CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-308

SUMMARY REVIEW

Division Director Review

Date	April 2, 2009
From	Wiley A. Chambers, M.D.
Subject	Besivance (besifloxacin ophthalmic suspension), 0.6%
NDA#	22-308
Applicant	Bausch & Lomb Incorporated
Date of Submissions	May 30, 2008 (June 2, 2008 stamp)
Dosage forms / Strength	ophthalmic suspension
Proposed Indication(s)	A quinolone antimicrobial indicated for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following bacteria: CDC coryneform group G, *Corynebacterium pseudodiphtheriticum**, *Corynebacterium striatum**, *Haemophilus influenzae*, *Moraxella lacunata**, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus hominis**, *Staphylococcus lugdunensis**, *Streptococcus mitis* group, *Streptococcus oralis*, *Streptococcus pneumoniae*, *Streptococcus salivarius** *Efficacy for this organism was studied in fewer than 10 infections.
Recommended:	Approval

1. Introduction

The active ingredient in Besivance, besifloxacin hydrochloride, is a fluoroquinolone anti-infective and a new chemical entity for ophthalmic use. Besifloxacin is an 8-chloro fluoroquinolone with a N-1 cyclopropyl group. The compound has activity against some Gram-positive and Gram-negative bacteria due to the inhibition of bacterial DNA gyrase and topoisomerase IV. DNA gyrase is an enzyme required for replication, transcription and repair of bacterial DNA. Topoisomerase IV is an enzyme required for partitioning of the chromosomal DNA during bacterial cell division. At the concentrations applied to the eye, besifloxacin is bactericidal.

Ophthalmologic products currently approved for the treatment of bacterial conjunctivitis include azithromycin ophthalmic solution, tobramycin ophthalmic solution, gentamicin ophthalmic solution, erythromycin ophthalmic ointment, ciprofloxacin ophthalmic solution, ofloxacin ophthalmic solution, levofloxacin ophthalmic solution, norfloxacin ophthalmic solution, gatifloxacin ophthalmic solution, and moxifloxacin ophthalmic solution

Ophthalmic anti-infectives are generally well tolerated and effective for bacterial conjunctivitis. There are no specific safety issues with this drug product.

Bacterial conjunctivitis is generally a self limited disease with a usual course of 7-14 days. The goal of therapy is to reduce the duration of the illness and minimize the chances of infecting other individuals. Efficacy is recommended to be demonstrated in at least two adequate and well-controlled, multi-center, independent trials of at least 7 days in duration. Independence refers to different investigators and different geographic locations between the trials. Demonstration of efficacy is recommended to include evidence of statistical significance and clinical relevance. Clinical relevance or a clinical cure is recommended to be defined as the resolution of signs and symptoms (i.e. a score of 0, normal conjunctiva and no discharge) for the infected patients who meet the inclusion criteria of the protocol.

The following are recommended demonstrations of efficacy:
1. Statistically significant superiority in replicated studies to the product's vehicle in the cure of the signs and symptoms of bacterial conjunctivitis in clinically infected patients who meet the inclusion criteria.

2. An alternative approach for drug substances which have already demonstrated efficacy in another anti-infective indication is to show superiority to vehicle in one trial and equivalence to tobramycin or one of the approved fluoroquinolones dosed qid in another trial.

Additionally, in trials which include the test product's vehicle in one arm, it is recommended that the cure rate of the vehicle should not be numerically superior to the cure rate of the test product for the Intent-to-Treat population.

2. Background

An End of Phase 1 Meeting was held on May 25, 2004, and an End of Phase 2 Meeting was held on December 6, 2005. A Pre-NDA meeting was held on June 6, 2007. At the end of each of the meetings, the Agency provided general guidance; there were no scientific disagreements.

On December 5, 2008 the Dermatologic and Ophthalmic Drug Advisory Committee reviewed NDA 22-308. The Advisory recommended approval of besifloxacin hydrochloride ophthalmic suspension, 0.6%.

3. CMC

From the original CMC Review:

DRUG SUBSTANCE:
Besifloxacin is an 8-chlorofluoroquinolone anti-infective for topical ophthalmic use. The ophthalmic product is indicated for the treatment of bacterial conjunctivitis caused by susceptible microorganisms. The structure of besifloxacin has been established by its route of

synthesis and elemental analysis, UV, FTIR, MS, ^{1}H NMR and $^{13}CNMR$ analysis. Impurities (related substances) introduced during synthesis or degradation products formed during synthesis and /or storage have been adequately studied. The synthetic processes as well as controls of starting materials, reagents, process intermediate, and the final drug substance are acceptable. The commercial batches will be manufactured at [redacted] Stability of the drug substance has been evaluated on 3 batches at long-term conditions (25°C/60%RH) for [redacted] and accelerated conditions (40°C/75%RH) for [redacted] The stability data support a [redacted] retest period for the drug substance. The quality of the drug substance is adequately controlled by identification tests, potency assay [redacted], moisture level, residual solvents, particle size distribution and heavy metals tests. Unidentified individual impurities of the drug substance are controlled at NMT [redacted] and total impurities at NMT [redacted] respectively. b(4) b(4)

DRUG PRODUCT:

Besivance (besifloxacin ophthalmic suspension) 0.6%) is a sterile, preserved ophthalmic suspension formulated for topical application. The inactive components include polycarbophil, mannitol, poloxamer 407, sodium chloride, and edetate disodium. Benzalkonium chloride is present as a preservative. The product is packaged in a white low density polyethylene (LDPE) bottle with a controlled dropper tip and a tan polypropylene cap. Besivance is manufactured as a sterile ophthalmic suspension and filled in two configurations. No leacheable has been reported above [redacted] in the tested stability batches by a validated GC/MS method after two years of long term storage. Besifloxacin impurities and degradation products are tested by a validated stability indicating method. The acceptance criterion for any individual unspecified impurity is NMT [redacted] and total impurities are NMT [redacted] in the product. The acceptance criteria for besifloxacin assay are [redacted] during its shelf life. Besivance™ has an expiration dating period of 24 months in the carton protected container. The physician sample (2 mL) has an expiration dating period of 18 months. The product should be protected from light. b(4)

REGULATORY SPECIFICATIONS:

Release and Shelf Life Specifications for Besifloxacin Ophthalmic Suspension 0.6%

TEST	PROCEDURE	RELEASE CRITERIA	SHELF LIFE CRITERIA
Appearance			
Identification A			
Identification B			
pH			
Viscosity			
Osmolality			
Besifloxacin HCl Potency Assay			
Besifloxacin HCl[4]			

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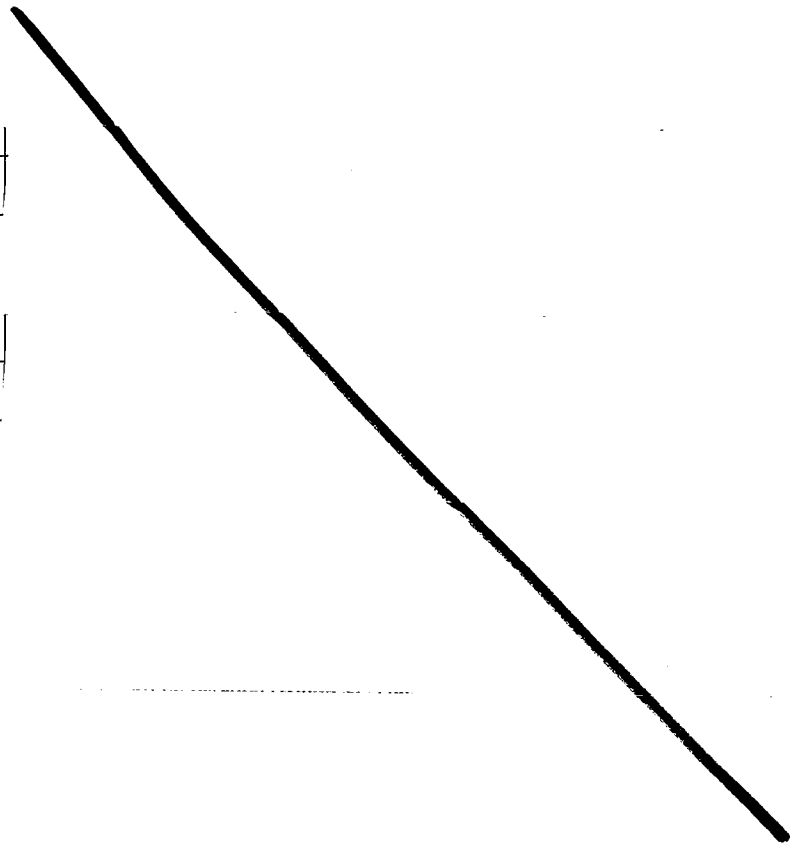
Benzalkonium Chloride Assay	
EDTA Assay	
Particle Size Analysis	
Fill Volume	
Weight Loss/Gain	
Preservative Efficacy[6]	
Sterility	
Endotoxin	



b(4)

All facilities were found acceptable for NDA 22-308 by Compliance. , an alternate analytical site for compendial testing for drug substance, was found acceptable by Office of Compliance on 2/11/09. b(4)

4. Nonclinical Pharmacology/Toxicology

From the original Pharmacology/Toxicology Review:

Systemic and ocular toxicology studies were conducted with besifloxacin. Ocular studies in rabbits and dogs demonstrated adequate local tolerance to the 0.6% ophthalmic suspension. Besifloxacin had a genotoxicity profile typical of a fluoroquinolone. It was mutagenic in some bacterial strains, clastogenic in Chinese hamster ovary cells, and positive in a mouse micronucleus assay *in vivo*. When administered orally, besifloxacin did not reduce fertility in

male or female rats at doses up to 500 mg/kg/day. It was not associated with fetal skeletal or visceral malformations when administered to pregnant rats at maternally toxic doses up to 1000 mg/kg/day. Besifloxacin was fetotoxic (postimplantation loss, neonatal mortality, developmental delays) at 1000 mg/kg/day, which provided exposure levels far in excess of what would occur after topical ocular administration. There was a clear NOAEL of 100 mg/kg/day for reproductive toxicity, and systemic exposure following this dose would still be far in excess of exposure that would occur after ocular dosing.

CARCINOGENICITY:
Carcinogenicity studies have not been performed with besifloxacin. They are not necessary for a product being developed for short term use in patients with bacterial conjunctivitis.

REPRODUCTIVE TOXICOLOGY:
A complete battery of reproductive and developmental toxicity studies was conducted with besifloxacin. Pregnancy Category C is recommended for this product. Besifloxacin did not impair the fertility of male or female rats given doses of up to 500 mg/kg/day (the highest dose tested in this study). Doses of 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 high dose was associated with maternal toxicity (reduced body weight gain and food consumption) and maternal mortality. At this dose, the mean Cmax and AUC in the rat dams were 20 µg/ml and 178 µg·hr/ml, respectively. Increased postimplantation loss was observed at 1000 mg/kg/day in the rat embryo-fetal development study. Fetal body weights were less than controls and decreased ossification was also observed at this high dose. The NOAEL for the rat embryo-fetal development study was the mid dose of 100 mg/kg/day (Cmax, 5 µg/ml; AUC, 23 µg·hr/ml). These findings were consistent with a rat study of pre- and postnatal development conducted using the same doses of besifloxacin (10, 100, and 1000 mg/kg/day). F_1 pups at the high dose weighed significantly less than controls and had a reduced neonatal survival rate. Attainment of developmental landmarks and sexual maturation were delayed at 1000 mg/kg/day, although surviving pups from this dose group that were reared to maturity did not demonstrate deficits in behavior, including activity, learning and memory, and their reproductive capacity appeared normal. The NOAEL for this pre- and postnatal developmental toxicity study in rats was 100 mg/kg/day. The sponsor also submitted data from besifloxacin embryo-fetal development studies conducted in rabbits. This species did not tolerate repeated dosing with besifloxacin (not unusual for certain classes of antimicrobials) and the dose range finding study should have demonstrated to the investigators that the rabbit was not an appropriate species to use for this type of study. Severe maternal toxicity (generally secondary to upset of gastrointestinal flora in the rabbit) led to the does consuming little food and aborting their litters at 20 mg/kg/day.

Due to the much greater systemic exposure of the rats given oral doses of besifloxacin in reproduction toxicity studies compared to systemic exposure following topical ocular application in humans, the reproductive toxicity of besifloxacin observed in animal studies is unlikely to be clinically relevant for this product.

5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review:

Studies C-02-403-001 and 424 characterized besifloxacin pharmacokinetics in plasma and tears respectively.

The C_{max} was 0.37 ng/mL in plasma with a range of 0.025 – 1.2.

The *in vitro* hERG study suggested that concentrations greater than 10,000 times the highest observed plasma concentration induced a 13% inhibition in hERG tail current, suggesting that it is unlikely that besifloxacin would impact cardiac repolarization. *In vitro* incubation with human hepatocytes suggest that besifloxacin is not significantly metabolized, and the plasma concentrations observed in clinical trials suggest that it is unlikely that besifloxacin would reach a high enough concentration to interfere with the metabolism of other drugs.

6. Sterility Assurance

From the original Clinical Pharmacology Review:

The applicant amended the NDA on 17 December 2008 with a release specification test method and acceptance criterion for bacterial endotoxins. The test method is the gel clot technique performed according to USP<85>, and its associated acceptance criterion is NMT 9 EU/mL. The endotoxin testing method was evaluated by a contract testing facility [redacted] The initial test method development studies demonstrated that a 1:100 dilution of the subject drug product was necessary to eliminate enhancement of the test results by the product (data presented in Table 3.2.P.5.3.7-1 of the subject submission). The contract testing facility performed a verification study to show that the stated test method is suitable for use with the subject drug product. Five lots of drug product were tested in the verification. The maximum valid dilution was determined to be 1:300 using the equation MVD = EL/λ or (9 EU/mL)/(0.03 EU/mL); where EL is the endotoxin limit and λ is the lysate sensitivity. The verification study was performed using product diluted 1:100 and spiked with endotoxin. Data from this verification are provided in Table 3.2.P.5.3.7-3 of the subject submission and meet the following acceptance criteria:

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A bacterial endotoxin test performed by the gel clot test is invalid due to any of the following conditions:

- The positive product controls are negative,
- The endotoxin standard series does not show the end point concentration to be within 2-fold dilution from the label claim sensitivity of the lysate,
- The lowest concentration of the standard solution does not show a negative result in all replicates,

- Any negative control is positive.

The applicant's acceptance criterion for bacterial endotoxins was considered acceptable from the Sterility Assurance Group.

The Ophthalmology Group has been recommending a limit be set on endotoxin and at the present time the Group does not information to suggest that 9 EU/mL would be unsafe for this product, particularly since the treatment of bacterial conjunctivitis is expected to involve an intact cornea.

7. Clinical/Statistical - Efficacy

From the original Medical Officer Review:

The applicant conducted three adequate and well controlled clinical trials. Studies 373 and 433 were superiority trials, and Study 434 was an equivalence trial comparing Besivance (besifloxacin hydrochloride ophthalmic suspension, 0.6%) to Moxifloxacin (moxifloxacin hydrochloride ophthalmic solution 0.5%).

Analysis of Primary Endpoint(s) – Clinical Resolution

Clinical Resolution was defined as absence of all three clinical signs: ocular discharge, bulbar conjunctival injection, and palpebral conjunctival injection.

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Intent To Treat (i.e., not necessarily culture positive) – Clinical Resolution

(For Study # 373 Safety Population is the same as ITT for Studies # 433 and #434)

Study 373	Besifloxacin	Vehicle	
Visit 2 - Day 4 (±1 day)	N= 136	N= 130	p= 0.0905[1]
Clinical Resolution	33 (24%)	20 (16 %)	(-0.0063, 0.1851)[2]
Visit 3 - Day 8 (+ 1 day)	N=136	N=130	p=0.0013[3]
Clinical Resolution	89 (65%)	59 (45%)	(0.0835, 0.3177)[2]

1 Pearson Chi-square Statistic 3.29, exact p-value
2 95% CI difference in proportions
3 Pearson Chi-square Statistic 10.83, exact p-value

Study 433	Besifloxacin	Vehicle	
Visit 2 (Day 5 ± 1 day)	N=455	N=457	p= 0.006 / 0.017[1]
Clinical Resolution	195 (43%)	160 (35%)	(1.5%, 14.2%)[2]
Visit 3 (Day 8 + 1 day)	N=444	N=431	p= <0.002 / <0.003[1]
Clinical Resolution	373 (84%)	327 (76%)	(2.8%, 13.4%)[2]

[1] p-Value for Comparison of Treatments; Cochran-Mantel-Haenszel test stratified by center / Pearson chi-squared test, resp.
[2] 95% CI for Difference in Percentages; Difference calculated as Besifloxacin minus Vehicle. Positive values favor Besifloxacin.

Study 434	Besifloxacin	Moxifloxacin	
Visit 2 (Day 5 ± 1 day)	N=566	N=564	p= 0.97 / 0.86[1]
Clinical Resolution	320 (56%)	322 (57%)	(-6.3%, 5.2%)[2]
Visit 3 (Day 8 + 1 day)	N=556	N=551	p= 0.78 / >0.99[1]
Clinical Resolution	483 (83%)	479 (83%)	(-4.0%, 4.9%)[2]

[1] p-Value for Comparison of Treatments; Cochran-Mantel-Haenszel test stratified by center / Pearson chi-squared test, resp.
[2] Difference calculated as Besifloxacin minus Moxifloxacin. Positive values favor Besifloxacin.

Besifloxacin ophthalmic suspension was superior to its vehicle in the Intent-to-Treat population in Studies #373 and # 433 and was equivalent to the moxifloxacin populations.

Modified Intent To Treat (i.e., culture positive) – Clinical Resolution
(For Study # 373 Intent To Treat is the same as modified ITT for Studies # 433 and #434)

Study 373	Besifloxacin	Vehicle	
Visit 2 - Day 4 (±1 day)	N=60	N=56	p=0.2434[1]
Clinical Resolution	14 (23%)	8 (14%)	(-0.0504, 0.2314)[2]
Visit 3 - Day 8 (+ 1 day)	N=60	N=56	p=0.0058[3]
Clinical Resolution	37 (62%)	20 (36%)	(0.0838, 0.4353)[2]

1 Pearson Chi-square Statistic 1.54, exact p-value
2 95% CI difference in proportions
3 Pearson Chi-square Statistic 7.81, exact p-value

Study 433	Besifloxacin	Vehicle	
Visit 2 (Day 5 ± 1 day)	N=194	N=179	p= 0.01 / 0.035[1]
Clinical Resolution	90 (46%)	63 (35%)	(1.2%, 21.2%)[2]
Visit 3 (Day 8 + 1 day)	N=190	N=173	p= 0.019 / 0.006[1]
Clinical Resolution	167 (88%)	132 (76%)	(3.7%, 19.5%)[2]

[1] p-Value for Comparison of Treatments; Cochran-Mantel-Haenszel test stratified by center / Pearson chi-squared test, resp.
[2] 95% CI for Difference in Percentages; Difference calculated as Besifloxacin minus Vehicle. Positive values favor Besifloxacin.

Study 434	Besifloxacin	Moxifloxacin	
Visit 2 (Day 5 ± 1 day)	N=251	N=274	p= 0.638 / 0.859[1]
Clinical Resolution	149 (59%)	165 (60%)	(-9.27%, 7.56%)[2]
Visit 3 (Day 8 + 1 day)	N=243	N=269	p= 0.03 / 0.079[1]
Clinical Resolution	220 (91%)	229 (85%)	(-0.31%, 11.1%)[2]

[1] p-Value for Comparison of Treatments; Cochran-Mantel-Haenszel test stratified by center / Pearson chi-squared test, resp.
[2] Difference calculated as Besifloxacin minus Moxifloxacin. Positive values favor Besifloxacin.

Besifloxacin ophthalmic suspension was superior to its vehicle in the Modified Intent-to-Treat (culture positive) population in Studies #373 and # 433 and was equivalent to the moxifloxacin populations.

Analysis of Secondary Endpoints(s)

Clinical Resolution by cultured organism (cured patients/total patients)

Organism	Besifloxacin - 373	Besifloxacin - 433	Besifloxacin-434	Vehicle-373	Vehicle-433	Moxafloxcin-434
Abiotrophia defectiva			1/1			
Achromobacter xylosoxidans		1/1		0/1		
Acinetobacter calcoaceticus			1/1			2/2
Acinetobacter species				0/1		1/1
Aerococcus viridans			3/3		2/2	4/5
Bacillus species		1/1				
Brevibacterium casei			1/1			
Brevibacterium vesicularies						1/1
Brevibacterium species		3/3	2/2		2/3	
CDC coryneform group G	0/2	7/7	6/7		½	9/11
CDC coryneform group II		1/1				
Citrobacter koseri						0/1
Coagulase negative staph		1/1		0/1		
Corynebacterium afermentans						1/1
Corynebacterium amycolatum						1/1
Corynebacterium argentoratense				0/1		1/1
Corynebacterium auris			1/1			
Corynebacterium jeikeium		2/2				
Corynebacterium macginleyi		1/1	0/1	0/1		1/3
Corynebacterium minutissimum		1/1	1/1			
Corynebacterium propinquum		1/1		0/1		3/4
Corynebacterium pseudodiphtheriticum	0/1		4/4			0/3
Corynebacterium species			2/2			0/1
Corynebacterium Striatum		3/3	1/2			2/3
Corynebacterium Urealyticum			1/1		1/1	
Eikenella Corrodens			1/1			
Enterobacter cloacae		1/1				
Enterobacter Sakazakii	0/1					
Entercocccus faecalis	0/1		0/2			2/2
Gemella Morbillorum		1/1	0/1			
Gemella species		2/2				
Granulicatella Adiacens			2/2			1/2
Haemophilus influenzae	21/25	56/63	73/81	11/21	48/66	82/88
Haemophilus parainfluenzae		1/1		1/2		2/2
Klebsiella Denitrificans			1/1			
Klebsiella oxytoca		1/2				
Klebsiella ozarnae			0/1			
Kocuria Kristine			1/1		1/1	
Leminorella species						1/1
Micrococcus species			1/1		0/1	
Moraxella catarrhalis		1/1	2/2	0/1	3/3	4/5

Organism	Besifloxacin - 373	Besifloxacin - 433	Besifloxacin-434	Vehicle-373	Vehicle-433	Moxafloxcin-434
Moraxella lacunta		1/1	4/4		2/3	1/1
Moraxella nonliquefaciens						1/1
Moraxella Species						1/1
Morganella morganii						1/1
Neisseria gonorrhoeae			2/2			
Neisseria meningitidis		1/1	1/1	0/1		
Neisseria sicca			1/1			
Neisseria subflava						1/1
Pasteurella multocida					0/1	1/3
Proteus mirabilis			1/1			2/4
Pseudomonas aeruginosa		2/2	1/2		1/1	2/3
Pseudomonas fluoresceins						1/1
Rothia mucilaginosa		1/1				
Serratia marcescens	0/1	2/2		0/1		5/5
Staphylococcus aureus	4/6	17/23	50/58	2/9	23/32	41/57
Staphylococcus capitis	0/1		1/3			1/1
Staphylococcus caprae		1/1	1/1		1/1	1/1
Staphylococcus chromogenes						1/1
Staphylococcus epidermidis	1/2	13/16	21/29	0/4	16/18	34/41
Staphylococcus haemolyticus			1/1		1/1	0/1
Staphylococcus hominis		2/2	3/4		1/2	0/1
Staphylococcus intermedius	0/1					
Staphylococcus lugdunensis		1/1	5/5			1/2
Staphylococcus simulans						
Staphylococcus warneri		1/1	2/2		0/1	1/1
Staphylococcus xylosus		1/1				0/1
Stenotrophomonas maltophilia	0/1		3/3	0/1		3/3
Streptococcus agalactiae				0/1		
Streptococcus anginosus			1/1			1/1
Streptococcus anginosus group			1/1			
Streptococcus dysgalactiae		1/1			1/1	
Streptococcus milleri group					1/1	
Streptococcus mitis		6/6	3/3	0/1	2/4	3/5
Streptococcus mitis group	1/1	7/9	10/11		9/10	14/14
Streptococcus oralis	0/2	2/3	5/6	1/1	0/1	4/4
Streptococcus parasanguinis			1/1			1/1
Streptococcus pneumoniae	15/24	60/74	51/58	5/14	45/66	53/64
Streptococcus pyogenes		0/1			1/2	2/2
Streptococcus salivarius		3/3	1/2		2/2	2/2
Streptococcus sanguis		1/2	1/2			
Streptococcus thermophilus			1/1			
Streptococcus species		1/2	3/3		2/4	2/4
Streptococcus viridans					1/1	

Efficacy was demonstrated in patients with cultures positive for:

Gram-positive microorganisms: CDC coryneform group G; *Corynebacterium pseudodiphtheriticum*; Corynebacterium striatum*; Staphylococcus aureus; Staphylococcus epidermidis; Staphylococcus hominis*; Staphylococcus lugdunensis*; Streptococcus mitis group; Streptococcus oralis; Streptococcus pneumoniae; Streptococcus salivarius*, and*

Gram-negative microorganisms: *Haemophilus influenzae; Moraxella lacunata**

*Efficacy of this organism was studied in fewer than 10 infections.

Clinical Microbiology – Bacterial Eradication
Bacterial Eradication is eradication of all pathogens above pathological threshold at baseline.

Study 373	Besifloxacin	Vehicle	
Visit 2 - Day 4 (±1 day)[1]	N=60	N=58	p=<0.0001 / <0.0001 [2]
Bacterial Eradication	54 (90%)	28 (48%)	(24.93%, 58.52%)[3]
Visit 3 - Day 8 (+ 1 day)[1]	N=60	N=58	p=0.0003 / 0.0006 [2]
Bacterial Eradication	53 (88%)	35 (60%)	(12.11%, 43.87%)[3]

1 Missing or Discontinued Subjects imputed as microbial eradication failures.
2 p-Values from the Cochran-Mantel-Haenszel test stratified by center / Pearson chi-squared test, respectively.
3 95% CI - Difference calculated as Besifloxacin minus Vehicle. Positive values favor Besifloxacin.

Study 433	Besifloxacin	Vehicle	
Visit 2 (Day 5 ± 1 day)[1]	N=193	N=173	p= <0.0001 / < 0.0001 [2]
Bacterial Eradication	181 (94%)	114 (66%)	(19.8%, 36.03%)[3]
Visit 3 (Day 8 + 1 day)[1]	N=189	N=172	p= <0.0001 / 0.0001 [2]
Bacterial Eradication	175 (93%)	137 (80%)	(5.8%, 20.1%)[3]

1 Missing or Discontinued Subjects imputed as microbial eradication failures.
2 p-Values from the Cochran-Mantel-Haenszel test stratified by center / Pearson chi-squared test, respectively.
3 95% CI - Difference calculated as Besifloxacin minus Vehicle. Positive values favor Besifloxacin.

Study 434	Besifloxacin	Moxifloxacin	
Visit 2 (Day 5 ± 1 day)[1]	N=249	N=267	p= <0.0001 / < 0.0001 [2]
Bacterial Eradication	241 (97%)	250 (94%)	(-0.6%, 6.8%)[3]
Visit 3 (Day 8 + 1 day)[1]	N=240	N=262	p= 0.048 / 0.21 [2]
Bacterial Eradication	223 (93%)	235 (90%)	(-1.7%, 8.2%)[3]

1 Missing or Discontinued Subjects imputed as microbial eradication failures.
2 p-Values from the Cochran-Mantel-Haenszel test stratified by center / Pearson chi-squared test, respectively.
3 95% CI - Difference calculated as Besifloxacin minus Moxifloxacin. Positive values favor Besifloxacin.

Adequate and well controlled studies (#373, #433 and #434) support the efficacy of besifloxacin hydrochloride ophthalmic suspension for the treatment of bacterial conjunctivitis for the susceptible organisms.

8. Safety

The three clinical studies (Studies #373, #433 and #434) were used to establish the safety of the drug product. Overall, the safety population included over 1000 subjects in the besifloxacin group, approximately 600 subjects in the besifloxacin vehicle group and approximately 550 subjects in the moxifloxacin group.

See the following table from the Medical Officer's original review, Section 7.3.3.

Pooled Adverse Event Table

	Besifloxacin (approx N=1187)	Vehicle (N=614)	Moxifloxacin (N=576)
Number of Patients with at Least One AE	139 (12%)	101 (16%)	54 (9%)
Eye irritation	17 (1.4%)	18(2.9%)	8 (1.4%)
Eye pain	22 (1.8%)	11 (1.8%)	7 (1.2%)
Worsening bacterial conjunctivitis	7 (0.6%)	9 (1.5%)	2 (0.3%)
Conjunctivitis	14 (1.2%)	15 (2.4%)	5 (0.9%)
Eye pruritus	13 (1.1%)	10 (1.6%)	2 (0.3%)
Vision blurred	25 (2.1%)	24 (3.9%)	3 (0.5%)
Eyelid oedema	5 (0.4%)	3 (0.5%)	5 (0.9%)
Eye discharge	3 (0.3%)	4 (0.6%)	3 (0.5%)
Conjunctival haemorrhage	4 (0.8%)	3 (0.5%)	3 (0.5%)
Conjunctival hyperaemia	6 (0.5%)	2 (0.3%)	0
Conjunctival oedema	6 (0.5%)	2 (0.3%)	1 (0.2%)
Corneal infiltrates	6 (0.5%)	1 (0.2%)	2 (0.3%)
Punctate keratitis	4 (0.3%)	2 (0.3%)	3 (0.5%)
Visual acuity reduced	3 (0.3%)	3 (0.5%)	2 (0.3%)
Conjunctivitis viral	6 (0.5%)	0	1 (0.2%)
Dry eye	3 (0.3%)	1 (0.2%)	3 (0.5%)
Eyelid margin crusting	3 (0.3%)	3 (0.5%)	1 (0.2%)
Limbal hyperemia	2 (0.2%)	2 (0.3%)	3 (0.5%)
Ocular hyperemia	3 (0.3%)	3 (0.5%)	1 (0.2%)
Conjunctival disorder	2 (0.2%)	1 (0.2%)	3 (0.5%)
Lacrimation increased	1 (0.1%)	3 (0.5%)	2 (0.3%)
Eye inflammation	1 (0.1%)	2 (0.3%)	2 (0.3%)
Foreign body sensation	3 (0.3%)	1 (0.2%)	0
Abnormal sensation in eye	0	3 (0.5%)	0
Conjunctival follicles	1 (0.1%)	0	2 (0.3%)
Erythema of eyelid	1 (0.1%)	1 (0.2%)	1 (0.2%)
Blepharitis	1 (0.2%)	1 (0.2%)	0
Corneal erosion	1 (0.1%)	1 (0.2%)	0

	Besifloxacin (approx N=1187)	Vehicle (N=614)	Moxifloxacin (N=576)
Eye infection	0	1 (0.2%)	1 (0.2%)
Eye swelling	0	2 (0.3%)	0
Eyelid disorder	1 (0.1%)	1 (0.1%)	0
Keratitis	1 (0.1%)	0	1 (0.2%)
Keratoconjunctivitis sicca	2 (0.2%)	0	0
Photophobia	1 (0.1%)	0	1 (0.2%)
Visual disturbance	2 (0.2%)	0	0
Adenoviral conjunctivitis	0	1 (0.2%)	0
Altered visual depth perception	1 (0.1%)	0	0
Anterior chamber inflammation	1 (0.1%)	0	0
Blepharitis allergic	0	1 (0.2%0	0
Blepharospasm	1 (0.1%)	0	0
Chalazion	0	1 (0.2%)	0
Conjunctival cyst	0	1 (0.2%)	0
Conjunctivitis allergic	1 (0.1%)	0	0
Corneal abrasion	0	0	1 (0.2%)
Corneal disorder	0	0	1 (0.2%)
Corneal opacity	1 (0.1%)	0	0
Episcleritis	1 (0.1%)	0	0
Eye disorder	1 (0.1%)	0	0
Eye movement disorder	0	1 (0.2%)	0
Eyelid irritation	0	0	1 (0.2%)
Herpes simplex ophthalmic	1 (0/1%)	0	0
Hordeolum	1 (0.1%)	0	0
Iritis	0	0	1 (0.2%)
Ocular discomfort	0	1 (0.2%)	0
Periorbital cellulitis	0	1 (0.2%)	0
Photopsia	1 (0.1%)	0	0
Pinguecula	0	0	1 (0.2%)
Vitreous floaters	0	1 (0.2%)	0
Drug hypersensitivity	0	0	1 (0.2%)
Instillation site irritation	0	1 (0.2%)	0
Instillation site pain	1 (0.1%)	0	0
Investigations- corneal staining	2 (0.2%)	1 (0.2%)	2 (0.3%)
Dermatitis contact	0	0	2 (0.3%)
Dry skin	1 (0.1%)	0	0
Skin ulcer	0	0	1 (0.2%)
Total Number of Systemic Events	107	64	45
Number of Patients with at Least One AE	75 (6%)	48 (8%)	31 (5%)
Lymphadenopathy	2 (0.2%)	0	0
Anaemia	1 (0.1%)	0	0
Leukocytosis	1 (0.1%)	0	0
Cardiac failure congestive	1 (0.1%)	0	0
Ear pain	1 (0.1%)	2 (0.3%)	0
Hypoacusis	1 (0.1%)	0	1 (0.2%)
Tinnitus	1 (0.1%)	0	0

	Besifloxacin (approx N=1187)	Vehicle (N=614)	Moxifloxacin (N=576)
Vertigo	1 (0.1%)	0	0
Eye pruritis	1 (0.1%)	0	0
Nausea	1 (0.1%)	1 (0.2%)	2 (0.3%)
Diarrhoea	1 (0.1%)	2 (0.3%)	0
Vomiting	1 (0.1%)	1 (0.2%)	1 (0.2%)
Abdominal pain upper	0	2 (0.3%)	0
Dysgeusia	1 (0.1%)	0	0
Glossodynia	0	0	1 (0.2%)
Tongue blistering	1 (0.1%)	0	0
Toothache	0	0	1 (0.2%)
Pyrexia	6 (0.5%)	4 (0.6%)	1 (0.2%)
Fatigue	1 (0.1%)	1 (0.2%)	0
Influenza like illness	1 (0.1%)	0	0
Pain	1 (0.1%)	0	1 (0.2%)
Seasonal allergy	1 (0.1%)	0	0
Upper respiratory tract infection	2 (0.2%)	2 (0.3%)	4 (0.7%)
Pharygitis streptococcal	3 (0.3%)	3 (0.5%)	1 (0.2%)
Nasopharyngitis	2 (0.2%)	2 (0.3%)	2 (0.3%)
Otitis media	4 (0.3%)	1 (0.2%)	0
Ear infection	2 (0.2%)	2 (0.3%)	1 (0.2%)
Bronchitis	2 (0.2%)	1 (0.2%)	1 (0.2%)
Sinusitis	3 (0.3%)	0	1 (0.2%)
Pneumonia	1 (0.1%)	1 (0.2%)	0
Viral upper respiratory tract infection	2 (0.2%)	0	0
Gastroenteritis	1 (0.1%)	0	0
Herpes zoster	0	0	1 (0.2%)
Urinary tract infection	1 (0.1%)	0	0
Viral infection	0	0	1 (0.2%)
Excoriation	1 (0.1%)	0	0
Head injury	1 (0.1%)	0	0
Sunburn	1 (0.1%)	0	0
Anorexia	1 (0.1%)	0	0
Decreased appetite	0	0	1 (0.2%)
Back pain	1 (0.1%)	0	0
Myalgia	0	0	1 (0.2%)
Pain in extremity	1 (0.1%)	0	0
Headache	21 (1.8%)	11 (1.8%)	9 (1.6%)
Dizziness	1 (0.1%)	0	1 (0.2%)
Loss of consciousness	1 (0.1%)	0	0
Migraine	0	1 (0.2%)	0
Sinus headache	1 (0.1%)	0	0
Somnolence	1 (0.1%)	0	0
Anxiety	1 (0.1%)	0	1(0.2%)
Depression	2 (0.2%)	0	0
Insomnia	0	1 (0.2%)	0
Pharyngolaryngeal pain	8 (0.7%)	5 (0.8%)	3 (0.5%)
Cough	4 (0.3%)	4 (0.6%)	1 (0.2%)

	Besifloxacin (approx N=1187)	Vehicle (N=614)	Moxifloxacin (N=576)
Asthma	2 (0.2%)	1 (0.2%)	1 (0.2%)
Nasal congestion	2 (0.2%)	1 (0.2%)	1 (0.2%)
Respiratory tract congestion	2 (0.2%)	0	1 (0.2%)
Epistaxis	1 (0.1%)	1 (0.2%)	0
Rhinorrhoea	1 (0.1%)	1 (0.2%)	0
Dyspnoea	0	1 (0.2%)	0
Nasal dryness	1 (0.1%)	0	1 (0.2%)
Rhinitis allergic	1 (0.1%)	0	0
Wheezing	0	1 (0.2%)	0
Rosacea	0	1 (0.2%)	1 (0.2%)
Blister	0	1 (0.2%)	0
Dermatitis allergic	1 (0.1%)	0	0
Dermatitis contact	0	1 (0.2%)	0
Eyelid pain	0	1 (0.2%)	0
Skin hyperpigmentation	0	0	1 (0.2%)
Swelling face	1 (0.1%)	0	0
Urticaria	1 (0.1%)	0	0

There were relatively few reported adverse experiences (individual events all less than 2% except for blurred vision occurring in 2.1%). Other frequently reported adverse experiences were eye pain, 1.8%; eye irritation, 1.4%, conjunctivitis bacterial, 1.2%, and eye pruritis, 1.1%.

9. Advisory Committee Meeting

The Dermatologic and Ophthalmic Drugs Advisory Committee of the Food and Drug Administration met on December 5, 2008 at the Hilton Washington/Rockville 1750 Rockville Pike, Rockville, Maryland. Michael X. Repka, M.D., chaired the meeting. There were approximately 60 audience members in attendance.

Attendance:
Dermatologic and Ophthalmic Drugs Advisory Committee Members present (voting):
Mary A. Majumder, J.D., Ph.D.
Temporary Voting Members:
Natalie Afshari, M.D., FACS ; Warren B. Bilker, Ph.D.; William G. Gates, M.D.; Philip Lavin, Ph.D.; Marijean M. Miller, M.D.; Michael X. Repka, M.D.; M. Roy Wilson, M.D., M.S.; Paula Cofer (Patient Representative) **Industry Representative (non-voting):** Ellen Strahlman, M.D.

The Advisory unanimously recommended approval of besifloxacin hydrochloride ophthalmic suspension, 0.6%.

10. Pediatrics

Ophthalmia neonatorum, in which bacterial conjunctivitis occurs within the first month of life appears to behave differently than bacterial conjunctivitis is older individuals. Ophthalmia neonatorum has not been studied in this application and therefore the safety and effectiveness of Besivance in infants below one year of age have not been established. The efficacy of Besivance™ in treating bacterial conjunctivitis in pediatric patients one year or older has been demonstrated in controlled clinical trials.

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.

11. Other Relevant Regulatory Issues

DSI
A Division of Scientific Investigations (DSI) audit was requested. An audit of the analytical and clinical portions of Studies 373, 433, and 434 noted minor regulatory violations in three of the four sites selected for audit because of the size of enrollment.

Per the DSI review dated February 23, 2009:

> Four clinical investigators, each of whom contributed large numbers of subjects to the study that they participated in and that were noted to have large numbers of protocol deviations reported in the NDA, were chosen for FDA PDUFA inspections. As the product was a new molecular entity an inspection of the Sponsor was also conducted. In addition, the Final Study Reports contained in NDA 22-308 identified a number of clinical investigators (CI) that had been terminated as CIs from studies early by the sponsor as a result of "continued major GCP non-compliance" and DSI determined that FDA For Cause/PDUFA inspections were indicated at two of these CI sites. The reasons that Bausch & Lomb Incorporated terminated these two sites are summarized below (from General Communication to IND 64, 335, Serial 0060, dated June 5, 2008):
>
> - Protocol #433 Noli R. Zosa, M.D. - Site failed to follow visit window and subject eligibility requirements (e.g. ocular discharge was absent at time to enrollment), investigator demonstrated a general lack of understanding of protocol requirements and awareness of GCP.
>
> - Protocol #434 Penny Asbell, M.D. - Site randomized subjects incorrectly, failed to follow visit window requirements and proper bacterial culture techniques (e.g. cultures

shipped under improper conditions); in addition to inadequate investigator supervision of study and informed consent process overall.

These investigators enrolled a small number of patients and analyses with or without their data do not significantly change the results of the clinical trials. For the purposes of labeling, the results from investigators Zosa and Asbell have not been included.

Name of CI, IRB, or Sponsor Location	Protocol # Site # # of Subjects	Inspection Date	Final Classification
Lee E. Rigel, O.D. VisionCare Associates 310 W. Lake Lansing Rd. Lansing, MI 48823	Protocol #373 Site #033 30 Subjects	09/08/2008-09/11/2008	VAI
Warren H. Heller, M.D. Arizona Center for Clinical Trials 515 W. Buckeye Rd, #206 Phoenix, AZ 85003	Protocol #433 Site #725416 78 Subjects	09/11/2008-09/15/2008	NAI
Bruce E. Kanengiser, M.D. Clinical Research Laboratories, Inc. 371 Hoes Lane Piscataway, NJ 08854 USA	Protocol #433 Site #700440 71 Subjects	08/26/2008-09/24/2008	VAI
Noli R. Zosa, M.D. 8337 Telegraph Road, Suite 125A Pico Rivera, CA 90660	Protocol #433 Site #691449 4 Subjects	10/02/2008-10/07/2008	Pending (Preliminary classification OAI)
Buhilda McGriff, M.D. Carolina Pediatric Eye Specialists 992 Copperfield Blvd Concord, NC 28025	Protocol #434 Site #750393 52 Subjects	08/28/2008-09/04/2008	VAI
Penny A. Asbell, M.D. 100th Street & Madison Ave Annennberg Bldg 22 Floor, Suite22 New York, NY 10029	Protocol #434 Site #748395 6 Subjects	Inspection pending	-
Bausch & Lomb Incorporated 1400 North Goodman Street Rochester, NY 14609	NDA #22-308 Protocol #373 Protocol #433 Protocol #434	09/02/2008-09/05/2008	VAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary, letter has not yet issued to the CI.

In general, Protocol #373, Protocol #433 and Protocol #434 appear to have been conducted adequately and the data in support of the NDA appear reliable and the monitoring was sufficient to identify investigators who were not conducting the study in an acceptable manner. Bausch & Lomb Incorporated correctly terminated the two sites, Zosa and Asbell. If the data from Zosa and Asbell are excluded, there is no significant change in either the safety or efficacy conclusions for this NDA.

The additional sites inspected by DSI (Rigel, Heller, McGriff, and Kanengiser) have violations which do not significantly affect the overall reliability of safety and efficacy data.

FINANCIAL DISCLOSURE
Bausch & Lomb has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.* There is no evidence to suggest that the results of the studies were impacted by any financial payments.

DDMAC
The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the proposed product labeling, including the package insert (PI), draft carton label, and draft container label for Tradename™ (besifloxacin ophthalmic suspension) submitted by the applicant on January 8, 2009. Their suggestions have been incorporated into the revised, final labeling where appropriate.

DMEPA
The Division of Medication Error Prevention and Analysis (DMEPA) objected to the use of the originally proposed proprietary name, Optura, for this product because it was vulnerable to name confusion that could lead to medication errors with Optivar and Optive. They recommended an alternative proprietary name be submitted for consideration. A second consult was requested regarding a trade name review for the alternative proposed name "Besivance." In a meeting held with the review team on February 27, 2009, DMEPA reported that the proposed tradename "Besivance" was acceptable. A total of thirty-two (32) names were analyzed to determine if the drug names could be confused with Besivance and if the drug name confusion would likely result in a medication error. Nineteen (19) of the names lacked convincing look-alike and/or sound-alike similarities with Besivance. One (1) name is used only in foreign countries (Fosavance). One (1) name was a proposed name that has never been used for a marketed product (Mesavant). Two (2) names were for products that have been withdrawn from the market/no generic available (Benisone, Beconase). Six (6) names were for products with no overlap in strength or dose. Two (2) names were for single-strength products that have multiple differentiating characteristics.

The final name, Besivance, was the subject of the DMEPA review. DMEPA reviewed the draft labeling submitted by B&L on January 8, 2009. Their suggestions have been incorporated into the revised, final labeling where appropriate.

12. Labeling

NDA 22-308 is recommended for approval for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following bacteria:

CDC coryneform group G, *Corynebacterium pseudodiphtheriticum*, Corynebacterium striatum*, Haemophilus influenzae, Moraxella lacunata*, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus hominis*, Staphylococcus lugdunensis*, Streptococcus mitis* group, *Streptococcus oralis, Streptococcus pneumoniae, Streptococcus salivarius**

*Efficacy for this organism was studied in fewer than 10 infections

Because the clinical trials dosed the drug product for 5 days and not 7 days, the Director of the Office of Anti-Microbial Products (OAP) believes that Besivance (besifloxacin ophthalmic suspension) 0.6% should be labeled to instill one drop in the affected eye(s) 3 times a day for 5 days. I do not agree. Day 5 was selected for the clinical studies because it is on the "steep" portion of the cure rates and therefore permitted a distinction between treatment and vehicle. Not all subjects were effectively treated with 5 days of treatment for bacterial conjunctivitis as measured in the clinical studies. Unlike the clinical studies conducted in this NDA, in clinical practice these subjects would not routinely be cultured nor would they be scheduled for a follow-up visit. In my opinion, there is an adequate safety margin to allow the use of besifloxacin ophthalmic solution to be dosed 3 times a day for 7 days in the affected eye(s). Bacterial conjunctivitis is usually a self limited condition, but without follow-up, an incomplete cure may not be recognized at day 5. Based on the knowledge that this is the steep portion of the cure and my clinical experience, I believe that clinical cure rate for seven days of treatment would be at least as high as five days of treatment and possibility higher. Textbook recommendations [Current Ocular Therapy, Fraunfelder/Roy editors] for the treatment of bacterial conjunctivitis are that adequate antibacterial treatment be given for a 7-10 days. There is no information in this application to established that 5 days is better, worse or equal to 7 days of therapy. Inadequately treated subjects with bacterial conjunctivitis may have the potential to infect others and produce resistant organisms. It is therefore my recommendation that while the proposed drug product would be safe and effective for the majority of patients with the proposed labeling, an improved labeling would provide for seven days of treatment.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
NDA 22-308 is recommended for approval for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following bacteria: CDC coryneform group G, *Corynebacterium pseudodiphtheriticum*, Corynebacterium striatum*, Haemophilus influenzae, Moraxella lacunata*, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus hominis*, Staphylococcus lugdunensis*, Streptococcus mitis* group, *Streptococcus oralis, Streptococcus pneumoniae, Streptococcus salivarius**

*Efficacy for this organism was studied in fewer than 10 infections

The labeling submitted by B&L on April 1, 2009.

RISK BENEFIT ASSESSMENT:
The application supports the safety and efficacy of Besivance (besifloxacin ophthalmic suspension), 0.6% for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following bacteria: CDC coryneform group G, *Corynebacterium pseudodiphtheriticum, Corynebacterium striatum, Haemophilus influenzae, Moraxella lacunata, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus hominis, Staphylococcus lugdunensis, Streptococcus mitis* group, *Streptococcus oralis, Streptococcus pneumoniae, Streptococcus salivarius*

Studies #373 and #433 demonstrate superiority over the drug product's vehicle, and Study #434 demonstrates equivalence to moxifloxacin in the primary efficacy endpoint of clinical resolution; these adequate and well controlled studies support the efficacy of besifloxacin hydrochloride ophthalmic suspension for the treatment of bacterial conjunctivitis for the susceptible organisms listed in the final labeling. Pooled adverse event data for these trials showed relatively few reported adverse experiences, the following individual events all approximately 2%: eye pain, eye irritation, conjunctivitis bacterial, and eye pruritis.

CMC, Pharmacology/Toxicology, Clinical Pharmacology, and Product Quality Microbiology have recommended approval for this application.

The Biostatistics consultative review states that this submission provided adequate statistical evidence that besifloxacin hydrochloride ophthalmic suspension (0.6% as base) is superior to vehicle for the treatment of bacterial conjunctivitis. Clinical Microbiology and the Medical Officer recommend approval.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:
There are no recommended additional proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product. No additional clinical studies are recommended at this time.

Wiley A. Chambers, MD
Acting Director, Division of Anti-Infective and Ophthalmology Products

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/s/

Wiley Chambers
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