical ocular instillation in humans = Cmax: 0.4 ng/mL
Table 9. Repeat Dose Ocular Toxicity

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Species/Strain/Sex/No per group</th>
<th>Route/Duration</th>
<th>Doses</th>
<th>Key Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular tolerance</td>
<td>Rabbit/Fauve de Bourgogne 5/sex/group</td>
<td>Ocular (topical) 4wk (+ 1wk reverse period)</td>
<td>0.6% besifloxacin QID</td>
<td>No noteworthy findings attributable to the API; few minor findings (late conjunctival enanthema and chemosis) attributable to formulation viscosity. The mean plasma concentration (M+F) 30 min after the 3rd instillation on Day 1 is ~1.22 ng/mL and 3.87 ng/mL at Day 28. Safety margin = 9.7-fold when NOAEL Cmax compared to avg plasma levels in humans.</td>
</tr>
<tr>
<td></td>
<td>Dog/Beagle 3/sex/group</td>
<td>Ocular (topical) 4wk</td>
<td>0.6% besifloxacin QID</td>
<td>No noteworthy findings. On day 0, mean Cmax for females was 6.7 ng/mL. In week 4, mean Cmax values for males and females were 12.2 and 10.1 ng/mL, respectively. Safety margin = 28-fold when NOAEL Cmax compared to avg plasma levels in humans.</td>
</tr>
</tbody>
</table>

* Systemic exposure after topical ocular instillation in humans = Cmax: 0.4 ng/mL.

Table 10. Local Tolerance

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Species/Strain/Sex/No per group</th>
<th>Route/Duration</th>
<th>Doses</th>
<th>Key Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photoirritation study</td>
<td>Mouse /BALB/c 6F/dose</td>
<td>Oral</td>
<td>100, 200, 400, and 800 mg/kg (+UVA)</td>
<td>Ear erythema and edema at ≥100 mg/kg</td>
</tr>
<tr>
<td>Photoirritation study</td>
<td>Guinea pig/Hartley 6F/dose</td>
<td>Topical</td>
<td>0.3% and 1% besifloxacin (+ UV)</td>
<td>No noteworthy findings</td>
</tr>
<tr>
<td>Photosensitization study</td>
<td>Guinea pigs/Dunkin Hartley 40M</td>
<td>Topical</td>
<td>0.6% besifloxacin QID (sensitization); QD (challenge) + UVA/B</td>
<td>No noteworthy findings (no photoallergenic, allergenic, photoirritant, irritant potentials)</td>
</tr>
</tbody>
</table>

F= female; M= male
### Table 11. Reproductive and Development Toxicity

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Species/Strain/Sex/No per group</th>
<th>Route/Duration</th>
<th>Doses</th>
<th>Key Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fertility and early embryonic development study</td>
<td>Rats/Sprague-Dawley 25/sex/dose</td>
<td>From 28d prior pairing to euthanasia (M), and from 14d prior pairing through GD7 (F)</td>
<td>20, 100, and 500 mg/kg</td>
<td>Increased salivation, red or brown material around the mouth or nose, soft feces and/or abnormal breathing, decrease BW (M) at high dose NOAEL (parental toxicity): 100 mg/kg NOAEL (reproductive toxicity): 500 mg/kg</td>
</tr>
<tr>
<td>Dose-range finding embryo-fetal development study</td>
<td>Rats/Sprague-Dawley 5F/dose</td>
<td>Oral From GD6 through GD17</td>
<td>30, 100, 300 and 1000 mg/kg</td>
<td>Increased salivation, decreased BW and food intake, decreased gravid uterine weight at high dose</td>
</tr>
<tr>
<td>Dose-range finding embryo-fetal development study</td>
<td>Rabbit/NZW 5F/dose</td>
<td>Oral From GD6 through GD18</td>
<td>10, 30, 100, 300, and 1000 mg/kg</td>
<td>Mortality and premature deliveries at ≥10 mg/kg; Few litter resorptions at 300 mg/kg; Soft/scant to absent feces, red material under the cage or discolored anogenital area at ≥10 mg/kg; decreased BW at ≥300 mg/kg; decreased food intake at ≥30 mg/kg</td>
</tr>
<tr>
<td>Embryo-fetal development study</td>
<td>Rat/Sprague-Dawley 25F/dose</td>
<td>From GD6 through GD17</td>
<td>10, 100, and 1000 mg/kg</td>
<td>Mortality, increased salivation, discolored material around the mouth or nose, sparse amount of ventral hair, decreased BW and food intake, decreased gravid uterine weight, increased resorptions and postimplantation loss, reduced fetal BW, delay in fetal ossification at high dose NOAEL (maternal and reproductive toxicity): 100 mg/kg (Cmax at NOAEL = 5100 ng/mL) Safety margin = 12750-fold when NOAEL Cmax compared to avg plasma levels in humans¹</td>
</tr>
<tr>
<td>Study Type</td>
<td>Species/Strain/Sex/No per group</td>
<td>Route/Duration</td>
<td>Doses</td>
<td>Key Results</td>
</tr>
<tr>
<td>------------------------------------</td>
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<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Embryo-fetal development study</td>
<td>Rabbit/NZW 23F/dose</td>
<td>From GD6 through GD18</td>
<td>0.2, 2, and 20 mg/kg</td>
<td>Reduced fecal output and red material under the cage, decreased BW and food intake, aborted and early deliveries, decreased gravid uterine weight and increased resorptions and post-implantation loss, reduced fetal BW at 20 mg/kg. NOAEL (maternal and reproductive toxicity): 2 mg/kg (Cmax at NOAEL = 110 ng/mL). Safety margin&gt; 275-fold when NOAEL Cmax compared to avg plasma levels in humans.</td>
</tr>
<tr>
<td>Prenatal and postnatal development study</td>
<td>Rat/Sprague-Dawley 25F/dose</td>
<td>From GD6 through lactation D20</td>
<td>10, 100, and 1000 mg/kg</td>
<td>Increased salivation, increased gestation time, litter size reduction, increased number of stillborn pups, pup survival decrease with developmental retardation, and F1 delayed sexual maturation at the high dose; decreased F0 BW and food intake at 100+ mg/kg (F). NOAEL (parental toxicity): 10 mg/kg. NOAEL (repro toxicity): 100 mg/kg.</td>
</tr>
</tbody>
</table>

GD = Gestation Day; F= female; M= male

1 Systemic exposure after topical ocular instillation in humans = Cmax: 0.4 ng/mL

Table 12. Genotoxicity

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Species/Strain/Sex/No per group</th>
<th>Route/Duration</th>
<th>Doses</th>
<th>Key Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ames test mutation assay with a confirmatory assay</td>
<td>Salmonella typhimurium: TA98, TA 100, TA 1535 and TA 1537 Escherichia coli: WP2uvrA</td>
<td>In vitro NA</td>
<td>0.00333 to 1 µg/plate for S. typhimurium and 0.01 to 3.33 µg/plate for E. coli</td>
<td>No increase in revertants in presence or in absence of S9 mix at any dose. No mutagenic potential.</td>
</tr>
<tr>
<td>Ames test mutation assay in the presence of solar-simulated light</td>
<td>Salmonella typhimurium: TA 102, TA 1537 Escherichia coli: WP2(pKM101)</td>
<td>In vitro NA</td>
<td>0.01 to 100 µg/plate for TA 102 and E coli and 0.001 to 3.33 µg/plate for TA 1537</td>
<td>No increase in revertants with TA 1537. Significant revertant increase with WP2(pK101) at 0.333 µg/plate and with TA 102 at 1 µg/plate in absence or in presence of light (no light dose relationship; positive.</td>
</tr>
<tr>
<td>Study Type</td>
<td>Species/Strain/Sex/No per group</td>
<td>Route/Duration</td>
<td>Doses</td>
<td>Key Results</td>
</tr>
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<tr>
<td>Chromosomal aberration assay</td>
<td>Chinese Hamster Ovary cells</td>
<td>In vitro</td>
<td>6.25 to 3470 µg/mL (w/o S9)</td>
<td>Increase in chromosome aberrations with and without metabolic activation NOEL: 50 µg/mL or 25 µg/mL after 3h or 20h, respectively</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 and 20h</td>
<td>72.2 to 405 µg/mL (w/ S9)</td>
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</tr>
<tr>
<td>Micronucleus test (racemate)</td>
<td>Mouse/ICR 3M/group</td>
<td>IP Single dose (with a 24h follow up)</td>
<td>125, 250, and 500 mg/kg</td>
<td>No noteworthy findings No clastogenic potential</td>
</tr>
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<tr>
<td>Micronucleus test</td>
<td>Mouse /CD-1 6M/group</td>
<td>Oral Single dose (with 24 and 48h follow up)</td>
<td>250, 500, 1000, 1500, and 2000 mg/kg</td>
<td>Micronuclei in the bone marrow PCEs at doses greater or equal to 1500 mg/kg; High level of cytotoxicity at 2000 mg/kg; NOAEL: 1000 mg/kg which was associated with a besifloxacin plasma concentration of 3.99 µg/mL</td>
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<tr>
<td>In vivo/in vitro Unscheduled DNA Synthesis assay</td>
<td>Rat/Fischer 4M/group</td>
<td>Oral Single dose (with a 16h follow up)</td>
<td>500, 1000, and 2000 mg/kg</td>
<td>No noteworthy findings</td>
</tr>
</tbody>
</table>

F= female; M= male; PCE= Polychromatic erythrocyte

**REFERENCES**


IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

PrBESIVANCE™
Besifloxacin ophthalmic suspension, 0.6% w/v

This leaflet is part III of a three-part “Product Monograph” published when BESIVANCE™ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about BESIVANCE™. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
BESIVANCE™ is an eye drop that is used to treat bacterial conjunctivitis (a type of eye infection). Antibacterial drugs like BESIVANCE™ treat only bacterial infections. They do not treat viral infections such as the common cold. Although you may feel better early in treatment, BESIVANCE™ should be used exactly as directed. Misuse or overuse of BESIVANCE™ could lead to the growth of bacteria that will not be killed by BESIVANCE™ (resistance). This means that BESIVANCE™ may not work for you in the future. Do not share your medicine.

What it does:
BESIVANCE™ kills certain bacteria (“germs”) that cause infection of the eye.

When it should not be used:
BESIVANCE™ should not be used if you are allergic to besifloxacin, other quinolones or any of the ingredients in this drug (See What the nonmedicinal ingredients are).

What the medicinal ingredient is:
BESIVANCE™ contains besifloxacin which belongs to a group of medicines called fluoroquinolones.

What the nonmedicinal ingredients are:
Benzalkonium chloride, edetate disodium dihydrate, mannitol, poloxamer 407, polycarbophil, sodium chloride, sodium hydroxide, and water for injection.

What dosage forms it comes in:
BESIVANCE™ is a sterile ophthalmic suspension (a liquid). It is supplied in a bottle with a dropper tip and cap. The bottle contains 5 mL of BESIVANCE™ suspension.

WARNINGS AND PRECAUTIONS

BEFORE you use BESIVANCE™, talk to your doctor or pharmacist if:
- You wear contact lenses. You should not wear contact lenses if you have bacterial conjunctivitis or if you are using BESIVANCE™
  - You are pregnant or plan on becoming pregnant
  - You are breastfeeding or planning to breastfeed
  - You are allergic to any medications

INTERACTIONS WITH THIS MEDICATION

Drug interactions were not studied with this drug and are not expected.

PROPER USE OF THIS MEDICATION

Before using BESIVANCE™, thoroughly wash hands.

Take care to avoid contaminating the applicator tip with material from the eye, fingers or other sources.

Invert closed bottle (turn 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).

Usual dose:
Instill one drop in the affected eye(s) 3 times a day for 7 days.

Although it is common to feel better early in the course of the therapy, this 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
2. Increase the likelihood that bacteria will develop resistance and will not be treatable by BESIVANCE™ or any other antibacterial drugs in the future.

Overdose:
No information is available on overdosage of BESIVANCE™. A topical overdose of BESIVANCE™ may be flushed from the eye(s) with warm tap water

In case of accidental oral ingestion, contact your doctor, hospital emergency department, or regional poison control centre.

Missed Dose:
If a dose of this medication has been missed, it should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM
Discontinue use immediately and contact your doctor at the first sign of an allergic reaction, such as symptoms of swollen eyes, face, and throat, difficulty in breathing, rash and itching.

Like all medicines, BESIVANCE™ can have unwanted effects. The most common side effects in patients treated with BESIVANCE™ are:
- Blurred vision
- Discharge from the eyes
- Eye pain
- Itching in the eye
- Eye irritation

This is not a complete list of side effects. For any unexpected effects while taking BESIVANCE™, contact your doctor or pharmacist.

HOW TO STORE IT


You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free to 1-866-234-2345
- Complete Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Bausch & Lomb Incorporated, at:
1-800-686-7720 (English)
1-800-686-0002 (French)

This leaflet was prepared by Bausch & Lomb.

Last revised: February 8, 2018.