



Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for besifloxacin hydrochloride

Proprietary Product Name: Besivance

Sponsor: Bausch & Lomb (Australia) Pty Ltd

Date of CER: February 2013

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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted] indicate confidential information has been deleted.
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List of abbreviations

Abbreviation	Meaning
AE	Adverse event
AST	antimicrobial susceptibility test
ATCC	American Type Culture Collection
AUC	Area under the Curve
AUC24	Area under the concentration-time curve from 0-24 h
BAK	benzalkonium chloride
besifloxacin	Free base form of besifloxacin hydrochloride
Besifloxacin hydrochloride	Hydrochloride salt form of besifloxacin
Besifloxacin ophthalmic suspension	Besifloxacin hydrochloride ophthalmic suspension, 0.6% as base
BID	Two times daily
CFR	Code of federal regulations
CFU	Colony forming units
CI	Confidence interval
CLSI	Clinical and Laboratory Standards Institute
C _{max}	Maximal observed besifloxacin concentration
CMH	Cochran-Mantel-Haenszel
CMI	Clinical Microbiology Institute
DNA	Deoxyribonucleic acid
EOP2	End of phase 2

Abbreviation	Meaning
FDA	US Food and Drug Administration
GI	Gastrointestinal
h	Hours
Hb	Haemoglobin
HS	At bedtime
ICH	International Conference on Harmonisation
ISV-403	Company code for besifloxacin hydrochloride ophthalmic suspension, 0.6% as base
ITT	Intent to treat
ISV	InSite Vision Inc
LC	Liquid chromatography
LOCF	Last observation carried forward
logMAR	Log of the minimal angle of resolution
MBC	Minimum bactericidal concentrations
MethR	methicillin resistant
MethS	methicillin sensitive
MIC	Minimum inhibitory concentration
MIC50	Minimum inhibitory concentration required to inhibit the growth of 50% of organisms
MIC90	Minimum inhibitory concentration required to inhibit the growth of 90% of organisms
mITT	Modified intent to treat
MPC	Mutant prevention concentration
MS	Mass spectrometry
NDA	New drug application
NF	National Formulary
OD	Right eye

Abbreviation	Meaning
PD	Pharmacodynamics
PISP	Penicillin intermediate <i>Streptococcus pneumoniae</i>
PK	Pharmacokinetics
PP	Per protocol
PRSP	Penicillin resistant <i>Streptococcus pneumoniae</i>
PSSP	Penicillin sensitive <i>Streptococcus pneumoniae</i>
QD	Once daily
QID	Four times daily
QRDR	quinolone resistance-determining region
SAE	Serious adverse event
SMRC	Specular Microscopy Reading Center
SS734	Company code for besifloxacin hydrochloride
TID or tds	Three times daily
URI	Upper respiratory infection
USP	United States Pharmacopeia
VA	Visual acuity

1. Clinical rationale

The globe of the eye is covered by a thin, transparent, mucous membrane called the conjunctiva. The conjunctiva serves to protect the eye and facilitates eye movement by providing lubrication. Conjunctivitis is an inflammation of this lining of the eye. Bacterial conjunctivitis is a common external ocular infection that affects persons of all ages. Conjunctivitis can also be caused by viruses for example adenovirus. The condition often presents as unilateral disease and can readily spread to the fellow eye as a contagious disease. Bacterial conjunctivitis is characterized by marked hyperaemia or redness of the eye, and mild to moderate purulent conjunctival discharge. Symptoms often include tearing, itching, and vague ocular irritation. The disease is generally self-limiting and usually does not cause permanent loss of vision or structural damage.¹ Treatment with a topical broad spectrum ocular antibiotic is standard of care for this

¹ Cavuoto K, et al. Update on bacterial conjunctivitis in South Florida. *Ophthalmology* 2008;115:51-6; Diamant JI, Hwang DG. Therapy for bacterial conjunctivitis. *Ophthalmol Clin North Am.* 1999;12(1):15-20; Sheikh A, Hurwitz B. Antibiotics versus placebo for acute bacterial conjunctivitis. *Cochrane Database Syst Rev.* 2006;Apr 19(2):CD001211.

condition, the rationale is to shorten the duration of the disease, reduce contagious spread, and enhances eradication of causative gram-positive and gram-negative organisms.

Note that, the bacterial conjunctivitis referred to in this application does not include congenital infections collectively referred to as Ophthalmia neonatorum caused by *Neisseria Gonorrhoea* and *Chlamydia trachomatis*.

Bacterial conjunctivitis is most commonly caused by the following organisms, many of which are normal commensals of the eyelid or nasopharynx i.e. *Staphylococcus aureus* and *Haemophilus influenza*, respectively.² Other common pathogens include *Streptococcus pneumoniae* and *Moraxella* species, but *Neisseria* species, *Corynebacterium* species, and other *Streptococcus* species also may cause bacterial conjunctivitis. As treatment of bacterial conjunctivitis is usually based on the likely causative pathogens, it is usual to treat empirically before the culture results are known. Bacterial conjunctivitis is commonly caused by both gram positive & negative organisms and as such, empiric treatment should have good activity against the likely culprits.

The active ingredient of Besivance topical ophthalmic suspension is besifloxacin hydrochloride a fluoroquinolone antibiotic. Antibacterial action is achieved through the inhibition of both bacterial DNA gyrase and topoisomerase IV. The spectrum of activity includes all the most common gram +ve and -ve bacterial conjunctivitis-causing organisms. Several other quinolone topical antibiotics are approved (not all in Australia) for this condition i.e. moxifloxacin, ciprofloxacin, gatifloxacin, ofloxacin. In addition, other broad spectrum antibiotics in topical formulation i.e. azithromycin (macrolide) and tobramycin (aminoglycoside) are available. Besifloxacin has similar spectrum of activity and is at least as potent as the other topical quinolone antibiotics but with longer half life within the eye as the DuraSite delivery system increases retention in the eye and reduces loss caused by blinking and tearing. This means less frequent dosing (i.e. TID) than other agents. This factor is important in improving compliance with the net effect of improved efficacy and reduced risk of microbial resistance.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The clinical dossier documented a full clinical development program of pharmacology, efficacy and safety studies.

The clinical submission consisted of 67 double sided volumes, comprising 8 clinical pharmacology studies including 2 providing pharmacokinetic data (1 ocular and 1 systemic PK studies), 3 pivotal efficacy/safety studies, 3 other safety studies, and relevant publications.

2.2. Paediatric data

The submission includes paediatric efficacy and safety data although numbers of children enrolled were small, especially in those aged 1 year or older to <2 years of age.

² Gigliotti F, et al. Etiology of acute conjunctivitis in children. *J Pediatrics* 1981;98:531-6; Brook I, et al. Anaerobic and anaerobic bacteriology of acute conjunctivitis. *Ann Ophthalmol* 1979; March: 389-393; Leeming JP. Treatment of ocular infections with topical antibacterials. *Clin Pharmacokinet.* 1999;37(5):351-360; Hammond RW, Edmondson W. Treatment of ocular bacterial infections: an update. *J Am Optom Assoc.* 1997;68(3):178-187.

2.3. Good clinical practice

All studies were carried out by experienced investigators and in accordance with GCP guidelines. The protocols complied with the 1996 version of the Declaration of Helsinki and with the GCP guidelines in use at the study outset. Each study was reviewed and approved by an ethical review committee (ERC). Deficiencies were detected at a couple of sites and resulted in FDA inspections of 4 sites that had contributed large numbers of subjects (FDA PDUFA inspection) because of high rates of protocol violations; another 2 sites ([information redacted]) in Studies 433 and 434 underwent Cause/PDUFA inspections because these sites were terminated by the sponsor for continued ICH-GCP breaches. Overall, no harm came to subjects as consequence of protocol violations at the high enrolling sites and integrity of the safety and efficacy data was not affected. When data from the early terminated sites was excluded, overall conclusions were not affected.

3. Pharmacokinetics

The bioanalytical methodology utilized for the quantitation of besifloxacin concentrations in animal ocular tissues and plasma consisted of specific HPLC assays coupled with ultraviolet (LC/UV) or mass spectrometry (LC/MS or LC/MS/MS) detection. Validated methods were developed for the quantitation of besifloxacin in mouse, rat, rabbit, and dog plasma, as well as rabbit ocular tissues. All of the bioanalytical methods used for the determination of besifloxacin concentrations in various biological matrices in support of GLP toxicology studies were validated in accordance with the FDA guidance on bioanalytical method validation.³ Subsequently, a validated high performance LC-MS/MS method for the determination of besifloxacin in human tears (collected on Schirmer tear test strips and quantitated after elution using appropriate buffer and aliquoting) was developed and utilised in the human trials of the agent.

The antimicrobial spectrum of besifloxacin was then evaluated against a variety of clinical isolates in nine studies conducted in the US and Japan using standard CLSI reference methods. The *in vitro* assessment of besifloxacin activity focused on the target pathogens associated with bacterial conjunctivitis. Besifloxacin and comparator drugs were tested against a wide spectrum of aerobic and anaerobic gram +ve & -ve bacteria. Some studies focused specifically on isolates of ophthalmologic origin while others focused on drug resistant strains. Overall, besifloxacin has potent antibacterial activity against a very broad spectrum of bacteria, including all species commonly isolated from those with bacterial conjunctivitis i.e. *Streptococcus* sp., *Staphylococcus* sp., *Haemophilus* sp., *Corynebacterium* sp., and *Moraxella* sp. The antibacterial potency of besifloxacin was similar to or greater than fluoroquinolone and non- fluoroquinolone comparator antibacterials. The PK/PD data for the relevant target conjunctivitis-causing organisms is described further in Table 1.

³ <<http://www.fda.gov/downloads/Drugs/Guidances/ucm070107.pdf>>

Table 1: Activity of Besivance against isolates from Besivance Clinical Studies.

organism	phenotype	N	BESIFLOXACIN	MOXIFLOXACIN	GATIFLOXACIN	LEVOFLOXACIN	CIPROFLOXACIN	OFLOXACIN	AZITHROMYCIN
all									
gram positive	All	1324	0.25	0.5	0.5	1	2	2	>8
gram negative	All	886	0.25	0.5	1	2	4	4	>8
CDC coryneform group G		29	0.125	0.25	0.5	1	0.5	2	>8
<i>Corynebacterium pseudodiphtheriticum</i>		8	0.25a	0.25a	0.5a	0.5a	0.5a	1a	>8a
<i>Corynebacterium striatum</i>		8	0.015a	0.03a	0.03a	0.06a	0.03a	0.125a	0.125a
<i>Haemophilus influenzae</i>		344	0.06	0.06	0.03	0.03	0.015	0.06	4
<i>Haemophilus influenzae</i> lactamase-negative		253	0.06	0.06	0.03	0.03	0.015	0.06	4
<i>Haemophilus influenzae</i> lactamase-positive		87	0.06	0.06	0.03	0.03	0.015	0.06	2
<i>Moraxella lacunata</i>		9	0.06a	0.06a	0.03a	0.06a	0.03a	0.12a	0.03a
<i>Staphylococcus aureus</i>	ALL	190	0.5	2	4	8	>8	>8	>8
	MethS; CipS	144	0.06	0.125	0.25	0.25	0.5	0.5	>8
	MethR; CipS	9	0.06a	0.06a	0.125a	0.25a	0.5a	0.5a	>8a
	MethS; CipR	17	2	>8	>8	>8	>8	>8	>8
	MethR; CipR	17	4	>8	>8	>8	>8	>8	>8
<i>Staphylococcus epidermidis</i>	ALL	111	0.5	4	2	8	>8	>8	>8
	MethS; CipS	50	0.06	0.125	0.25	0.25	0.25	0.5	>8
	MethR; CipS	27	0.06	0.125	0.25	0.25	0.25	0.5	>8
	MethS; CipR	10	1	8	8	>8	>8	>8	>8
	MethR; CipR	24	4	>8	>8	>8	>8	>8	>8
<i>Staphylococcus hominis</i>		9	0.06a	0.06a	0.125a	0.125a	0.125a	0.125a	4a
<i>Staphylococcus lugdunensis</i>		8	0.125a	0.25a	0.25a	0.25a	0.25a	1a	0.5a
<i>Streptococcus mitis</i> group		45	0.25	0.25	0.5	2	4	4	8
<i>Streptococcus oralis</i>		18	0.25	0.25	1	2	4	4	>8
<i>Streptococcus pneumoniae</i>	All	302	0.125	0.125	0.5	1	1	2	>8
	PSSP	220	0.125	0.125	0.5	1	1	2	0.25
	PISP	71	0.06	0.125	0.5	1	0.5	2	>8
	PRSP	11	0.125	0.125	0.5	1	1	2	>8
<i>Streptococcus salivarius</i>		9	0.125a	0.25a	0.5a	1a	2a	2a	8a

3.1. Studies providing pharmacokinetic data

None of the PK studies had deficiencies that excluded their results from consideration.

3.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional PK studies.

3.2.1. Physicochemical characteristics of the active substance

Chemical name: 3-quinolinecarboxylic acid,7-[(3R)-3-aminohexahydro-1H-azepin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-, monohydrochloride. Molecular formula: C₁₉H₂₁ClFN₃O₃·HCl; molecular weight of 430.30.

Besifloxacin hydrochloride is a white to pale yellowish-white powder. Besivance 0.6% is a sterile ophthalmic suspension of besifloxacin. This is an isotonic suspension with osmolality of 290 mOsm/Kg. Each mL of Besivance contains 6.63mg besifloxacin hydrochloride equivalent to 6mg besifloxacin base. Besifloxacin may exist as the racemic mixture of the R- (+) and S- (-) isomers; the active pharmaceutical ingredient for the proposed ophthalmic product is the R-enantiomer with a limit of S-enantiomer of no more than 0.5% w/w. Both enantiomers possess antibacterial activity. The compound is an 8-chloro fluoroquinolone for topical use and has broad-spectrum activity against aerobic and anaerobic bacteria.

3.2.2. Pharmacokinetics in healthy subjects

Binding of besifloxacin to plasma proteins is <50% in humans; besifloxacin is not associated with extensive distribution into blood cells. Besifloxacin is eliminated from ocular tissues with an apparent half-life of >5 h for most ocular tissues. To the extent that besifloxacin reaches the systemic circulation, it distributes at low levels into most tissues undergoing minimal metabolism; eliminated primarily unchanged in urine and faeces.

Study 424, a phase 1 ocular PK study demonstrated that single dose besifloxacin ophthalmic suspension 0.6% afforded high besifloxacin levels (C_{max} of 610 ± 540 µg/g) in tears that were sustained above 1.6 µg/g, on average, for at least 24 h. Total exposure to besifloxacin in tears

after single dose, based on AUC₂₄ was 1232 µg·h/g. Elimination of besifloxacin from tears occurred with an estimated half-life of 3.4 h. Based on the observed concentration of besifloxacin in human tears at 24 h (1.60 µg/g) and observed elimination rate constant (0.20 h⁻¹), besifloxacin concentrations in human tears would be predicted to decrease to <LLOQ of the bioanalytical assay (0.2 µg/g) approximately 34 h after last dose.

3.2.2.1. Absorption

3.2.2.1.1. Sites and mechanisms of absorption

Study C-02-403-001 showed bilateral ocular administration of besifloxacin ophthalmic suspension (0.3% and 0.6%) QID for 7 days in healthy volunteers resulted in minimal systemic exposure. Plasma besifloxacin levels observed were on average <0.35 ng/mL.

Several studies have evaluated the impact of various formulation factors on ocular PK of besifloxacin. Results demonstrate that ocular exposure to besifloxacin is dose-related over the range from 0.1% to 0.6%; moreover, the DuraSite vehicle enhances the absorption of besifloxacin into intact cornea following a single topical administration. Variability in the besifloxacin particle size in the ophthalmic suspension was **not found** to be a critical factor in its absorption, at least over a relevant, but relatively narrow, range of particle sizes.

Although the rabbit was selected as the primary species for ocular PK studies, the ocular PK of besifloxacin was evaluated and found comparable in cynomolgus monkeys following a single topical ocular administration of 0.6%. Low systemic exposure was observed in rabbits and monkeys, with maximal concentrations of 7.6 and 9.2 ng/mL, respectively, after single topical instillation. Following repeated topical administration (BID and TID for 4 days), ocular and systemic exposure to besifloxacin was similar following the last daily dose on day 1 and day 4. No substantial accumulation observed after BID or TID dosing. Results of the 424 ocular PK study in humans are detailed above.

3.2.2.2. Bioavailability

3.2.2.2.1. Absolute bioavailability

No bioavailability study was included in the application. This product is for ocular use and is intended to act without systemic absorption. A full justification was provided.

3.2.2.2.2. Bioavailability relative to an oral solution or micronised suspension

Not applicable, topical agent.

3.2.2.2.3. Bioequivalence of clinical trial and market formulations

Details of formulation development and the commercialised product were provided.

3.2.2.2.4. Bioequivalence of different dosage forms and strengths

Not applicable.

3.2.2.2.5. Bioequivalence to relevant registered products

Not applicable.

3.2.2.2.6. Influence of food

Not applicable, topical agent.

3.2.2.2.7. Dose proportionality

Not applicable.

3.2.2.2.8. Bioavailability during multiple-dosing

Not applicable.

3.2.2.2.9. *Effect of administration timing*

Not applicable.

3.2.2.3. **Distribution**

Formal distribution and excretion studies have not been conducted in humans. Plasma concentration monitoring after multiple dosing demonstrate low systemic exposure to besifloxacin, with maximum concentrations of <0.5 ng/mL. Of note, absorption of besifloxacin into the systemic circulation and the distribution of besifloxacin into non-ocular tissues was studied following single and repeated instillations (QID for 5 days) of [14C]besifloxacin to pigmented rabbits. After single dose, the highest concentrations of radioactivity in the treated eye were observed in bulbar and palpebral conjunctivae, extraocular muscles, sclera, and cornea. For non-ocular tissues, the highest levels of radioactivity were observed in kidney, urinary bladder, and GI tract. QID administration was associated with low systemic exposure (C_{max} <0.025 µg/g in all non-excretory organs), though exposure in most tissues was higher following QID dosing vs. single dose. The apparent increase in exposure with QID dosing was most prevalent in pigmented ocular tissues. The prolonged retention of besifloxacin in pigmented tissues suggested that this compound binds to melanin, a characteristic shared by other fluoroquinolones.⁴ No consistent sex-related differences in the ocular and systemic distribution of besifloxacin observed. The systemic distribution of besifloxacin was evaluated after oral administration of [14C]besifloxacin to rats and showed besifloxacin is widely distributed into most tissues in the body, with the highest concentrations observed in excretory organs.

3.2.2.3.1. *Volume of distribution*

In vitro, besifloxacin is ~30-33% and ~39-44% proteins bound in rat and human plasma respectively. Besifloxacin was approximately evenly distributed between plasma and the cellular components of rat and human blood indicating low binding to proteins or blood cells.

3.2.2.3.2. *Plasma protein binding*

<50% in rats and humans. However, systemic absorption of this topical antibiotic is minimal.

3.2.2.3.3. *Erythrocyte distribution*

Nil.

3.2.2.3.4. *Tissue distribution*

Not studied in humans.

3.2.2.4. **Metabolism**

3.2.2.4.1. *Interconversion between enantiomers*

Not studied in humans, both enantiomers have antimicrobial activity.

3.2.2.4.2. *Sites of metabolism and mechanisms / enzyme systems involved*

Results from *in vitro* and *in vivo* studies demonstrate besifloxacin is metabolically stable, with little or no chiral interconversion to the (-) enantiomer. Following *in vitro* incubation with hepatocytes, 8 metabolites were observed and putative structures were proposed, however, the relative amount of each metabolite was small and overall extent of metabolism very low. *In vivo*,

⁴ Ono C, Tanaka M: Binding characteristics of fluoroquinolones to synthetic levodopa melanin. *J Pharm Pharmacol* 2003;55:1127-1133; Tanaka M, Ono C, Yamada M: Absorption, distribution and excretion of 14Clevofloxacin after single oral administration in albino and pigmented rats: binding characteristics of levofloxacin-related radioactivity to melanin in vivo. *J Pharm Pharmacol* 2004;56:463-469; Siefert HM, et al. Pharmacokinetics of the 8-methoxyquinolone, moxifloxacin: tissue distribution in male rats. *J Antimicrob Chemother* 1999;43(Suppl B):61-67; Perez S, et al. Pharmacokinetics and ocular penetration of grepafloxacin in albino and pigmented rabbits. *J Antimicrob Chemother* 2002;50:541-545.

unchanged besifloxacin accounted for the majority of radioactivity in plasma, urine and faeces after oral administration to rats. Three metabolites were observed by TLC analysis in plasma and a single metabolite was observed in urine and faeces. Each metabolite accounted for <10% of the radioactivity in any of the *in vivo* samples collected. Because of the very low levels of metabolites observed in nonclinical studies, monitoring of metabolites in clinical studies was deemed unnecessary.

3.2.2.4.3. *Non-renal clearance*

Not applicable.

3.2.2.4.4. *Metabolites identified in humans*

3.2.2.4.4.1. *Active metabolites*

Not studied in humans.

3.2.2.4.4.2. *Other metabolites*

Not applicable.

3.2.2.4.5. *Pharmacokinetics of metabolites*

Not studied in humans.

3.2.2.4.6. *Consequences of genetic polymorphism*

Not applicable.

3.2.2.5. Excretion

3.2.2.5.1. *Routes and mechanisms of excretion*

Not studied in humans. Following oral administration of [14C]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. ~73% of administered dose recovered in faeces; 23% of the dose recovered in the urine. In animal models the drug is largely excreted unchanged in urine and faeces.

3.2.2.5.2. *Mass balance studies*

Not applicable.

3.2.2.5.3. *Renal clearance*

Not studied.

3.2.2.5.4. *Intra- and inter-individual variability of pharmacokinetics*

None studied.

3.2.3. Pharmacokinetics in the target population

Plasma besifloxacin concentrations were measured in adults with suspected bacterial conjunctivitis (Study 478) who received Besivance bilaterally TID for 5 days with a single dose on the morning of Day 6 (16 doses total). Following the first and last dose, variability in plasma concentrations of besifloxacin between patients was large, and the maximum plasma besifloxacin concentration in each patient was <1.3 ng/mL. The mean C_{max} of besifloxacin was 0.37 ng/mL on Day 1 and 0.43 ng/mL on Day 6 indicating only a slight accumulation of besifloxacin. Systemic exposure was very low following topical ocular administration. There was an apparent terminal elimination half-life of approximately 6.8 h. In summary, the absorption of besifloxacin into the systemic circulation appears to be similar/comparable in healthy eyes and in eyes with clinical signs of bacterial conjunctivitis.

Data on PK in tears during repeated dosing is not available in humans as sampling of tears was not performed in any of the multi-dose studies.

3.2.4. Pharmacokinetics in other special populations

Not assessed.

3.2.4.1. Pharmacokinetics in subjects with impaired hepatic function

Not applicable, not studied. PK only study in healthy subjects or in otherwise healthy subjects with bacterial conjunctivitis.

3.2.4.2. Pharmacokinetics in subjects with impaired renal function

Not applicable, not studied.

3.2.4.3. Pharmacokinetics according to age

Not assessed. Note: children 1 year and older were eligible for participation in the efficacy and safety studies, 373, 433 and 434.

3.2.4.4. Pharmacokinetics related to genetic factors

Not applicable, not studied.

3.2.4.5. Pharmacokinetics related to ethnic factors

Not applicable, not specifically studied. The Phase III safety and efficacy study 434 included sites in Asia and hence subjects of Asian ethnicity were included.

3.2.5. Pharmacokinetic interactions

3.2.5.1. Pharmacokinetic interactions demonstrated in human studies

Systemic absorption of topical besifloxacin is so low that potential for D-D interactions is minimal and was not studied.

3.2.5.2. Clinical implications of in vitro findings

None.

3.3. Evaluator's overall conclusions on pharmacokinetics

Clinical investigation of besifloxacin hydrochloride ophthalmic suspension pharmacokinetics in humans has included two pivotal pharmacokinetic studies. Both these studies explored besifloxacin hydrochloride ophthalmic suspension, 0.6% as base in the healthy and inflamed eyes, showing high besifloxacin levels with very low systemic exposure. These data coupled with the safety of the 0.6% suspension (Study C-02-403-001) resulted in the 0.6% formulation moving forward into further clinical development.

No bioavailability study was included in the application. This product is for ocular use and is intended to act without systemic absorption. As both pharmacokinetics studies included in this application in the healthy eye and in the inflamed eye demonstrate minimal systemic absorption, the clinical evaluator feels the lack of specific bioavailability studies is justified.

4. Pharmacodynamics

Primary PD studies are not directly applicable to antibacterials. Antibacterial agents differ from other drugs by exerting their pharmacological action on susceptible bacteria within the host and not the host itself. Summaries of Studies 373, 433 and 434 with clinical and microbiological response rates are included. Sensitivity of isolates from subjects with positive eye cultures enrolled in these studies (as expressed by MIC) to besifloxacin, other quinolones and the macrolide, azithromycin, are summarised in Table 1. To evaluate the PK/PD relationship of besifloxacin, results the ocular PK study in humans were used (Study 424), along with the *in*

in vitro MIC90 values for prevalent bacterial pathogens isolated from subjects with bacterial conjunctivitis.

Compartmental PK analysis was performed on the composite mean besifloxacin concentration versus time data and the best-fit model was used to simulate ocular concentration versus time profiles for besifloxacin with a **simulated** TID dosing regimen (the proposed dosing for treatment and indeed the approved dose in several countries including USA and Canada). The simulated TID AUC24 was used to calculate AUC24/MIC90 ratios, while the observed C_{max} was used to calculate the C_{max}/MIC90 ratios.

An additional consideration in this analysis is the potential role of protein binding, which could effectively lower the concentration of free (unbound) besifloxacin. The inhibitory effect of protein binding on antibacterial efficacy has been reported for β-lactams; however, there is no general consensus about the role of protein binding on the antibacterial activity of fluoroquinolones.⁵ Based on the fact that besifloxacin is approximately 40% bound to proteins in human plasma (similar to other fluoroquinolones), and assuming a similar extent of binding to proteins in ocular tissue, the corresponding C_{max} and AUC24 values for free (unbound) besifloxacin would be approximately 60% of the values determined for total (bound and free). In order to evaluate the potential theoretical maximum impact of protein binding on besifloxacin activity, C_{max}/MIC90 and AUC24/MIC90 ratios were calculated based on the PK estimates for total (bound and free) and free besifloxacin.

4.1. Studies providing pharmacodynamic data

The relationship between the concentration of besifloxacin in human tear fluid and the concentration required for antimicrobial activity was quantified by calculating the ratios of C_{max}/MIC90 and AUC24/MIC90. For the purpose of calculating these PK/PD ratios, a PK model was developed based on the single-dose human tear PK data for besifloxacin. This model was used to **simulate** besifloxacin concentrations with TID dosing. Based on the observed C_{max} for besifloxacin in human tears and the AUC24 for the simulated TID dosing regimen (3801 µg·h/g), C_{max}/MIC90 and AUC24/MIC90 values were calculated using MIC90 values for several prevalent bacterial pathogens isolated from patients with bacterial conjunctivitis (*S. aureus*, *S. pneumoniae*, *S. epidermidis*, and *H. influenzae*). Using this approach, C_{max}/MIC90 ratios of 732 to 10167, and AUC24/MIC90 ratios of 4561 to 63350 were obtained. These PK/PD ratios are higher than the published target values associated with bacterial eradication in plasma for fluoroquinolones (i.e., C_{max}/MIC90 ratio of >10 and AUC/MIC90 ratio of >100-125), regardless of whether total besifloxacin (bound and free) or only unbound besifloxacin concentrations were considered. Taken together, these results provide a PK/PD-based rationale that supports the efficacy observed with besifloxacin (studies 373, 433 and 434) in the treatment of bacterial conjunctivitis.

4.2. Summary of pharmacodynamics

The information in the following summary is derived from the pivotal efficacy Studies 373, 433 and 434. These 3 studies provided clinical isolates, the MIC of these isolates and couple this

⁵ Merrikin DJ, Briant J, Rolinson GN. Effect of protein binding on antibiotic activity *in vivo*. *J Antimicrob Chemother.* 1983 Mar;11(3):233-8; Drusano GL. Role of pharmacokinetics in the outcome of infections. *Antimicrob Agents Chemother.* 1988 Mar;32(3):289-97; Craig WA, Ebert SC. Protein binding and its significance in antibacterial therapy. *Infect Dis Clin North Am.* 1989 Sep;3(3):407-14; Turnidge J. Pharmacokinetics and pharmacodynamics of fluoroquinolones. *Drugs.* 1999; 58 Suppl 2:29-36; Bergogne-Bérézin E. Clinical role of protein binding of quinolones. *Clin Pharmacokinet.* 2002; 41(10):741-50; Zeitlinger M, Saueremann R, Fille M, Hausdorfer J, Leitner I, Müller M. Plasma protein binding of fluoroquinolones affects antimicrobial activity. *J Antimicrob Chemother.* 2008 Mar; 61(3):561-7.

information with clinical response data for besifloxacin or comparator (Moxifloxacin in Study 434).

4.2.1. Mechanism of action

Besifloxacin has broad-spectrum activity against aerobic, facultative, and anaerobic Gram-positive and Gram-negative bacteria due to inhibition of bacterial DNA gyrase and topoisomerase IV. 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 several other antibiotic classes e.g. aminoglycoside, macrolide and β -lactams and the drug may be active against pathogens that are resistant to these antibacterials and vice versa. *In vitro* studies demonstrated cross-resistance between besifloxacin and some other fluoroquinolones. *In vitro* resistance to besifloxacin develops via **multiple-step mutations** and occurs at a general frequency of $<3.3 \times 10^{-10}$ for *S. aureus* and $<7 \times 10^{-10}$ for *S. pneumoniae*. The concentration of besifloxacin in tear fluid (Study 424) exceeds the mutant prevention concentration (MPC) for *S. aureus* and *S. pneumoniae*.

4.2.2. Pharmacodynamic effects

4.2.2.1. Primary pharmacodynamic effects

The primary PD effect is inhibition of both bacterial DNA gyrase and topoisomerase IV, key enzymes for many aerobic and anaerobic bacteria and hence the drug is cidal.

4.2.2.2. Secondary pharmacodynamic effects

None.

4.2.3. Time course of pharmacodynamic effects

These are imputed as described above.

4.2.4. Relationship between drug concentration and pharmacodynamic effects

Topical ocular application of 0.6% besifloxacin ophthalmic suspension result in high therapeutic levels of besifloxacin in human tears, with concentrations at 24 h ($1.60 \pm 2.28 \mu\text{g/g}$) which were above the MIC₉₀ values for prevalent ocular pathogens. Favorable ratios for effective and resistance-limiting levels of anti-infectives have been proposed to be $C_{\text{max}}/\text{MIC}_{90} \geq 10$ and $\text{AUC}_{24}/\text{MIC}_{90} \geq 30-50$ for gram-positive bacteria or $\geq 100-125$ for gram-negative bacteria.⁶ These ratios are useful for evaluating plasma concentrations and have also been proposed for evaluating tissue concentrations for local infections.⁷ The predicted PK/PD ratios for besifloxacin with TID dosing are imputed as described above, but suggest that the $C_{\text{max}}/\text{MIC}_{90}$ and $\text{AUC}_{24}/\text{MIC}_{90}$ are substantially above target values published for fluoroquinolones regardless of whether total besifloxacin concentrations or only unbound besifloxacin concentrations are considered.

Besifloxacin MBCs within 1-2 dilutions of the MIC (MBC:MIC ratios ≤ 2) were observed for the majority of ocular isolates tested (*S. pneumoniae*, *S. epidermidis*, *H. influenzae*, and *S. aureus*).

⁶ Wright DH, et al. Application of fluoroquinolone pharmacodynamics. *J Antimicrob Chemother.* 2000 Nov; 46(5):669-83; Allen GP, et al. In vitro activities of mutant prevention concentration targeted concentrations of fluoroquinolones against *Staphylococcus aureus* in a pharmacodynamic model. *Int J Antimicrob Agents.* 2004 Aug; 24(2):150-60; Metzler K, et al. Comparison of minimal inhibitory and mutant prevention drug concentrations of 4 fluoroquinolones. *Int J Antimicrob Agents.* 2004 Aug; 24 (2):161-7; Smith HJ, et al. Mutant prevention concentrations for single-step fluoroquinolone-resistant mutants of wild-type, efflux positive, or *ParC* or *GyrA* mutation-containing *Streptococcus pneumoniae* isolates. *Antimicrob Agents Chemother.* 2004 Oct; 48 (10):3954-8; Hermsen ED, et al. Mutant prevention concentrations of ABT-492, levofloxacin, moxifloxacin, and gatifloxacin against three common respiratory pathogens. *Antimicrob Agents Chemother.* 2005 Apr; 49(4):1633-5.

⁷ Nightingale CH. Future in vitro and animal studies: development of pharmacokinetic and pharmacodynamic efficacy predictors for tissue-based antibiotics. *Pharmacotherapy.* 2005 Dec; 25(12 Pt 2):146S-149S.

Besifloxacin MBCs were within 4-fold of the MIC for more than 80% of the isolates tested. Among staphylococci, equivalent besifloxacin MBC:MIC ratios were observed for both ciprofloxacin susceptible or resistant isolates, as well as for methicillin susceptible (MethS) **or resistant** (MethR) isolates. The MBC:MIC ratios observed with besifloxacin were similar to or slightly lower than for comparator fluoroquinolones. In summary, against the majority of ocular isolates tested, the MBC did not exceed 2-fold the initial MIC, **indicating a bactericidal mode of action for besifloxacin.**

This *in vitro* antimicrobial activity of besifloxacin is supported by results from two *in vivo* studies conducted in animal models - staphylococcal infections and ocular inflammation in a rabbit model of endophthalmitis and systemic pneumococcal infections in mice. More importantly, Studies 373, 433 and 434 assessed clinical and microbiological efficacy in humans. In general, the US and Asian sites were similar with respect to isolates, phenotypes, and sensitivities. From a microbiological perspective, the baseline pathogen distribution was similar across the besifloxacin, vehicle, and Vigamox treatment groups of all three studies. Table 1 summarises the isolates from these studies and the MIC of the organisms to Besifloxacin, a range of other quinolones and azithromycin. The relative frequency of organisms isolated at threshold levels or higher from these studies, *H. influenzae*, *S. pneumoniae*, *S. aureus* and *S. epidermidis* were similar to previous studies of bacterial conjunctivitis. See the 'Clinical efficacy' section of this clinical evaluation report for more details of these studies. Overall, microbiological eradication rates for besifloxacin ophthalmic suspension in these studies were similar to those seen when treating with topical moxifloxacin and superior to the vehicle control.

In summary, a total of 1324 isolates were recovered from subjects at baseline (Visit 1) in the mITT as treated population species specific study eye across all treatment groups. Overall MIC50/MIC90 values for the 1324 isolates of all species were 0.06/0.25 µg/mL for besifloxacin. Of the 1324 bacterial isolates, 886 (66.9%) were Gram positive, while the remaining 438 (33.1%) were Gram-negative. The besifloxacin MIC50/MIC90 values were 0.06/0.25 µg/mL for Gram-positive bacteria and 0.03/0.5 µg/mL for Gram-negative bacteria. Because higher proportions of quinolone-resistant strains were present in the non-clinical studies than were recovered during besifloxacin clinical trials, the overall non-clinical isolate MIC90 value was 4-fold higher than the clinical MIC90 value (1 and 0.25 µg/ml, respectively). However, besifloxacin MIC distributions were similar when clinical isolates were compared to only the 910 quinolone susceptible non-clinical isolates, with equivalent MIC50/MIC90 values between all clinical isolates and quinolone susceptible non-clinical isolates (0.06/0.25 and 0.06/0.12 µg/ml, respectively).

4.2.4.1. Mechanisms of resistance

The primary target of quinolones is bacterial DNA gyrase and topoisomerase IV. DNA gyrase is responsible for maintaining negative supercoiling of bacterial chromosomes and comprises two subunits, GyrA & GyrB. Topoisomerase IV is essential for decatenation of interlinked bacterial chromosomes after replication. Topoisomerase IV is composed of two subunits, ParC and ParE (also known as GrlA and GrlB, respectively). DNA gyrase and topoisomerase IV are similar in sequence, structure and function. Mutations through amino acid substitutions and deletions in the genes encoding these enzymes are the primary cause of clinically relevant levels of fluoroquinolone resistance in *S. aureus*. Mutations that confer high-level fluoroquinolone resistance are frequently found in the quinolone resistance-determining region (QRDR). The addition of a fluoroquinolone traps the drug, the enzyme, and the cleaved DNA in a ternary cleavage complex that ultimately results in the death of the cell. Fluoroquinolone treatment

leads to selection of strains that contain mutations in DNA gyrase and topoisomerase IV.⁸ While ciprofloxacin & ofloxacin preferentially target one enzyme more than the other, the structural modifications of newer fluoroquinolones including besifloxacin, results in targeting of **both** enzymes with resultant greater activity against gram-positive bacteria and reduced risk of resistance.

Resistance to fluoroquinolones is via single-step or multi-step mutations. Single-step mutations mainly occur within genes that encode for 1 of the 2 principal target enzymes or in the genes involved in efflux pumps or membrane permeability proteins. These mutations, mostly produce **low-level** antibiotic resistance. Multi-step mutations, where organisms acquire mutations in genes encoding **both principal target enzymes**, are more likely when bacteria are repeatedly exposed to **low levels of antibiotic or with use of intermittent or tapered dosing over long periods**.⁹ Acquisition of such high-level fluoroquinolone resistance is likely a serial process of chromosomal mutations and not related to gene transfer.

4.2.4.2. What is the risk of besifloxacin as a topical agent for bacterial conjunctivitis in regards to microbial resistance?

Currently, there are 5 fluoroquinolones registered for human use in Australia. Of these two, ciprofloxacin and ofloxacin are registered for **topical ophthalmic use**. In addition, there are a number of quinolones including ophthalmic preparations for use in animal husbandry.

Gram positive pathogens accounted for 52.5% of positive cultures, 72.1% of which were *S. aureus*¹⁰ in bacterial conjunctivitis. Staphylococci infections are more common in adults; *S. pneumoniae* and *H. influenzae* are more common in children. Bacterial conjunctivitis is generally self-limiting, with clinical resolution without any treatment in most patients in seven days. However, treatment with broad-spectrum topical antibiotics can accelerate the rate of clinical resolution and decrease the risk of contagious spread and this is the rationale for the use of these topical antibiotic agents.

In vitro resistance to besifloxacin develops via **multiple-step mutations**. Besifloxacin is associated with a low MPC (Mutant prevention concentration), which suggests that spontaneously emerging mutants might not be able to gain much in terms of an increased resistance (higher Minimum Inhibition Concentration). For example, in *Staphylococcus aureus* and *Streptococcus pneumoniae*, MPCs were only 4 times higher than the MICs for those organisms. Correspondingly, very few drug-resistant mutants were obtained *in vitro* for those two species (< 1 mutant per 10¹⁰ cells). These data are consistent with the dual enzyme targeting action of besifloxacin, which reduces the risk of resistance especially if exposure is limited to no more than 7 days, the proposed use of Besivance.

4.2.4.3. Methicillin-resistant staphylococcus aureus (MRSA and Community-Acquired (CA-MRSA))

MRSA and CA-MRSA are growing problems globally and in Australia. Utilising MRSA isolates from the US, the 38 MRSA isolates analysed fell into the 2 clusters typical for hospital-associated MRSA (HA-MRSA) (n=22) or CA-MRSA (n=16). These results confirm that CA-MRSA poses a risk for ocular infections. However, while CA-MRSA tends to be more virulent, HA-MRSA is generally highly drug resistant. MIC₉₀ (µg/ml) values for HA-MRSA and CA-MRSA were 256 and 16 for ciprofloxacin, 64 and 2 for moxifloxacin and gatifloxacin, and 4 and 0.5 for besifloxacin, respectively indicating that for HA-MRSA quinolones cannot be used (as expected). Resistance

⁸ Sanfilippo CM, Hesje CK, Haas W, Morris T. Topoisomerase Mutations that are Associated with High-level resistance to earlier Fluoroquinolones in *Staphylococcus aureus* have less effect on the antibacterial activity of Besifloxacin. *Chemotherapy* 2011; 57:363-371.

⁹ Karpecki P, Paterno M and Comstock T. Limitations of Current Antibiotics for the Treatment of Bacterial Conjunctivitis. *Optom Vis Sci* 201; 87:908-919.

¹⁰ Bertino JS. Impact of antibiotic resistance in the management of ocular infections: the role of current and future antibiotics. *Clinical Ophthalmology* 2009; 3:507-521.

development to besifloxacin was not observed in the isolates recovered from besifloxacin clinical studies (Table 1).

Overall, besifloxacin ophthalmic suspension is unlikely to contribute to fluoroquinolone resistance development for the following reasons:

1. High ocular besifloxacin concentrations with high bacterial eradication, even among bacteria considered resistant by *in vitro* assessments;
2. Systemic exposure very low compared to orally administered quinolones;
3. Risk of overgrowth of non-susceptible organisms resulting from prolonged use unlikely with restriction of the labelled use to 7 days;
4. No systemic counterparts, theoretically eliminating the contribution of systemic use to the emergence of resistance although cross-resistance amongst quinolones is well recognised.

The sponsor of this drug has undertaken, since 2009, annual prospective surveillance of antibiotic resistance of ocular isolates i.e. The Antibiotic Resistance Monitoring in Ocular microorganisms (ARMOR). While this study is conducted in the US, there is no reason to believe the results are not applicable to Australia, where rates of quinolone resistance are in fact generally lower. Compared to 2009, there is growing resistance of many organisms:

1. non-susceptibility to penicillin remained steady at 5% among *Streptococcus pneumoniae* isolates, although more strains were resistant in 2010 and fewer were intermediate;
2. Azithromycin resistance rose to 29% in *Streptococcus pneumoniae*. An increase in resistance to moxifloxacin, azithromycin, and oxacillin was noted for *Staphylococcus aureus* and coagulase-negative staphylococci (CNS) isolates;
3. Among all staphylococci, non-susceptibility rates were 38-44% for moxifloxacin, 40-47% for gatifloxacin, 66-75% for azithromycin, and 50-65% for oxacillin. In addition, 25% of *S. aureus* isolates were resistant to clindamycin in 2010, showing an increase from 2009;
4. Imipenem resistance increased to 17% in *Pseudomonas aeruginosa*, while tobramycin resistance decreased;
5. *Haemophilus influenzae* isolates from 2010 were generally susceptible to all test agents as they were in 2009.

Importantly, MIC values of besifloxacin during ARMOR 2009 and ARMOR 2010 remained stable. The only organism with significant resistance was *Pseudomonas aeruginosa* (PA). But, besifloxacin should not be used for PA and the application does not seek to use Besivance for this organism.

4.2.5. Genetic-, gender- and age-related differences in pharmacodynamic response

Not applicable.

4.2.6. Pharmacodynamic interactions

None identified.

4.3. Evaluator's overall conclusions on pharmacodynamics

The clinical evaluator thinks there is adequate pharmacodynamics data and strongly supports the ongoing systematic collection of isolates obtained from ophthalmological infections in the US. The US results are likely applicable to Australia. Prospective surveillance (and preferably at the local level) of this nature is really the only means by which we can monitor patterns of microorganisms and their antibiotic resistance profiles under increasing selection pressure from the widespread use/misuse of antibiotics in clinical and vet practice.

5. Dosage selection for the pivotal studies

The clinical evaluator concurs that the dose used in the pivotal studies was appropriate as it took into consideration the safety of the 0.6% formulation (Study C-02-403-001), the imputed PK/PD ratio for reliable activity against likely bacterial conjunctivitis causing organisms and low systemic absorption of the topical formulation which reduces the risk of toxicity, drug-interaction and antimicrobial resistance. The clinical evaluator's only criticism, also raised by the FDA, is that the dosing in the pivotal studies should have been TID for **7 days** rather than 5 days.

6. Clinical efficacy

Standard methodology used when examining the eyes, for grading bacterial conjunctivitis and ocular adverse events as described below.

6.1. Eye examination

6.1.1. Assessment of VA

A pin-holed habitual (unaided) or historical correction was measured using Snellen charts. Lea Symbols used in children unable to use Snellen charts; **Biomicroscopy**: ophthalmic examination of the eye with slit lamp and magnifying lens. Rated as normal/abnormal for each anatomical location of the eye i.e. lids, limbus, conjunctiva, cornea, anterior chamber, lens, vitreous humour; **Specular Microscopy**: Specular microscopes calibrated using the SMRC instruction manual. Endothelial cell density determined by submission of images to SMRC (masked) for image analysis; **Ophthalmoscopy**: Severity ratings of fundus pathology measured. Shift tables of ophthalmoscopy scores used to describe changes.

6.1.2. Grading of bacterial conjunctivitis

Ocular discharge and bulbar/palpebral conjunctival injection assessed on 0-3 scale i.e. **Ocular discharge** rated as: **0. Absent**; **1. Mild**: Small amount of mucopurulent or purulent discharge noted in lower cul-de-sac. No true matting of eyelids in morning upon awakening; **2. Moderate**: Moderate amount of mucopurulent or purulent discharge noted in lower cul-de-sac. Frank matting together of eyelids in morning upon awakening; **3. Severe**: Profuse amount of mucopurulent or purulent discharge noted in lower cul-de-sac and in the marginal tear strip. Eyelids tightly matted together in the morning upon awakening requiring warm soaks to pry the lids apart. **Bulbar conjunctival injection** assessed by evaluating four quadrants (inferior, superior, temporal and nasal) using the following scale: **0. Normal**: Normal vascular pattern; **1. Trace**: Awareness eye is slightly pink color in one quadrant; **2. Moderate**: Diffuse pink color in at least (3) quadrants; **3. Severe**: Vasodilation in at least (3) quadrants, reddish hue. **Palpebral conjunctival injection** rated as follows: **0. Normal**: Normal vascular pattern; **1. Trace**: Trace hyperaemia; **2. Moderate**: Moderate hyperaemia or definable papillary reaction; **3. Severe**: Diffuse vasodilation.

6.1.3. Microbiological techniques (STANDARD)

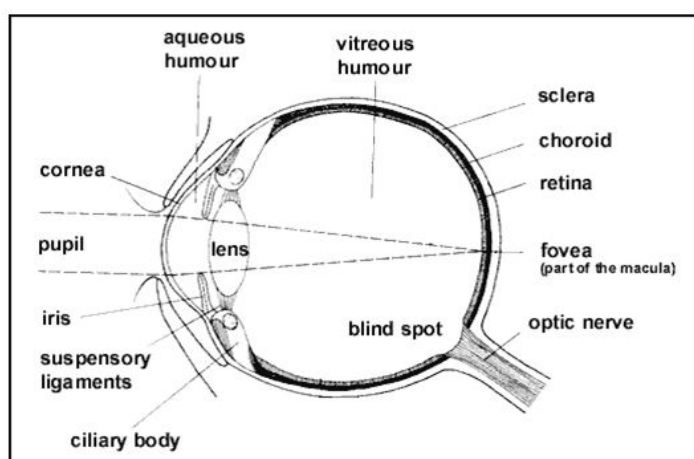
A culture of the cul-de-sac i.e. starting at lower conjunctival fornix nasal margin passing the swab along the fornix to temporal margin, rotating the swab through 180 degrees and re-passing the swab to its nasal margin (avoiding contact with eyelids) of the infected eye(s) taken without topical anaesthetic. One swab placed in the transport medium (PBS – 20% Glycerol) for bacterial and fungal culture; the other into M4 transport medium for viral cultures. **Culture Test Methods**: Standard microbiological techniques used to inoculate the relevant agar plates (Chocolate agar and 5% Sheep blood) and two serial, ten-fold dilutions all incubated at 35C in 5-7% carbon dioxide atmosphere. Bacterial colonies counted after 48 hours of incubation and

determine the bacterial Colony Forming Units per ml (CFU/ml) - done by multiplying colony count with appropriate dilution factor. Fungal (yeast) colonies counted after a total of 120 hours (5 days) of incubation and Fungal Colony Forming Units per ml (CFU/ml) determined by multiplying the colony count with the appropriate dilution factor. **Determination of Pathogen Identification:** a primary system of identification for organisms was used, but if the identification was inadequate, then a secondary system was used along with supplemental biochemicals and/or bacterial DNA fragments using gel analysis software to identify the organism(s) as needed. **For MIC,** 3-5 isolated colonies selected to create a direct suspension approximating $1-2 \times 10^8$ colony forming units (CFU)/mL according to the FDA-approved manufacturer's guidelines for this system. This suspension then diluted in cation-adjusted Mueller Hinton broth (CAMHB) for the nonfastidious organisms to a final concentration approximating 5×10^5 CFU/mL. For Haemophilus species, Haemophilus Test Medium (HTM) broth was used to obtain a final concentration approximating 5×10^5 CFU/mL. Accordingly, final inoculum of approximately 5×10^4 CFU delivered to each microtiter well containing 0.1 mL of antibiotic suspension. For Streptococcus species, CAMHB with 2-5% lysed horse blood was used for inoculum preparation and antibiotic suspensions in the microtiter wells. All organisms of concern incubated at 35C in ambient atmospheric conditions. MIC incubations for Staphylococcus species occur for 16-20 hours for most antibiotics (exception was oxacillin, which requires a full 24 hours of incubation); Streptococcus pneumonia isolates incubated for 20-24 hours; Enterococci incubated for 16-20 hours for most antibiotics (exception vancomycin, always receiving 24 hours of incubation). Medical technologists used inverted viewing mirrors for interpretation of endpoint MIC values. The MIC recorded as the lowest antibiotic concentration where **complete growth inhibition** observed. Antibiotic interpretive breakpoint criteria recorded for each patient result, following NCCLS guidelines for FDA-approved agents. Quality Control (QC) measures were performed according to NCCLS guidelines (M7-A6, January 2003) related to 30-day QC validations, weekly QC, and daily QC. The NCCLS-defined QC ranges for antibiotics that are available for the selected American Type Culture Collection (ATCC) bacterial strains (M100-S14, January 2004) were used to monitor the proper performance of the Antimicrobial Susceptibility Test (AST). **Processing and Interpretation of Viral Culture Specimen:** Tissue culture tubes used for viral cultures included Rhesus monkey kidney (RMK); MRC5, A549; 0.2ml of specimen into each decanted tissue culture tube. Inoculate for one hour at 36C, then washed, re-fed with maintenance medium and observed daily for the cytopathic effect indicative of viral growth for 2-3 weeks.

6.1.4. Ocular adverse events

6.1.4.1. Ocular comfort

Stinging/burning, itching, blurring; foreign body sensation were graded on a 4 point scale (0=none; 1=mild; 2= moderate; 3= severe); **Duration of ocular comfort:** symptoms reported above were estimated for duration after instillation of study drug i.e. <1 minutes, 1-5 minutes, >5 minutes; **Visual acuity:** changes in VA after instillation of study drug; **Biomicroscopy and Fundoscopy changes:** descriptive for each anatomical part of the eye as detailed above and in Figure 1. **Intraocular pressure (IOP):** descriptive changes in IOP.

Figure 1: Anatomy of the eye.

6.2. Pivotal efficacy studies: Besivance for the treatment of bacterial conjunctivitis in adults and children (1 year or older)

There are 3 pivotal efficacy studies for Besivance: 373, 433 and 434. In 373 and 433 the comparator was Vehicle and besifloxacin was superior to Vehicle in regards to clinical resolution and eradication of baseline infection. In 434, the comparator was Moxifloxacin ophthalmic solution, a licensed fluoroquinolone for the treatment of bacterial conjunctivitis; here, besifloxacin ophthalmic suspension was non-inferior to Vigamox for clinical resolution and microbial eradication of baseline bacterial infection. Each of these studies is described in the detail required for this section.

In Study 373, clinical resolution at the primary analysis visit (day 8) occurred in 73.3% (44/60) of besifloxacin-treated subjects with culture-confirmed conjunctivitis vs. 43.1% (25/58) of vehicle subjects ($p < 0.001$). Bacterial eradication occurred in 88.3% (53/60) of patients in the besifloxacin group vs. 60.3% (35/58) of vehicle-treated subjects ($p < 0.001$). In Study 433, clinical resolution at the primary analysis visit (Day 5) occurred in 45.2% (90/199) of besifloxacin-treated patients with culture-confirmed conjunctivitis vs. 33.0% (63/191) of patients receiving vehicle ($p = 0.0084$), while bacterial eradication occurred in 91.5% (182/199) of patients in the besifloxacin group versus 59.7% (114/191) of vehicle-treated patients ($p < 0.0001$). In the non-inferiority study 434, besifloxacin and moxifloxacin, clinical resolution at the primary analysis visit (Day 5) occurred in 58.3% and 59.4% of patients (besifloxacin and moxifloxacin, respectively; $p = 0.652$; CI, -9.48% to 7.29%), and bacterial eradication occurred in 93.3% and 91.1% (besifloxacin and moxifloxacin, respectively; $p = 0.1238$; CI, -2.44% to 6.74%), confirming the non-inferiority of besifloxacin to moxifloxacin for bacterial conjunctivitis.

6.3. Analyses performed across trials (pooled & meta analyses)

Integrated clinical and microbial efficacy data from the vehicle-controlled studies, Study 373 and Study 433 is presented in this section. In addition, data from the active-controlled Study 434 was used for analyses of microbial efficacy on individual bacterial species.

A few important methodological issues should be noted i.e.

- The time point for the first follow-up visit (Visit 2) was different for Study 373 and Study 433 (and Study 434) i.e. Visit 2 was defined as Day 4, ± 1 day (Study 373) and Day 5, ± 1 day (Study 433). In Studies 373 and 433 (and 434), clinical assessments and culture of infected eye(s) at Visit 2 occurred prior to administration of the first daily dose of study drug. Furthermore, efficacy analyses were conducted on data collected at this visit. Hence, the use

of the terminology 'after 5 days of treatment' to describe the treatment received prior to assessment of the primary efficacy variables in Study 433 (and 434) could be misleading because Visit 2 may have occurred as early as Day 4 (i.e. after 3 days of treatment) or as late as Day 6 (i.e. after 5 days of treatment). There is no adjustment in the analysis for this potential difference in duration of exposure to the study drug;

- Definitions for clinical diagnosis and clinical resolution of bacterial conjunctivitis were different for Study 373 and Study 433 (and Study 434). In 373, included subject had to have a minimum grade 1 for ocular discharge and a minimum of grade 1 for either bulbar or palpebral conjunctival injection. For 433, a minimum of grade 1 for ocular discharge and bulbar conjunctival injection was required for inclusion;
- Clinical resolution was defined as absence of ocular discharge and bulbar **and** palpebral conjunctival injection for 373 and as absence of ocular discharge and bulbar conjunctival injection for 433.

These methodological differences may have impacted on differences between the study results i.e.

- Rates of clinical resolution between besifloxacin and vehicle groups at Visit 2 (Day 4, ± 1 day) were not statistically significant for Study 373; in contrast, rates of clinical resolution between besifloxacin and vehicle groups at Visit 2 (Day 5, ± 1 day) for Study 433 were statistically significant. In the original analysis for Study 373, the primary efficacy analysis was conducted at Visit 3 (Day 8, +1 day). The apparent difference in rate of clinical resolution between these studies may be accounted for by different visit days, Visit 2 being conducted one day earlier in 373 than 433;
- In addition, clinical resolution for 373 required absence of 3 clinical signs (conjunctival discharge, bulbar and palpebral conjunctival injection) whereas in 433 clinical resolution required absence of 2 clinical signs (conjunctival discharge and bulbar conjunctival injection). In a further analysis of Study 373, clinical resolution at Visit 2 based on 2 clinical signs did not result in a statistically significant difference between treatment groups, although rates of resolution for both treatment groups increased. At Visit 3 (Day 8, +1 day), the difference in the rates of clinical resolution between the besifloxacin and vehicle groups was statistically significant for both studies, although overall rates were lower for 373 (original analysis) than for 433. At this visit, the difference in clinical resolution rates between these studies can be accounted for by the different definitions of clinical resolution. When the data for Study 373 was analysed with clinical outcome definition as per 433 (conjunctival discharge and bulbar conjunctival injection), the difference in the rates of clinical resolution between the besifloxacin ophthalmic suspension and vehicle treatment groups at Visit 3 was in favour of besifloxacin and higher than the rates originally reported in 373;
- When the rates of clinical resolution are compared between the vehicle-controlled Study 433 and the active-controlled Study 434, rates of clinical resolution were higher for subjects in the besifloxacin group in Study 434 compared to the besifloxacin group in Study 433. However, microbial eradication rates for subjects in the besifloxacin ophthalmic suspension treatment groups were similar in both studies. Differences in the control may have contributed to this finding by introducing an expectation bias in the active-controlled study;
- Overall microbial eradication rates for besifloxacin subjects were high at Visit 2 and sustained through Visit 3 (Day 8, +1 day) for both Study 373 and Study 433. Differences in eradication rates between besifloxacin and vehicle groups were statistically significant at both study visits. Despite the difference of 1 day between studies (and hence duration of exposure to drug) for Visit 2, besifloxacin produced equally high levels of bacterial eradication, confirming rapid treatment effect.

6.3.1. Efficacy in special populations

The primary efficacy endpoints of clinical resolution and microbial eradication (at Visits 2 and 3) were analysed for all study eyes within the specified study population as well as by gender (Males/Females), race (White/Asian/Black or African American/Other), ethnicity (Hispanic or Latino/Not Hispanic and Not Latino), and age (<2 years, 2-19 years, 20-59 years and ≥60 years).

Findings:

- Clinical resolution rates at Visit 2 tended to be slightly lower for males in the besifloxacin group and slightly higher for males in the vehicle groups vs. females in each group. Similar trends were seen in the besifloxacin group, but not the vehicle group, at Visit 3;
- At Visits 2 and 3, the difference in clinical resolution rates between besifloxacin and vehicle groups was statistically significant for females ($p < 0.0053$). For males, however, the difference in clinical resolution rates between besifloxacin vs. vehicle treatment groups was only statistically significant at Visit 3 ($p = 0.0257$). Comparing point estimates of clinical resolution rates between besifloxacin and vehicle groups, males had a lower rate of clinical resolution at both Visit 2 and Visit 3 vs. females. Moreover, this difference could not be explained by different gender proportions in the studies;
- Microbial eradication rates were statistically significantly higher in the besifloxacin vs. vehicle for both males and females at Visit 2 and Visit 3 and were similar to the overall mITT 'as randomized' population. Rates of clinical resolution in these studies tended to be higher in the younger age groups at both Visit 2 and Visit 3 for both besifloxacin and vehicle. In general, treatment differences on clinical resolution rates within each age group were similar to overall, with besifloxacin higher than vehicle, with the exception of Visit 2 in the >60 year old age group where clinical resolution rates **were low overall**. Rates of microbial eradication, on the other hand, tended to be higher in the older age groups. In general, the treatment differences on microbial eradication rates within each age group were similar to overall, with besifloxacin ophthalmic suspension rates higher than vehicle;
- Due to small sample sizes, statistical comparisons within race groups other than 'White' do not have sufficient power to be conclusive. At Visit 2, rates of clinical resolution for 'Blacks or African Americans' were consistent with rates observed for overall mITT 'as randomized' population. At Visit 3, rates of clinical resolution for this subgroup were ~10% lower in the besifloxacin group and approximately 15% higher in the vehicle treatment group than for the overall mITT 'as randomized' population. Microbial eradication rates in those of 'Black' race were high, with higher rates for besifloxacin than vehicle, at both Visit 2 and Visit 3 and did not follow the same trend seen for clinical resolution. For subjects who reported race as 'Other', rates of microbial eradication at Visit 2 were slightly lower in both treatment groups when compared to the overall mITT 'as randomized' population although the difference between treatment groups remained consistent with overall findings. For the 'Hispanic and Latino' ethnicity group, rates of clinical resolution at Visit 3 were slightly higher in both treatment groups when compared to the overall mITT 'as randomized' population although the difference between treatment groups remained consistent with overall.

6.4. Evaluator's conclusions on clinical efficacy for besivance

The 0.6% concentration of besifloxacin hydrochloride and TID dosing is supported by pharmacokinetic/pharmacodynamic relationship analysis and data from the submitted preclinical studies and clinical trials. The pivotal studies confirm the efficacy and safety of Besivance versus placebo (Vehicle) and in a head to head study with an appropriate comparator, that is, the topical ophthalmic formulation of moxifloxacin (same class of antibiotic and approved for this indication). It is important to note, however, that topical moxifloxacin for ophthalmological use is not approved in Australia. Other alternative topical antimicrobial

agents approved in Australia for **bacterial conjunctivitis include** are: chloramphenicol, sulfacetamide sodium, tobramycin (aminoglycoside), gentamicin (aminoglycoside), framycetin sulphate (aminoglycoside), ciprofloxacin and ofloxacin (both quinolones).

7. Clinical safety

7.1. Studies providing evaluable safety data

The following studies provided evaluable safety data, Study C-02-403-001, 507, ROC2-05-070, 373, 433 and 434.

7.1.1. Pivotal efficacy studies

- In the pivotal efficacy studies, the following safety data were collected: General adverse events (AEs) were assessed by patient report and investigator assessment at each visit – targeted in regards to eye symptoms/signs and open-ended in regards to other symptomatology; Ophthalmologic events were assessed by measures of visual acuity (VA), slit lamp biomicroscopy and ophthalmoscopy;
- Laboratory tests i.e. biochemistry, haematology and urinalysis were not performed in the pivotal efficacy study as systemic absorption is so low. Safety lab data was provided in C-02-403-001 only;
- ECG readings were collected before and after dosing in the Phase 1 safety study, C-02-403-001 only.

7.1.2. Pivotal studies that assessed safety as a primary outcome

Studies C-02-403-001, 507, ROC2-05-070 were pivotal studies assessing safety as a primary outcome. Safety data was collected for the Pivotal efficacy studies, 373, 433 and 434.

7.2. Pivotal studies that assessed safety as a primary outcome

There were 3 studies, C-02-403-001, 507 and ROC2-05-070 that assessed safety as a primary outcome.

7.3. Patient exposure

The application includes exposure information from 4 clinical studies conducted in 161 healthy volunteers and 4 clinical studies conducted in 2507 subjects with a clinical diagnosis of bacterial conjunctivitis (Studies 478, 373, 433, 434). Overall, 1445 subjects received besifloxacin (0.3% or 0.6%), 644 subjects received Vehicle, and 598 subjects received the comparator drug Vigamox. Of the 1445 subjects receiving besifloxacin ophthalmic suspension, 1433 received the proposed therapeutic concentration. Duration of dosing for those receiving the proposed concentration ranged from one day (one drop) to 7 days. The frequency of dosing ranged from a single instillation up to QID, representing total exposure of at least 6658 besifloxacin ophthalmic suspension subject-days, 6574 of them using the 0.6% formulation.

7.4. Adverse events

Monitored through patient report, investigator questioning (open and directed) and eye examinations as described in the 'Clinical efficacy' section.

7.4.1. All adverse events (irrespective of relationship to study treatment)

7.4.1.1. Treatment-emergent, non-ocular adverse events

There were no statistically significant differences between besifloxacin ophthalmic suspension and vehicle treatment groups for any non-ocular AE reported in the integration of Studies 373, 433 and 434.

7.4.1.2. Pivotal studies

Headache was the most common AE in all treatment groups. 21/1192 (1.8%) subjects treated with besifloxacin ophthalmic suspension reported headaches. Nine events were designated by the Investigator to be unrelated to the study drug, 4 unlikely, 6 possibly, and 2 probably related. A majority of these events (16) were mild in severity, 5 were moderate. A total of 11 of the 616 (1.8%) subjects treated with vehicle reported headaches of which 3 were unrelated to study drug, 6 unlikely related to study drug and 2 possibly related to study drug. A majority of these events (9) were mild in severity, 2 were moderate. A total of 9 of the 579 (1.6%) subjects in the Vigamox treatment group reported headaches, of which 6 were mild in severity and 3 were moderate. The majority of these events (7) were unrelated to study drug and 1 event each were classified as unlikely and possibly related to study drug.

7.4.2. Treatment-related adverse events (adverse drug reactions)

7.4.2.1. Treatment-emergent, ocular adverse events

Treatment-Emergent, Ocular AEs Occurring in $\geq 0.5\%$ of Eyes in either treatment Group, all treated Eyes, safety Population (Studies 373, 433, 434) are presented in Table 2. Treatment-emergent, ocular AEs were more common than non-ocular AEs for all treated eyes in the safety population, including both study and fellow eyes. A total of 13.8 % (249/1810) of eyes in the besifloxacin group had at least 1 ocular AE, 19.8% (190/961) of eyes in the vehicle treatment group and, 14.0% (120/855) of eyes in the Vigamox treatment group each experienced at least 1 ocular AE.

Table 2: Treatment-Emergent, Ocular AEs Occurring in $\geq 0.5\%$ of Eyes in either Treatment Group, All Treated Eyes, Safety Population (Studies 373, 433, 434).

	Besifloxacin Suspension (N = 1810)	Vehicle (N = 961)	Vigamox (N = 855)	p-Value
Total Number of AEs	227	235	153	
Number of Eyes With at Least One AE	249 (13.8%)	190 (19.8%)	120 (14.0%)	<0.0001
EYE DISORDERS	243 (13.4%)	188 (19.7%)	113 (13.2%)	<0.0001
Conjunctivitis	47 (2.6%)	31 (3.3%)	33 (3.9%)	0.0223
Vision blurred	88 (4.9%)	39 (4.1%)	4 (0.5%)	0.0035
Conjunctivitis bacterial	32 (1.8%)	27 (2.8%)	22 (2.6%)	0.0736
Eye irritation	26 (1.4%)	27 (2.8%)	12 (1.4%)	0.0167
Eye pain	26 (1.5%)	17 (1.8%)	9 (1.1%)	0.6386
Eye pruritus	10 (0.6%)	18 (1.9%)	3 (0.4%)	0.0761
Conjunctival haemorrhage	7 (0.4%)	5 (0.5%)	4 (0.5%)	0.7627
Eye discharge	6 (0.3%)	6 (0.6%)	3 (0.4%)	0.3615
Eyelid oedema	6 (0.3%)	4 (0.4%)	5 (0.6%)	0.7457
Conjunctival hyperaemia	10 (0.6%)	3 (0.3%)	0 (0.0%)	0.5617
Punctate keratitis	5 (0.3%)	3 (0.3%)	5 (0.6%)	>0.9999
Ocular hyperaemia	6 (0.3%)	5 (0.5%)	1 (0.1%)	0.529
Conjunctivitis viral	10 (0.6%)	0 (0.0%)	1 (0.1%)	0.0185
Dry eye	5 (0.3%)	2 (0.2%)	4 (0.5%)	>0.9999
Lidial hyperaemia	4 (0.2%)	3 (0.3%)	4 (0.5%)	0.6994
Lacrimation increased	1 (0.1%)	6 (0.6%)	2 (0.2%)	0.0085

N = all treated eyes for the specified treatment group and includes study and fellow eyes

The number of eyes with at least 1 treatment-emergent, ocular AE was significantly lower for the besifloxacin group vs. vehicle ($p < 0.0001$). The most prevalent ocular AEs were consistent with the underlying ocular disease being studied i.e. bacterial conjunctivitis. Five ocular AEs, were reported at statistically different rates between the besifloxacin and vehicle treatment groups i.e.

1. Conjunctivitis and blurred vision were reported at lower rates in the eyes treated with besifloxacin vs. vehicle, $p=0.0223$ and $p=0.0035$, respectively;
2. Eye irritation and increased lacrimation were reported at lower rates in eyes treated with besifloxacin vs. vehicle, $p=0.0187$ and $p=0.0085$ respectively;
3. Viral conjunctivitis was reported in eyes treated with besifloxacin ophthalmic suspension whereas it was not reported for vehicle treated eyes ($p=0.0185$).

In Study ROC2-05-070 (besifloxacin ophthalmic suspension vs. Vigamox), besifloxacin ophthalmic suspension drop resulted in statistically significant worse high contrast/high illumination VA immediately after drop instillation with means of 0.27 logMAR (20/37 Snellen equivalent) and -0.06 logMAR (20/17 Snellen equivalent), respectively. In addition, eyes receiving besifloxacin experienced a longer recovery time to baseline VA (58 seconds) compared to eyes that received Vigamox (21 seconds). In the larger safety and efficacy studies, blurred vision was reported at a rate of 2.1% for subjects in the besifloxacin group and the majority of the events were mild.

7.4.2.1.1. Rates of AEs in subgroups

The incidence of treatment-emergent ocular and non-ocular AEs were compared between the besifloxacin group and vehicle group for sub-groups by gender (M/F), race (White/Asian/Black/Other), ethnicity (Hispanic/Latino vs. not), age (<2 years, 2-19 years, 20-59 years, and 60 years or older). Consistent with rates observed in the overall safety population, rates of AEs observed in subgroups were low and no significant differences were observed between the besifloxacin and vehicle groups. Since clinical trials did not enroll infants below 1 year of age, the safety and effectiveness of besifloxacin ophthalmic suspension in this age group has not been established.

7.4.2.1.2. Relationship of AEs to dose, dose regimen, and treatment duration

0.6% dose used was used in the pivotal studies. In the Phase I study, Study C-02-403-001, no AEs were reported in the 0.3% besifloxacin group, 6 subjects in the vehicle group reported a total of 10 AEs; 2 subjects in the 0.6% besifloxacin group each reported a single AE. However, the overall low incidence of reported AEs means drawing conclusions regarding dose-relatedness is not possible.

7.4.3. Deaths and other serious adverse events

7.4.3.1. Pivotal studies

No deaths; 4 SAEs reported in efficacy studies:

1. 1 SAE in besifloxacin subject (Study 373) – hospitalisation for dehydration, underlying liver cirrhosis; considered unrelated by investigator & Sponsor;
2. 1 SAE in besifloxacin subject (Study 434) – difficulty breathing on background of sleep apnoea in [information redacted]; found to have CCF and a pericardial effusion; considered unrelated by investigator & Sponsor;
3. 1 SAE in moxifloxacin subject (Study 434) – a [information redacted] with acute viral syndrome with associated renal failure; considered unrelated by investigator & Sponsor;
4. 1 SAE in a [information redacted] individual (Study 433), at Day 4 the subject presented was hospitalized with pneumonia; Investigator & Sponsor considered event unrelated.

No deaths/SAEs reported for any other clinical studies.

7.4.4. Discontinuation due to adverse events

7.4.4.1. Pivotal studies

Study 373, one discontinuation in the vehicle treatment group – moderate preseptal cellulitis in both eyes. Investigator considered event unrelated to study drug. In Study 433, 4 and 5 subjects in the besifloxacin and vehicle groups respectively discontinued due to AEs. One discontinued subject in the besifloxacin group, and 2 in the vehicle group, had worsening conjunctivitis. Positive viral cultures (adenovirus) were returned for the besifloxacin subject. Another 2 subjects in the vehicle treatment group had ocular surface inflammation, conjunctival oedema, and corneal infiltrates specifically, as the AE associated with discontinuation. Other AEs associated with discontinuation were: earache (vehicle), URTI (besifloxacin); skin rash (besifloxacin), fellow eye with conjunctivitis (besifloxacin) for which Vigamox, rather than study drug, was initiated. One subject discontinued due to an SAE (pneumonia). In Study 434: 16 subjects discontinued due to AEs: 11 and 5 in the besifloxacin and Vigamox treatment groups, respectively. 1 subject was discontinued after being hospitalized for unrelated congestive heart failure. In 4 cases, subjects were discontinued due to the need for systemic treatment of URTI with disallowed medications. Hypersensitivity to the Vigamox was reported for 1 subject. Four subjects required disallowed ocular medications for ocular conditions that were presumed non-infectious. The remaining 6 subjects were discontinued due to either worsening conjunctivitis (3 subjects in besifloxacin group), the development of a nonspecific keratitis (1 subject in besifloxacin group and 1 Vigamox subject), or the diagnosis of Herpes simplex keratitis (1 besifloxacin subject). Positive viral culture results (adenovirus) were returned in 2 of the 3 cases with worsening conjunctivitis and in the Herpes simplex keratitis case.

7.4.4.2. Other studies

No subjects discontinued due to AEs in the other clinical trials (C-02-403-001, R0C2-05-070, 507, 478 and 424) conducted in support of this application.

7.5. Laboratory tests

Lab tests were only conducted in one of the Safety studies, C-02-403-001.

7.5.1. Liver function

7.5.1.1. Pivotal studies

Not applicable.

7.5.1.2. Other studies

Assessed in study C-02-403-001. No changes.

7.5.2. Kidney function

Creatinine clearance significantly reduced at 1000mg/kg dose levels but not at 100mg/kg dose in rats dosed orally. The maximum plasma concentration (C_{max}) following the oral administration of 100mg/kg besifloxacin in rats is about 1000-fold higher than the plasma levels following topical administration. Risk of renal toxicity following topical besifloxacin administration is negligible.

7.5.2.1. Pivotal studies

Not applicable.

7.5.2.2. Other studies

Assessed in study C-02-403-001. No changes.

7.5.3. Other clinical chemistry**7.5.3.1. Pivotal studies**

Not applicable.

7.5.3.2. Other studies

Not applicable.

7.5.4. Haematology**7.5.4.1. Pivotal studies**

Not applicable.

7.5.4.2. Other studies

Assessed in study C-02-403-001. No changes.

7.5.5. Urinalysis**7.5.5.1. Pivotal studies**

Not applicable.

7.5.5.2. Other studies

Assessed in study C-02-403-001. No changes.

7.5.6. Electrocardiograph**7.5.6.1. Pivotal studies**

Not applicable.

7.5.6.2. Other studies

QT-interval prolongation has been associated with the systemic use of some fluoroquinolones in humans. Besifloxacin induced a minimal inhibitory effect on hERG (human Ether-à-go-go Related Gene) tail current in stably-transfected HEK-293 (Human Embryonic Kidney 293) cells. The cardiovascular study in animals indicates that the drug has the potential to prolong QT interval when administered systemically. However, as the systemic exposure is so low when the drug is administered topically, QT prolongation is not a concern. Assessed in C-02-403-001. No changes in QT/QTc intervals or other parameters on the ECG between active drug at 2 different concentrations (0.3 and 0.6%) and Vehicle only.

7.5.7. Vital signs**7.5.7.1. Pivotal studies**

Not applicable.

7.5.7.2. Other studies

Assessed in study C-02-403-001. Minor increases were observed in heart rate and BP – but there were changes in all groups irrespective of whether active drug was contained in the Vehicle or not.

7.6. Post-marketing experience

Periodic safety update reports which included two investigational studies initiated during this reporting period (2011) provided in this application. No new safety data from any source including the investigational studies one of which, BL-646 is being conducted in Subjects from Birth to 31 Days of Age.

7.7. Safety issues with the potential for major regulatory impact

None.

7.7.1. Liver toxicity

Not applicable, topical agent, low/no systemic absorption.

7.7.2. Haematological toxicity

Not applicable, topical agent, low/no systemic absorption.

7.7.3. Serious skin reactions

None.

7.7.4. Cardiovascular safety

None.

7.7.5. Unwanted immunological events

Not applicable.

7.8. Other safety issues

None.

7.8.1. Safety in special populations

No data for pregnant/breastfeeding woman or children under 1 year of age as they were specifically excluded. No safety signal revealed in age group including children aged 1 year or older with bacterial conjunctivitis. No reports of arthropathy (ref: paediatric population) or Achilles tendonitis (ref adults) as reported with systemic quinolones.

7.8.2. Safety related to drug-drug interactions and other interactions

Not performed due to low systemic exposure of besifloxacin following topical administration.

7.9. Evaluator's overall conclusions on clinical safety

Treatment with besifloxacin ophthalmic suspension resulted in no serious adverse events (SAEs) related to study drug. Overall, rates of non ocular and ocular adverse events (AEs) were low. The majority of non ocular AEs were unrelated to study drug; the most prevalent ocular AEs were consistent with study treatment and/or underlying ocular disease being studied. Importantly, the main treatment emergent ocular AEs, that is, conjunctivitis, vision blurred, eye irritation and eye pain can all be associated with the underlying disorder and all occurred with lower frequency than when bacterial conjunctivitis was treated with besifloxacin compared to treatment with vehicle alone. A potential risk with any anti infective is the development of antibiotic resistance and this is discussed in detail in the clinical evaluation report.

8. First round benefit-risk assessment

Bacterial conjunctivitis is characterised by marked hyperaemia or redness of the eye and mild to moderate purulent conjunctival discharge. Symptoms often include watery eyes, itching, and vague ocular irritation. The disease is generally self limiting and usually does not cause permanent loss of vision or structural damage. Intervention with use of a topical broad spectrum ocular anti infective is the standard of care in the management.

8.1. First round assessment of benefits

The benefits of Besivance in the proposed usage are:

- Well tolerated topical agent of proven efficacy against the common forms of bacterial conjunctivitis, that is, superior to placebo and equivalent to a comparator topical ocular quinolone agent;
- TID dosing means adherence to the scheduled dosing is more likely;
- High ocular levels well above the MIC for the common bacteria causing conjunctivitis;
- Nil meaningful systemic absorption therefore the risk of inducing potential quinolone resistance is low, coupled with the fact that resistance to besifloxacin probably requires at least two steps.

8.2. First round assessment of risks

The risks of Besivance in the proposed usage are:

- Use for conjunctivitis that is not bacterial in aetiology;
- Inappropriate use for deeper (more than conjunctival) bacterial infections of the eye;
- Development of microbial resistance at the local level or treatment failure because patterns of global antibiotic resistance are changing rapidly, such that organisms currently sensitive to this agent are no longer similarly sensitive in the future. Some of these issues may be compounded by the fact that a swab for bacterial and viral culture may not be routine in clinical practice, that is, the diagnosis is made clinically and swabs are only performed if there is a clinical failure to empiric antimicrobial therapy.

However, these risks are not unique to Besivance, they apply equally to this product and all currently approved topical antibiotics for ocular use in this setting.

8.3. First round assessment of benefit-risk balance

The benefit-risk balance of 0.6% Besifloxacin hydrochloride ophthalmic (Besivance), given the proposed usage, is favourable for the following reasons: equivalent clinical and microbiological efficacy to a licensed topical antibiotic to all common bacterial (Gram +ve and Gram -ve) causes of conjunctivitis with minimal safety concerns revealed through the development programme. Potential for enhanced adherence as Besivance administered **TID** (as opposed to more frequently). The clinical evaluator agrees that the recommended course should be 7 days of treatment even though the clinical trials of this agent used 5 day dosing. The rationale is that the drug is clearly very safe and this additional two days of treatment will ensure the “later” responders are adequately treated. Moreover, microbial resistance did not emerge during the efficacy studies of besifloxacin or its comparator, moxifloxacin. However, this will need to be monitored as part of post marketing surveillance. A key strategy in minimising antibiotic resistance is to minimise inappropriate use (that is, for viral conjunctivitis), perform microscopy, culture and sensitivity (M, C & S) test of purulent material, switch rapidly to another antibiotic if resistance is detected, ensure patients understand exactly how to administer the agent and adhere fully with the dosing schedule (TID for 7 days) and last, ensure exposure is not extended beyond 7 days.

9. First round recommendation regarding authorisation

The clinical evaluator recommends approval of this drug for the indication listed in the PI as it stands.

10. Clinical questions

None; the clinical evaluator is satisfied with the scope of this clinical application as submitted.

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