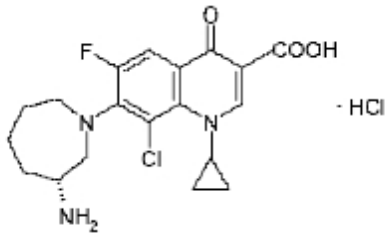
PRODUCT INFORMATION

Besivance® 0.6% eye drops, suspension

Name of the medicine

Name: besifloxacin hydrochloride

Chemical structure:



CAS number: 405165-61-9

Description

Chemical name: (+)-7-[(3R)-3-aminohexahydro1H-azepin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-4oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride.

Empirical formula: $C_{19}H_{21}ClFN_3O_3.HCl$

Molecular weight: 430.30

pKa = 5.65 (carboxylic acid) and pKa = 9.91 (primary amine)
Log $D^{7.0}$ = -0.53.

Besifloxacin hydrochloride is a white to pale yellowish-white powder. It is an 8-chloro fluoroquinolone anti-infective for topical ophthalmic use.

Besivance 0.6% is a sterile ophthalmic suspension of besifloxacin. It is an isotonic suspension with an osmolality of approximately 290 mOsm/kg. Each mL of Besivance contains 6.63 mg besifloxacin hydrochloride equivalent to 6 mg besifloxacin base.

Excipients: benzalkonium chloride 0.01% (preservative), polycarbophil, mannitol, poloxamer, sodium chloride, disodium edetate, sodium hydroxide and water for injection.

Pharmacology

<u>Microbiology</u>

Besifloxacin is an 8-chloro fluoroquinolone with an N-1 cyclopropyl group. The compound has activity against Gram-positive and Gram-negative bacteria due to the inhibition of both bacterial DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme required for replication, transcription and repair of bacterial DNA.

Topoisomerase IV is an essential enzyme required for partitioning of the chromosomal DNA during bacterial cell division. Besifloxacin is bactericidal with minimum bactericidal concentrations (MBCs) generally within one dilution of the minimum inhibitory concentrations (MICs).

The mechanism of action of fluoroquinolones, including besifloxacin, is different from that of aminoglycoside, macrolide, and β-lactam antibiotics. Therefore, besifloxacin may be active against pathogens that are resistant to these antibiotics and these antibiotics may be active against pathogens that are resistant to besifloxacin. In vitro studies demonstrated cross-resistance between besifloxacin and some fluoroquinolones.

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

Besifloxacin has been shown to be active against most isolates of the following bacteria both in vitro and/or in conjunctival infections treated in clinical trials as described below:

CDC coryneform group G
Haemophilus influenzae
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus mitis group
Streptococcus oralis
Streptococcus pneumoniae

Pharmacokinetics

Plasma concentrations of besifloxacin were measured in adult patients with suspected bacterial conjunctivitis who received Besivance bilaterally three times a day (16 doses total). Following the first and last dose, the maximum plasma besifloxacin concentration in each patient was less than 1.3 ng/mL. The mean besifloxacin C_{max} was 0.37 ng/mL on day 1 and 0.43 ng/mL on day 6. The average elimination half-life of besifloxacin in plasma following multiple dosing was estimated to be 7 hours.

Clinical trials

Three independent, adequate and well controlled studies (Studies 373, 433 and 434) were carried out to assess the safety and efficacy of besifloxacin hydrochloride ophthalmic suspension for the treatment of bacterial conjunctivitis. Studies 373 and 433, evaluated the clinical and microbial efficacy of besifloxacin ophthalmic suspension compared to vehicle for the treatment of bacterial conjunctivitis. Study 434 evaluated the clinical and microbial

efficacy of besifloxacin ophthalmic suspension compared to Vigamox® (moxifloxacin HCl ophthalmic solution 0.5% as base) for the treatment of bacterial conjunctivitis.

Study 373

Study 373 was a randomized, double-masked, vehicle-controlled, parallel group clinical trial. Besifloxacin hydrochloride ophthalmic suspension administered 3 times a day (TID) for 5 days compared to vehicle TID for 5 days in the treatment of bacterial conjunctivitis. Adults and children 1 year of age or older required a clinical diagnosis of acute bacterial conjunctivitis exhibiting a minimum protocol defined score of grade 1 for purulent conjunctival discharge (crusty or sticky eyelids) and a minimum score of grade 1 for either bulbar or palpebral conjunctival injection in at least 1 eye to be eligible for entry into the study. If a subject had 2 eyes qualify for the study, the study eye was designated as the eye with the highest combined ocular discharge and redness score at baseline.

The primary efficacy endpoints of the study were clinical resolution and microbial eradication of baseline bacterial infection at Visit 3 (Day 8, + 1 day). For this study, clinical resolution was defined as absence of the following 3 clinical signs; conjunctival discharge, bulbar conjunctival injection and palpebral conjunctival injection. Microbial eradication was defined as the absence of all accepted ocular bacterial species that were present at or above threshold levels at baseline. Secondary efficacy endpoints included clinical resolution and microbial eradication of baseline bacterial infection at Visit 2 (Day 4, ± 1 day); individual clinical outcomes at each follow-up visit for ocular discharge, bulbar and palpebral conjunctival injection, clinical outcome and Investigator's global rating; and microbial and clinical outcome at each follow-up visit for each accepted ocular bacterial species that was present at or above threshold at baseline.

As shown in Table 1, when the last non-missing post-baseline observation was carried forward, 61.7% (37/60) of subjects randomized to besifloxacin ophthalmic suspension experienced clinical resolution (based on 3 clinical signs) compared to 35.7% (20/56) of subjects randomized to vehicle at Visit 3. The difference in the proportion of subjects with clinical resolution at Visit 3 (Day 8, +1 day) between the 2 cohorts was statistically significant when adjusting for center effects (CMH p=0.0013).

Table 1: Clinical Resolution at Visit 3, Study Eyes, Study 373 ITT Population

	Visit 3 (Day 8, +1 day)	
	Besifloxacin Suspension (N = 60)	Vehicle (N = 56)
Yes	37 (61.7%)	20 (35.7%)
No	23 (38.3%)	36 (64.3%)
CMH p-Value	0.0013	

Cochran-Mantel-Haenszel (CMH) statistic stratifying by center: 10.36

At Visit 3 (Day 8, +1 day), when the last non-missing post-baseline observation was carried forward, 90.0% (54/60) of subjects randomized to besifloxacin ophthalmic suspension experienced microbial eradication compared to 69.1% (38/55) of subjects randomized to vehicle (Table 2). The difference in the proportion of subjects with bacterial eradication at Visit 3 between the 2 cohorts was statistically significant when adjusting for center effects (CMH p=0.0041).

Table 2: Microbial Eradication at Visit 3, Study Eyes, Study 373 ITT Population

	Besifloxacin Suspension (N = 60)	Vehicle (N = 55)
Yes	54 (90.0%)	38 (69.1%)
No	6 (10.0%)	17 (30.9%)
CMH p-Value	0.0041	

CMH statistic stratifying by center: 8.24

Study 433

Study 433 was similar in design to Study 373. The primary efficacy endpoints of the study were clinical resolution, defined as the absence of both conjunctival discharge and bulbar conjunctival injection, at Visit 2 and; microbial eradication, defined as the absence of all accepted ocular bacterial species that were present at or above threshold at baseline, at Visit 2. Secondary efficacy endpoints were clinical resolution and microbial eradication at Visit 3 (Day 8); individual clinical outcomes at each follow-up visit for ocular discharge, bulbar conjunctival injection, clinical outcome and Investigator's global rating; and microbial and clinical outcome at each follow-up visit for each accepted ocular bacterial species that was present at or above threshold at baseline.

Table 3 presents the primary efficacy endpoint data for clinical resolution evaluated on the baseline-designated study eye, mITT population 'as randomized'. At Visit 2 (Day 5, ± 1 day), when missing values and discontinued subjects were imputed as clinical resolution failures, 45.2% (90/199) and 33.0% (63/191) of subjects randomized to the besifloxacin ophthalmic suspension and vehicle treatment groups respectively had clinical resolution. The difference between treatment groups was statistically significant, whether adjusting for center effects, CMH p=0.0084 or not, exact Pearson chi-squared p=0.0169.

[Table 3 next page]

Table 3 Clinical resolution at Visit 2, study eyes, Study 433 mITT "as randomized" Population

	Besifloxacin Suspension (N = 199)	Vehicle (N = 191)
Subjects with Non-Missing Data	195	179
Clinical Resolution (Data 'as observed')		
Yes	90 (46.2%)	63 (35.2%)
No	105 (53.8%)	116 (64.8%)
p-Value[1]	0.0104 / 0.0354	
95% CI for Difference[2]	(0.95%, 20.97%)	
Clinical Resolution (Missing or Discontinued Subjects Imputed as 'no')		
Yes	90 (45.2%)	63 (33.0%)
No	109 (54.8%)	128 (67.0%)
p-Value[1]	0.0084 / 0.0169	
95% CI[2]	(2.52%, 21.97%)	

[1] p-Values from CMH test stratified by center /exact Pearson chi-squared test, respectively.
[2] Difference calculated as besifloxacin minus vehicle. Positive values favor besifloxacin.
NOTE: For summaries including imputed scores, percentages are based on the number of subjects indicated in the column heading. For other summaries, percentages are based on the number of subjects presenting non-missing data.

Table 4 presents data for microbial eradication evaluated on the baseline-designated study eye, mITT population 'as randomized'. A total of 91.5% (182/199) and 59.7% (114/191) of subjects randomized to the besifloxacin ophthalmic suspension and vehicle treatment groups respectively had microbial eradication at Visit 2 (Day 5, ± 1 day), when missing values and discontinued subjects were imputed as microbial eradication failures.
The difference between groups was statistically significant and the p-values were the same whether adjusting for center effects (CMH) or not, exact Pearson chi-squared, $p<0.0001$.

[Table 4 next page]

Table 4 Microbial Eradication at Visit 2, Study Eyes, Study 433 mITT 'as randomized' Population

	Besifloxacin Suspension (N = 199)	Vehicle (N = 191)
Subjects with Non-Missing Data	194	173
Microbial Eradication (Data 'as observed')		
Yes	182 (93.8%)	114 (65.9%)
No	12 (6.2%)	59 (34.1%)
p-Value[1]	<0.0001 / <0.0001	
95% CI[2]	(19.80%, 36.04%)	
Microbial Eradication (Missing or Discontinued Imputed as 'no')		
Yes	182 (91.5%)	114 (59.7%)
No	17 (8.5%)	77 (40.3%)
p-Value[1]	<0.0001 / <0.0001	
95% CI[2]	(23.25%, 40.29%)	

[1] p-Values from CMH test stratified by center/exact Pearson chi-squared test, respectively.
[2] Difference calculated as besifloxacin minus vehicle. Positive values favor besifloxacin.
NOTE: For summaries including imputed scores, percentages are based on the number of subjects indicated in the column heading. For other summaries, percentages are based on the number of subjects presenting non-missing data.

Study 434

Study 434 was a randomized, double-masked, active-controlled, parallel group clinical trial. Besifloxacin ophthalmic suspension administered TID for 5 days compared to Vigamox (moxifloxacin eye drops) TID for 5 days in the treatment of culture-confirmed conjunctivitis. Adults and children one year of age or older required a clinical diagnosis of acute bacterial conjunctivitis exhibiting a minimum grade 1 for purulent conjunctival discharge (crusty or sticky eyelids) and a minimum grade 1 for bulbar conjunctival injection in at least one eye to be eligible for entry into the study.

The primary efficacy endpoints of the study were clinical resolution, defined as the absence of both conjunctival discharge and bulbar conjunctival injection, at Visit 2 (Day 5) and; microbial eradication, defined as the absence of all accepted ocular bacterial species that were present at or above threshold at baseline, at Visit 2. Secondary efficacy endpoints were clinical resolution and microbial eradication at Visit 3 (Day 8); individual clinical outcomes at each follow-up visit for ocular discharge, bulbar conjunctival injection, clinical outcome and Investigator's global rating; and microbial and clinical outcome at each follow-up visit for each accepted ocular bacterial species that was present at or above threshold at baseline.

Table 5 presents the primary efficacy endpoint data for clinical resolution evaluated on the baseline-designated study eye, mITT population 'as randomized'. At Visit 2 (Day 5, ±1 day), when missing values and discontinued subjects were imputed as clinical resolution failures, 58.4% (149/255) and 59.4% (165/278) of subjects randomized to the besifloxacin ophthalmic suspension and Vigamox treatment groups respectively had clinical resolution.

Based on the 95% CI of the difference (-9.30%, 7.46%), besifloxacin ophthalmic suspension was non-inferior to Vigamox for clinical resolution at Visit 2 (Day 5, ±1 day), and there was no significant difference in clinical resolution between treatment groups, p=0.8603 (exact Pearson chi-squared). Results were similar when the comparison between groups was analyzed using the CMH statistic, adjusting for center effects, p=0.6838. Results were also similar for baseline-designated study eyes in the mITT 'as treated' population.

Table 5: Clinical Resolution at Visit 2, Study Eyes, Study 434 mITT 'as randomized' Population

	Besifloxacin Suspension (N = 255)	Vigamox (N = 278)
Subjects with Non-Missing Data	251	274
Clinical Resolution (Data 'as observed')		
Yes	149 (59.4%)	165 (60.2%)
No	102 (40.6%)	109 (39.8%)
p-Value[1]	0.6377 / 0.8589	
95% CI[2]	(-9.27%, 7.56%)	
Subjects on Study with Missing Data	0	1
Subjects Discontinued at or before Visit 2	4	3
Clinical Resolution (Missing or Discontinued Subjects Imputed as 'no')		
Yes	149 (58.4%)	165 (59.4%)
No	106 (41.6%)	113 (40.6%)
p-Value[1]	0.6838 / 0.8603	
95% CI[2]	(-9.30%, 7.46%)	

[1] p-Values from CMH test stratified by center / exact Pearson chi-squared test respectively.

[2] Difference calculated as besifloxacin minus *Vigamox*. Positive values favor besifloxacin.

NOTE: For summary including imputed scores, percentages are based on the number of subjects in the column heading. For other summaries, percentages are based on the number of subjects presenting non-missing data.

Table 6 presents data for microbial eradication evaluated on the baseline-designated study eye, mITT population 'as randomized'. A total of 94.5% (241/255) and 89.9% (250/278) of subjects randomized to the besifloxacin ophthalmic suspension and Vigamox treatment groups respectively had microbial eradication at Visit 2 (Day 5, ±1 day), when missing values and discontinued subjects were imputed as microbial eradication failures. Differences between groups were statistically significant, p=0.0183 when analyzed using the CMH statistic, adjusting for center effects. Differences between groups were not significant, p=0.0544, when compared using the exact Pearson chi-squared test. The 95% CI of the differences (-0.01%, 9.17%) demonstrated that besifloxacin ophthalmic

suspension met the condition of non-inferiority when compared to Vigamox for microbial eradication at Visit 2 (Day 5, ±1 day), imputing missing values and discontinued subjects as failures. This was further supported by the results of the 'as treated' population.

Table 6: Microbial Eradication at Visit 2, Study Eyes, Study 434 mITT 'as randomized' Population

	Besifloxacin Suspension (N = 255)	Vigamox (N = 278)
Subjects with Non-Missing Data	249	267
Microbial Eradication (Data 'as observed')		
Yes	241 (96.8%)	250 (93.6%)
No	8 (3.2%)	17 (6.4%)
p-Value[1]	0.0683 / 0.1046	
95% CI[2]	(-0.56%, 6.87%)	
Subjects on Study with Missing Data	2	8
Subjects Discontinued at or before Visit 2	4	3
Microbial Eradication (Missing or Discontinued Imputed as 'no')		
Yes	241 (94.5%)	250 (89.9%)
No	14 (5.5%)	28 (10.1%)
p-Value[1]	0.0183 / 0.0544	
95% CI[2]	(-0.01%, 9.17%)	

[1] p-Values from CMH test stratified by center / exact Pearson chi-squared test respectively.
[2] Difference calculated as besifloxacin minus *Vigamox*. Positive values favor besifloxacin.
NOTE: For summary including imputed scores, percentages are based on the number of subjects indicated in the column heading. For other summaries, percentages are based on the number of subjects presenting non-missing data.

Indications

Besivance is indicated for the treatment of severe, confirmed bacterial conjunctivitis caused by besifloxacin sensitive bacteria.

Besivance is indicated for adults and children 12 months and older.

Contraindications

Hypersensitivity to any component of the product.

Precautions

Besivance is for topical ophthalmic use only, and should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.

Besivance is not indicated for long-term use and administration of this drug should not exceed the recommended 7 day course. As with other anti-infectives, prolonged use of Besivance may result in overgrowth of non-susceptible organisms, including fungi. If super-infection occurs, discontinue use and institute alternative therapy. Whenever clinical

judgment dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy, and, where appropriate, fluorescein staining.

Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with Besivance.

Although Besivance is not intended to be administered systemically, quinolones administered systemically have been associated with hypersensitivity reactions, even following a single dose. Patients should be advised to discontinue use immediately and contact their physician at the first sign of a rash or allergic reaction.

Effects on fertility

In a fertility and early embryonic development study in rats, besifloxacin did not impair the fertility of male or female rats at oral doses of up to 500 mg/kg/day. This is over 10,000 times higher than the recommended total daily human ophthalmic dose.

Use in pregnancy **Category B3**

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.

Oral doses of besifloxacin up to 1000 mg/kg/day were not associated with visceral or skeletal malformations in rat pups in a study of embryo-fetal development, although this dose was associated with maternal toxicity (reduced body weight gain and food consumption) and maternal mortality. Increased post-implantation loss, decreased fetal body weights, and decreased fetal ossification were also observed. At this dose, the mean C_{max} in the rat dams was approximately 12.34 µg/mL, >31,000 times the mean plasma concentrations measured in humans. The No Observed Adverse Effect Level (NOAEL) for this embryo-foetal development study was 100 mg/kg/day (C_{max}, 5.1 µg/mL, >12,750 times the mean plasma concentrations measured in humans).

In a prenatal and postnatal development study in rats, the NOAELs for both fetal and maternal toxicity were also 100 mg/kg/day. At 1000 mg/kg/day, the pups weighed significantly less than controls and had a reduced neonatal survival rate. Attainment of developmental landmarks and sexual maturation were delayed, although surviving pups from this dose group that were reared to maturity did not demonstrate deficits in behaviour, including activity, learning and memory, and their reproductive capacity appeared normal.

Use in lactation

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.

Genotoxicity

No in-vitro mutagenic activity of besifloxacin was observed in an Ames test (up to 3.33 mcg/plate) on bacterial tester strains *Salmonella typhimurium* TA98, TA100, TA1535,

TA1537 and *Escherichia coli* WP2uvrA. However, it was mutagenic in *S. typhimurium* strain TA102 and *E. coli* strain WP2(pKM101). Positive responses in these strains have been observed with other quinolones and are likely related to topoisomerase inhibition.

Besifloxacin induced chromosomal aberrations in CHO cells in vitro and it was positive in an in vivo mouse micronucleus assay at oral doses ≥ 1500 mg/kg. Besifloxacin did not induce unscheduled DNA synthesis in hepatocytes cultured from rats given the test compound up to 2,000 mg/kg by the oral route.

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

Use in children
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 paediatric patients one year or older has been demonstrated in controlled 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.

Use in the elderly
No overall differences in safety and effectiveness have been observed between elderly and younger patients.

Interactions with other medicines
There have been no formal clinical studies to evaluate the medicine interactions of Besivance.

Adverse effects
The most frequently reported adverse events (occurring in >1% of subjects) in clinical trials (Studies 373, 433, 434) were blurred vision, eye pain and eye irritation, conjunctivitis, conjunctivitis bacterial, and headache.

Tabulated adverse events of incidence >1% from clinical trials (studies 373, 433, 434) comparing besivance to vehicle/comparator are provided in Table 7.

[Table 7 next page]

Table 7: Adverse events in Besivance and vehicle/comparator groups from clinical studies 373†, 433†, 434††			
Ocular Adverse Events (all treated eyes)	**Besivance (n=1810)*** (%)	**Vehicle† (n=961)*** (%)	**Vigamox (moxifloxacin eye drops)†† (n=855)*** (%)
Conjunctivitis	2.6	4.3	3.9
Eye pain	1.5	1.8	1.1
Eye irritation	1.4	2.8	1.4
Vision Blurred	2.1	4.1	0.5
Conjunctivitis bacterial	1.8	2.8	2.6
Systemic Adverse Events	**Besivance (n=1192)**** (%)	**Vehicle† (n=616)**** (%)	**Vigamox†† (n=579)**** (%)
Headache	1.8	1.8	1.6

*n=all treated eyes for the specified treatment group and includes study and fellow eye
**n= number of subjects for the specified treatment group

Uncommon ocular adverse events (occurring ≥0.1% to <1% of subjects) included eyelid oedema, conjunctival oedema, corneal infiltrates, punctate keratitis, eye discharge, conjunctival hemorrhage, conjunctival disorder, dry eye, limbal hyperemia, conjunctival hyperemia, conjunctivitis viral, ocular hyperemia, visual acuity reduced, erythema eyelid, keratoconjunctivitis sicca, corneal staining, eyelid margin crusting.

Uncommon systemic adverse events (occurring ≥0.1% to <1% of subjects) included otitis media, ear infection, sinusitis, nasopharyngitis, upper respiratory tract infection, pharyngolaryngeal pain, nasal congestion, respiratory tract congestion, asthma, cough and depression.

Post-marketing Events:
The following adverse reactions are classified according to the following convention (% of total AEs reported for Besivance): very common (≥10%), common (≥1% to <10%), uncommon (≥0.1% to <1%), rare (≥0.01% to <0.1%), very rare (≥0.001% to <0.01%), or not known (cannot be estimated from the available data) according to system organ classes. The adverse reactions have been observed during post-marketing experience. The frequency is based on the total number of adverse events reported in post-marketing data.

Congenital, familial and genetic disorders:

Uncommon (≥0.1 to <1%): corneal dystrophy

Eye disorders:

Common (≥1% to <10%): corneal deposits, corneal disorders, corneal infiltrates, corneal oedema, corneal opacity, corneal striae, dry eye, eye irritation, eye oedema, eye pain, foreign body sensation in eyes, lacrimation increased, ocular discomfort, ocular hyperemia, photophobia, punctate keratitis, vision blurred and off label use.

Uncommon (≥0.1% to <1%): anterior chamber disorder, blepharitis, corneal pigmentation, corneal scar, corneal thickening, eye discharge, eye inflammation, eye pruritus, eye swelling, eyelid margin crusting, eyelid oedema, glare, halo vision, Meibomian gland dysfunction, strabismus, ulcerative keratitis, visual acuity reduced, visual impairment.

Gastrointestinal disorders:

Uncommon (≥0.1% to <1%): diarrhea, dysphagia, frequent bowel movements, gingival pain, glossodynia, mucous stools, nausea, and sensitivity of teeth.

General disorders and administrative site conditions:

Common (≥1% to <10%): Impaired healing, medication residue, oedema
Uncommon (≥0.1% to <1%): drug ineffective, drug ineffective for unapproved indication, gait disturbance, instillation site pain, malaise, oedema peripheral, and pyrexia.

Infections and infestations:

Uncommon (≥0.1% to <1%): candidiasis, endophthalmitis, hypopyon, staphylococcal infection.

Injury, poisoning and procedural complications:

Common (≥1% to <10%): corneal flap complication, diffuse lamellar keratitis
Uncommon(≥0.1% to <1%): eye burn, eye injury, foreign body in eye, inappropriate schedule of drug administration, incorrect dose administered, incorrect drug dosage form administered.

Investigations:

Uncommon (≥0.1% to <1%): blood glucose increased, blood pressure increased, intraocular pressure increased, visual acuity test abnormal

Metabolism and nutrition disorders:

Uncommon (≥0.1% to <1%): hypokalemia.

Musculoskeletal and connective tissue disorders:

Uncommon (≥0.1% to <1%): muscle spasm.

Nervous system disorder:

Uncommon (≥0.1% to <1%): dizziness, dysgeusia, headache, presyncope.

Psychiatric disorders:

Uncommon (≥0.1% to <1%): disorientation, insomnia.

Respiratory, thoracic and mediastinal disorders:

Uncommon (≥0.1% to <1%): dry throat, dyspnea, throat tightness.

Skin and subcutaneous tissue disorders:

Uncommon (≥0.1% to <1%): cold sweat, madarosis, photosensitivity reaction.

Surgical and medical procedure:

Common (≥1% to <10%): Off label use.

Vascular disorders:

Uncommon (≥0.1% to ≤1%): endothelial dysfunction.

Dosage and administration

Adults and children 12 months and older: Instil one drop in the affected eye(s) 3 times a day, four to twelve hours apart for 7 days.

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).

Besivance eye drops are not to be shared between patients to ensure minimisation of possible cross-contamination.

Overdosage

Systemic overdose: In the event of accidental ingestion of Besivance 5 mL, 30 mg of besifloxacin would be ingested. This amount does not appear to be clinically significant in terms of overdose. However, there would be an increased potential for systemic reactions (see Adverse Reactions).

Topical overdose: Following the administration in the eyes overdose symptoms are unlikely to occur.

If the eye drops are accidently ingested by infants or young children, contact the Poisons Information Centre on 131 126. The medication should be kept out of reach of children.

Presentation and storage conditions

Presentation

Besivance (besifloxacin eye drops, suspension) 0.6%, is supplied as a sterile eye drops 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.

Besivance 0.6% eye drops, suspension; 2 mL and 5 mL.

For individual patient use only.

Storage Conditions

Store below 25°C. Protect from light. Discard container four weeks after opening.

Name and address of sponsor

Bausch & Lomb Australia Pty Ltd
Ground Floor, 16 Giffnock Avenue,
Macquarie Park NSW 2113

Poison schedule of the medicine

S4 – Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (ARTG)

07 November 2013