PRODUCT MONOGRAPH

Pr**BESIVANCE**TM

Besifloxacin ophthalmic suspension, 0.6% w/v

Antibacterial (ophthalmic)

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

Imported in Canada by:
Valeant Canada LP/S.E.C.
Laval, QC H7L 4A8

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[Pr]BESIVANCE™

besifloxacin ophthalmic suspension, 0.6% w/v

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

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

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: Safety[1])

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

[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

Tissue	Dose Regimen/ Study Day	C_{max}	$t_{½}$ (h)	$AUC_{(0-t)}$
Plasma[1]	0.6% TID Day 1	0.37 ± 0.27 ng/mL	4.3 ± 2.2	$AUC_{(0-6)}$ 1.45 ± 0.87 ng*h/mL
	0.6% TID Day 6[2]	0.43 ± 0.30 ng/mL	6.8 ± 2.1	$AUC_{(0-6)}$ 1.95 ± 1.31 ng*h/mL $AUC_{(0-12)}$ 3.21 ± 2.50 ng*h/mL
Tears[3]	0.6% Single Dose Day 1	610 ± 540 µg/g	3.4	$AUC_{(0-24)}$ 1232 µg*h/g

[1] Data from human subjects with clinically diagnosed bilateral bacterial conjunctivitis.
[2] Subjects received 3 doses per day for 5 days and a single dose on Day 6 (16 doses total).
[3] 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

Store at 15°- 25°C (59° - 77°F). Protect from light.

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

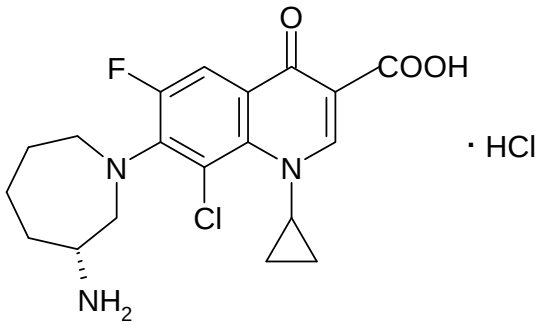
Common name: besifloxacin hydrochloride

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

Molecular formula: $C_{19}H_{21}ClFN_3O_3 \bullet HCl$

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

Structural formula:



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

Study #	Trial design	Efficacy Parameters	Dosage, route of administration and duration	Study subjects mITT[1] (n=number)	Mean age (Range)	Gender (%M/F)
BL-433 US	Multicenter, randomized, parallel-group, double masked, placebo (vehicle) controlled	Clinical Resolution and Microbial Eradication in mITT[1] Day 5 ±1 day	Topical Ocular 0.6% besifloxacin suspension (5 days, TID)[2] versus Topical Ocular vehicle (5 days, TID)	198 191	22.2 (1-98) 24.4 (1-87)	37.9/62.1 40.8/59.2
Others						
BL-373 US	Multicenter, randomized, parallel-group, double masked, placebo (vehicle) controlled	Clinical Resolution and Microbial Eradication in ITT[3] Day 4 ±1 day	Topical Ocular 0.6% besifloxacin suspension (5 days, TID) versus Topical Ocular vehicle (5 days, TID)	60 58	28.7 (1-89) 34.7 (1-81)	41.7/58.3 46.6/53.4
BL-434 US Asia	Multicenter, randomized, parallel-group, double masked, active controlled	Clinical Resolution and Microbial Eradication in mITT[1] Day 5 ±1 day	Topical Ocular 0.6% besifloxacin suspension (5 days, TID) versus Topical Ocular moxifloxacin HCl ophthalmic solution 0.5% (5 days, TID)	255 278	31.2 (1-92) 38.7 (0[4]-100)	43.5/56.5 49.3/50.7

[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[1] (mITT Population)

	BL-433		BL-373		BL-434	
Outcome[2]	**Besifloxacin (N=198) n (%)**	**Vehicle (N=191) n (%)**	**Besifloxacin (N=60) n (%)**	**Vehicle (N=58) n (%)**	**Besifloxacin (N=255) n (%)**	**Comparator (N=278) n (%)**
Clinical Resolution (%)[3]	90 (45.5)	63 (33.0)	20 (33.3)	10 (17.2)	149 (58.4)	165 (59.4)
p-value[5] 95% CI[6]	0.0084 / 0.0129 2.73%/ 22.21%		0.0691/ 0.0574 0.21%/ 31.97%		0.6838/ 0.8603 -9.30%/ 7.46%	
Microbial Eradication (%)[4]	181 (91.4)	114 (59.7)	54 (90.0)	27 (46.6)	241 (94.5)	250 (89.9)
p-value[5] 95% CI[6]	<0.0001 / <0.0001 23.19%/ 40.26%		<0.0001 / <0.0001 26.53%/ 60.37%		0.0183/0.0544 -0.01%/ 9.17%	

[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[1] Results Across Safety and Efficacy Studies at Visit 2[2] (PP Population[3])

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

[1] Microbiologic eradication does not always correlate with clinical outcome in anti-infective trials.

[2] Visit 2: Day 4 ± 1 day for Study 373 and Day 5 ± 1 day for Studies 433 and 434.
[3] 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.
[4] 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.

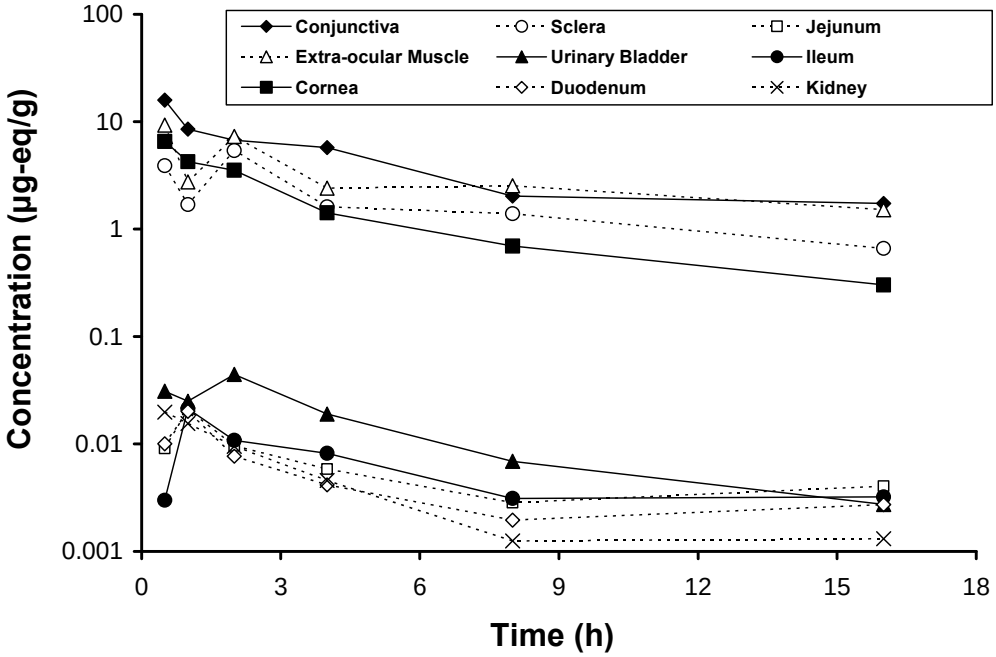
***In Vivo* studies**

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 [^{14}C]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 [^{14}C]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 [^{14}C]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

(based on Cmax) higher in the DuraSite formulation group.

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[1]

Pathogen	N	MIC Range µg/mL	MIC_{50} µg/mL	MIC_{90} µg/mL
Aerobic, Gram-Positive				
CDC coryneform group G	29	0.008-2	0.015	0.125
Staphylococcus aureus	190	0.008-8	0.03	0.5
Staphylococcus epidermidis	111	0.03-4	0.06	0.5
Streptococcus mitis	20	0.06-0.25	0.125	0.125
Streptococcus oralis	18	0.015-0.25	0.125	0.25
Streptococcus pneumoniae	302	0.03-0.25	0.06	0.125
Aerobic, Gram-Negative				
Haemophilus influenzae	344	0.008-0.5	0.03	0.06

[1] 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**™ 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

Pathogen	N	MIC Range µg/mL	MIC_{50} µg/mL	MIC_{90} µg/mL
Aerobic, Gram-Positive				
Staphylococcus haemolyticus	101	0.015 -4	0.5	1
Staphylococcus hominis	50	0.015 - 2	0.25	1
Staphylococcus lugdunensis	15	0.015-2	0.06	0.5
Staphylococcus saprophyticus	101	0.015 – 0.25	0.06	0.12
Staphylococcus warneri	50	0.015 - 2	0.06	1
Streptococcus agalactiae	100	0.03 – 0.12	0.06	0.06
Streptococcus Group C, F, G	50	0.015 – 0.25	0.03	0.06
Streptococcus pyogenes	101	0.03 – 0.06	0.03	0.06

viridans streptococci	156	0.015 – 2	0.06	0.12
Aerobic, Gram-Negative				
Citrobacter koseri	100	0.03 - >8	0.06	0.25
Klebsiella oxytoca	50	0.06 - 8	0.12	1
Legionella pneumophilia	50	0.015 – 0.06	0.03	0.03
Moraxella catarrhalis	101	0.015 – 0.12	0.03	0.03
Neisseria gonorrhoeae	103	0.004 - 2	0.015	0.015
Anaerobic, Gram-Positive				
Clostridium perfringens	21	0.12 – 0.25	0.25	0.25
Propionibacterium acnes	21	0.12 – 0.25	0.25	0.25
Anaerobic, Gram-Negative				
Bacteroides fragilis	20	0.25 - 2	0.5	1
Fusobacterium species	21	0.12 – 8	0.25	1

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

Study Type	Species/Strain/Sex/No per group	Route/Duration	Doses	Key Results
Single-dose/7-day repeated dose intravenous injection/oral gavage toxicity and toxicokinetic study	Rat/Sprague-Dawley IV: 1-2/sex Oral single dose: 1/sex Oral 7d: 5/sex	IV then oral Single dose then up to 7d (oral)	5 to 400 mg/kg, IV then 40 to 2000 mg/kg/d, oral	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[1]

Study Type	Species/Strain/Sex/No per group	Route/Duration	Doses	Key Results
Escalating dose range-finding toxicokinetic study	Dog/Beagle 4d: 2/sex 14d: 1/sex	IV and oral 4d (dose-escalation) then up to 14d	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	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
28-day oral gavage toxicity study	Rat/Sprague-Dawley 10/sex (control group) 19/sex (drug-treated groups - includes satellite animals)	Oral 4wk	10, 100, and 500 mg/kg/d	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[1]
28-day oral gavage toxicity study followed by a 2-week recovery	Dog/Beagle 6/sex/group	Oral 4wk	0.5, 5, and 50 mg/kg/d	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[1]

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

Table 9. Repeat Dose Ocular Toxicity

Study Type	Species/Strain/Sex/No per group	Route/Duration	Doses	Key Results
Ocular tolerance	Rabbit/Fauve de Bourgogne 5/sex/group	Ocular (topical) 4wk (+ 1wk reverse period)	0.6% besifloxacin QID	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[a]
Ocular tolerance	Dog/Beagle 3/sex/group	Ocular (topical) 4wk	0.6% besifloxacin QID	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[a]

[a] Systemic exposure after topical ocular instillation in humans = Cmax: 0.4 ng/mL

Table 10. Local Tolerance

Study Type	Species/Strain/Sex/No per group	Route/Duration	Doses	Key Results
Photoirritation study	Mouse /BALB/c 6F/dose	Oral Single dose (+ 48h follow up)	100, 200, 400, and 800 mg/kg (+UVA)	Ear erythema and edema at ≥100 mg/kg
Photoirritation study	Guinea pig/Hartley 6F/dose	Topical Single application 30 min+72h follow up	0.3% and 1% besifloxacin (+ UV)	No noteworthy findings
Photosensitization study	Guinea pigs/Dunkin Hartley 40M	Topical 2wk (sensitization) then single dose (challenge)	0.6% besifloxacin QID (sensitization); QD (challenge) + UVA/B	No noteworthy findings (no photoallergenic, allergenic, photoirritant, irritant potentials)

F= female; M= male

Table 11. Reproductive and Development Toxicity

Study Type	Species/Strain/Sex/No per group	Route/Duration	Doses	Key Results
Fertility and early embryonic development study	Rats/Sprague-Dawley 25/sex/dose	From 28d prior pairing to euthanasia (M), and from 14d prior pairing through GD7 (F)	20, 100, and 500 mg/kg	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
Dose-range finding embryo-fetal development study	Rats/Sprague-Dawley 5F/dose	Oral From GD6 through GD17	30, 100, 300 and 1000 mg/kg	Increased salivation, decreased BW and food intake, decreased gravid uterine weight at high dose
Dose-range finding embryo-fetal development study	Rabbit/NZW 5F/dose	Oral From GD6 through GD18	10, 30, 100, 300, and 1000 mg/kg	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
Embryo-fetal development study	Rat/Sprague-Dawley 25F/dose	From GD6 through GD17	10, 100, and 1000 mg/kg	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 humans[1]

Study Type	Species/Strain/Sex/No per group	Route/Duration	Doses	Key Results
Embryo-fetal development study	Rabbit/NZW 23F/dose	From GD6 through GD18	0.2, 2, and 20 mg/kg	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> 275-fold when NOAEL Cmax compared to avg plasma levels in humans[1]
Prenatal and postnatal development study	Rat/Sprague-Dawley 25F/dose	From GD6 through lactation D20	10, 100, and 1000 mg/kg	Increased salivation, increased gestation time, litter size reduction, increased number of stillborn pups, pup survival decrease with developmental retardation, and F_1 delayed sexual maturation at the high dose; decreased F_0 BW and food intake at 100+ mg/kg (F) NOAEL (parental toxicity): 10 mg/kg NOAEL (repro toxicity): 100 mg/kg

GD = Gestation Day; F= female; M= male
[1] Systemic exposure after topical ocular instillation in humans = Cmax: 0.4 ng/mL

Table 12. Genotoxicity

Study Type	Species/Strain/Sex/No per group	Route/Duration	Doses	Key Results
Ames test mutation assay with a confirmatory assay	Salmonella typhimurium: TA98, TA 100, TA 1535 and TA 1537 Escherichia coli: WP2uvrA	*In vitro* NA	0.00333 to 1 µg/plate for S. typhimurium and 0.01 to 3.33 µg/plate for E. coli	No increase in revertants in presence or in absence of S9 mix at any dose No mutagenic potential
Ames test mutation assay in the presence of solar-simulated light	Salmonella typhimurium: TA 102, TA 1537 Escherichia coli: WP2(pKM101)	*In vitro* NA	0.01 to 100 µg/plate for TA 102 and E coli and 0.001 to 3.33 µg/plate for TA 1537	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

Study Type	Species/Strain/Sex/No per group	Route/Duration	Doses	Key Results
				response in presence of light lower than in absence of light)
Chromosomal aberration assay	Chinese Hamster Ovary cells	*In vitro* 3 and 20h	6.25 to 3470 µg/mL (w/o S9) 72.2 to 405 µg/mL (w/ S9)	Increase in chromosome aberrations with and without metabolic activation NOEL: 50 µg/mL or 25 µg/mL after 3h or 20h, respectively
Micronucleus test (racemate)	Mouse/ICR 3M/group	IP Single dose (with a 24h follow up)	125, 250, and 500 mg/kg	No noteworthy findings No clastogenic potential
Micronucleus test	Mouse /CD-1 6M/group	Oral Single dose (with 24 and 48h follow up)	250, 500, 1000, 1500, and 2000 mg/kg	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 ug/mL
In vivo/in vitro Unscheduled DNA Synthesis assay	Rat/Fischer 4M/group	Oral Single dose (with a 16h follow up)	500, 1000, and 2000 mg/kg	No noteworthy findings

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

REFERENCES

1. Karpecki P, DePaolis M, Hunter JA, White E, Rigel L, Brunner LS, et al. Besifloxacin ophthalmic suspension 0.6% in patients with bacterial conjunctivitis: A multicenter, prospective, randomized, double-masked, vehicle-controlled, 5-day efficacy and safety study. Clin Ther 2009 Mar;31(3):514-26.
2. Ward KW, Lepage J-F, Driot J-Y. Nonclinical pharmacodynamics, pharmacokinetics, and safety of BOL-303224-A, a novel fluoroquinolone antimicrobial agent for topical ophthalmic use. J Ocul Pharmacol Ther 2007;23:243-256.

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

[Pr]BESIVANCE™

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, difficultly 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

Store **BESIVANCE™** at 15º - 25ºC (room temperature). Protect from light.

Keep out of reach of children.

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)

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