CLINICAL REVIEW

Application Type	NDA
Submission Number	21-493
Submission Code	S-009 (b) (4)
Letter Date	March 30, 2009
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Reviewer Name	Martin P. Nevitt, M.D., M.P.H.
Review Completion Date	August 3, 2009
Established Name	Gatifloxacin ophthalmic solution, 0.3%
(Proposed) Trade Name	Zymar
Therapeutic Class	fluroquinolone anti-infective
Applicant	Allergan, Inc.
Priority Designation	S
Formulation	Ophthalmic solution, 0.3%
Dosing Regimen	One drop in the affected eye(s) three times a day for six days
Indication	Treatment of bacterial conjunctivitis
Intended Population	(b) (4)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

(b) (4)

1.2 Risk Benefit Assessment

(b) (4)

1.3 Recommendations for Postmarketing Risk Management Activities

Not applicable.

1.4 Recommendations for other Post Marketing Study Commitments

Not applicable.

2 Introduction and Regulatory Background

2.1 Product Information

Name: Zymar (gatifloxacin ophthalmic solution) 0.3%
Therapeutic Class: fluoroquinolone anti-infective

(b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

(b) (4)

2.3 Availability of Proposed Active Ingredient in the United States

Zymar (gatifloxacin ophthalmic solution) 0.3% is currently approved for marketing in over 30 countries.

In the United States, Zymar was approved under NDA 21-493 on 28 March 2003. Zymar (gatifloxacin ophthalmic solution) 0.3% is currently labeled in the US for the treatment of bacterial conjunctivitis in subjects 1 year of age and older.

2.4 Important Safety Issues With Consideration to Related Drugs

Ophthalmic anti-infectives are generally well tolerated and effective for bacterial conjunctivitis. There are no specific issues which warrant special attention.

In patients receiving **systemic** quinolones, including gatifloxacin, serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal, or facial edema), airway obstruction, dyspnea, urticaria, and itching. If an allergic reaction to gatifloxacin occurs, discontinue the drug. Serious acute hypersensitivity reactions may require immediate emergency treatment. Oxygen and airway management should be administered as clinically indicated.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On October 4, 2001 a Written Request with subsequent amendments on July 2, 2002, May 7, 2004, and July 13, 2007, were submitted to conduct a clinical study to provide pediatric

information on Zymar (gatifloxacin ophthalmic solution) 0.3%. Additionally, a type C meeting was held on October 30, 2006.

Agreement with the FDA was obtained from the pediatric written request to conduct studies in neonates (birth to 31 days of age). One clinical study, 198782-003, was designed and conducted according to the criteria specified in the written request to assess the safety and efficacy of Zymar in this age group.

Based on the conductance of pediatric study 198782-003, pediatric exclusivity was granted May 19, 2009.

2.6 Other Relevant Background Information

Zymar (gatifloxacin ophthalmic solution) 0.3% has been on the market for approximately 6 years, and periodic safety updates have been provided to the FDA since February 2005. No regulatory actions have been taken for safety reasons.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

A Division of Scientific Investigations (DSI) audit was requested on April 24, 2009. At the time of this review, the DSI report has not been completed. Refer to the Cross Discipline Team Leader Review.

3.2 Compliance with Good Clinical Practices

The is no evidence to suggest that the clinical trials were not conducted in compliance with good clinical practices.

3.3 Financial Disclosures

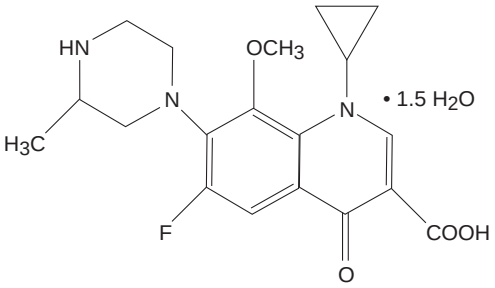
Pursuant to 21 CFR§314.50(k), §312.53(c)(4), and §54.4, financial disclosure information has been provided by Allergan, Inc. for clinical study 198782-003 submitted in this application.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There are no proposed changes to the Chemistry and Manufacturing Controls for Zymar in this supplemental application.

ZYMAR® sterile ophthalmic solution is an 8-methoxy fluoroquinolone anti-infective for the treatment of bacterial conjunctivitis. Its chemical name is (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate. Its molecular formula is $C_{19}H_{22}FN_3O_4 \cdot 1.5\ H_2O$, and its molecular weight is 402.42. Its chemical structure is:



ZYMAR® is a sterile, clear, pale yellow colored isotonic unbuffered solution. It has an osmolality of 260-330 mOsm/kg.

ZYMAR® contains **Active:** gatifloxacin 0.3% (3 mg/mL); **Inactives:** benzalkonium chloride 0.005%; edetate disodium; purified water; and sodium chloride. May contain hydrochloric acid and/or sodium hydroxide to adjust pH to approximately 6.

4.2 Clinical Microbiology

Refer to Clinical Microbiology review.

ZYMAR® (gatifloxacin ophthalmic solution) 0.3% is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:

Aerobic Gram-Positive Bacteria:
*Corynebacterium propinquum**
Staphylococcus aureus
Staphylococcus epidermidis
*Streptococcus mitis**
Streptococcus pneumoniae

Aerobic Gram-Negative Bacteria:
Haemophilus influenzae
* Efficacy for this organism was studied in fewer than 10 infections.

4.3 Preclinical Pharmacology/Toxicology

No new nonclinical studies were conducted. The toxicology evaluation of gatifloxacin was performed on studies submitted under the initial NDA (topical ocular administration), NDA 21-061 (oral administration) and NDA 21-062 (IV administration).

4.4 Clinical Pharmacology

No additional clinical pharmacology studies were conducted in this pediatric efficacy supplement.

4.4.1 Mechanism of Action

Gatifloxacin is a synthetic, broad-spectrum 8-methoxy fluoroquinolone anti-infective agent that exerts its antibacterial action by inhibiting DNA gyrase (an enzyme involved in the replication, transcription and repair of bacterial DNA) and topoisomerase IV (an enzyme that plays a key role in the partitioning of the chromosomal DNA during bacterial cell division).

4.4.2 Pharmacodynamics

Refer to Section 4.4.2 Pharmacokinetics.

4.4.3 Pharmacokinetics

In the original NDA application for Zymar, gatifloxacin ophthalmic solution 0.3% or 0.5% was administered to one eye of 6 healthy male subjects each in an escalated dosing regimen starting with a single 2 drop dose, then 2 drops 4 times daily for 7 days and finally 2 drops 8 times daily for 3 days. At all time points, serum gatifloxacin levels were below the lower limit of quantification (5 ng/mL) in all subjects.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Type of Study	Study #	Study Design / Type of Control	Study Objective(s)	Products: Dosing; Route of Administration	Number of Subjects	Primary Endpoint
Safety and Efficacy	198782-003	Multicenter randomized, double-masked parallel / Positive comparator (Vigamox)	Evaluate clinical and microbial efficacy of test product vs. Vigamox in treatment of bacterial conjunctivitis	Zymar (gatifloxacin ophthalmic solution) 0.3% ; TID for 6 days: topical ocular Vigamox (moxifloxacin ophthalmic solution) 0.5%; TID for 6 days: topical ocular	171 (85-study drug, 86 positive comparator)	Clinical success rate (proportion of subjects with clearing of both conjunctival erythema and conjunctival discharge in the study eye at day 7).

5.2 Review Strategy

The applicant conducted a single adequate and well controlled clinical trial (Study 198782-003) in subjects less than 1 year of age (birth to 31 days old) for the treatment of bacterial conjunctivitis. Study 198782-003 was a superiority trial with Zymar (gatifloxacin ophthalmic solution) 0.3% versus Vigamox (moxifloxacin ophthalmic solution) 0.5%; each were dosed three times a day for six days.

5.3 Discussion of Individual Studies

Safety and Efficacy Trial:

Study 178872-003

Title: A 7-Day, Randomized, Double-Masked, Parallel-Group, Multicenter Study To Evaluate the Safety and Efficacy of Topical Gatifloxacin 0.3% Ophthalmic Solution Compared with Topical Moxifloxacin 0.5% Ophthalmic Solution for the Treatment of Presumed Bacterial Conjunctivitis in Subjects from Birth to 31 Days of Age

Selection of Patient Population

Inclusion Criteria

1. Male or female subject, from birth to 31 days of age, in good general health

2. Clinically diagnosed with presumed bacterial conjunctivitis or bacterial blepharo-conjunctivitis as defined by the presence of mild, moderate, or severe conjunctival erythema and discharge
3. Written informed consent obtained from the parent/legally authorized representative
4. Written Authorization for Use and Release of Health and Research Study Information (US sites only) obtained from the parent/legally authorized representative
5. Written documentation obtained from the parent/legally authorized representative in accordance with the relevant country and local privacy requirements, where applicable
6. Ability for the parent/legally authorized representative to understand the informed consent and follow study instructions
7. Subject is likely to complete all required visits and procedures

Exclusion Criteria

1. Chemical or foreign body trauma to either eye or to the ocular adnexa of either eye
2. Presence of any evidence of orbital cellulitis affecting either eye
3. Corneal infiltrates or ulcer in either eye
4. Conjunctivitis signs and/or symptoms suggestive of fungal, protozoal, or viral etiology in either eye
5. Clinical diagnosis of Chlamydia or Gonorrhea infection in either eye
6. Treatment with ophthalmic corticosteroids during the 1 week prior to the Day 1 (Baseline) visit or anticipated use at any time during the study
7. Use of systemic or topical non-prophylactic antimicrobial therapy less than 96 hours prior to the Day 1 (Baseline) visit or anticipated use of antimicrobial therapy (other than study medication) at any time during the study
8. Use of topical antimicrobial therapy for routine prophylaxis (eg, at the time of birth) less than 24 hours prior to the Day 1 (Baseline) visit
9. Topical fluoroquinolone therapy at any time prior to the Day 1 (Baseline) visit
10. Breastfed subject whose mother or wet nurse was treated with systemic antimicrobial therapy less than 96 hours prior to the Day 1 (Baseline) visit or whose mother or wet nurse is anticipated to use systemic antimicrobial therapy at any time during the study
11. Low birthweight < 5.5 pounds (2.5 kg), preterm birth (earlier than 37 completed weeks gestation), or intrauterine growth retardation
12. Birthweight ≥ 10 pounds (4.5 kg)
13. Subject is being treated for retinopathy of prematurity or is at risk for eye problems (eg, subjects with a family history of congenital cataracts, retinoblastoma, or other relevant genetic disorders)
14. History of phototherapy treatment or anticipated phototherapy treatment at

any time during the study
15. Known clinically significant cardiac, liver, or kidney abnormality
16. Known metabolic abnormality or inborn errors of metabolism
17. History of hypopituitarism
18. History of hypoglycemia, hyperglycemia, or hyperinsulinemia
19. Subject's birth mother has a history of diabetes, gestational diabetes or other dysglycemia
20. Subject's birth mother was treated with beta-agonist tocolytic agents (such as terbutaline) within 2 weeks prior to the Day 1 (Baseline) visit
21. Subject is known to be immunosuppressed, immunocompromised, or is known to be infected with human immunodeficiency virus (HIV)
22. Subject's birth mother or wet nurse is known to be immunosuppressed, immunocompromised or HIV positive
23. Subject has congenital deformities associated with a higher than normal risk of associated metabolic or endocrine disorders
24. Allergy, sensitivity, or poor tolerance to the study medications or their components
25. Current enrollment of the subject or the subject's birth mother in an investigational drug or device study or participation in such a study within 30 days of entry into this study
26. Subject has a condition or is in a situation which in the investigator's opinion may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study.

Study Procedures

	Scheduled Visits					
					Exit	
	Day 1 (Baseline)	Day 2 [a]	Day 3	Day 5 [a]	Day 7 [b]	Unqualified Eye Follow-up [c]
Informed consent and privacy forms	X					
Medical and ophthalmic history	X					
Demographics (gender, race, date of birth)	X					
Concomitant medications/ concurrent procedures	X	X	X	X	X	X
Physical exam	X	X	X	X	X	X
Vital signs (heart rate, respiratory rate, temperature)	X	X	X	X	X	X
Subject body weight	X	X	X	X	X	X
Ocular exam of both eyes	X		X		X[d]	X[d]
Ocular exam (required if an unqualified eye becomes clinically diagnosed with bacterial conjunctivitis)		X[e]		X[e]		
Conjunctival swab (qualified eye(s))[f]	X				X	
Conjunctival swab (unqualified eye - if this eye becomes clinically diagnosed with bacterial conjunctivitis)		X[g]	X[g]	X[g]		X
Serious medical events	X					
Randomization	X					
Instill first dose of study medication[h]	X					
Adverse events	X	X	X	X	X	X
Dispense study medication	X	X[i]	X[i]	X[i]		
Collect study medication from subjects exiting the study					X	X

a The Day 2 and Day 5 visits can be performed either by telephone or by office visit at the discretion of the investigator. If a telephone visit is performed for either of these visits the only assessment to be completed is the collection of adverse events.
b The Day 7 visit should occur between 12 hours (minimum) to 48 hours (maximum) after the last dose of study medication is administered in the qualified eye(s). If an unqualified eye becomes clinically diagnosed with bacterial conjunctivitis at Day 7, the subject should be exited from the study and treated off study based on standard of care. The Day 7 visit will be considered the exit visit for subjects who do not become clinically diagnosed with bacterial conjunctivitis in an unqualified eye prior to the Day 7 visit.
c An Unqualified Eye Follow-up visit(s) is required for subjects who become clinically diagnosed with bacterial conjunctivitis in an unqualified eye after the Day 1 visit and prior to the Day 7 visit. The subjects should be followed after Day 7 either by telephone or office visit(s) at the discretion of the investigator. These visit(s) should be performed every 2 days or less until the subject exits the study. The duration of treatment for the unqualified eye will be left to the discretion of the investigator, but should not exceed 6 days. The final Unqualified Eye Follow-up visit requires an office visit and will be considered the exit visit for subjects who become clinically diagnosed with bacterial conjunctivitis in an unqualified eye and should occur after the last dose of study medication is administered.
d The ocular exam at the Day 7 and the final Unqualified Eye Follow-up visit must be performed by the ophthalmologist.
e If an unqualified eye becomes clinically diagnosed with bacterial conjunctivitis after Day 1 and prior to Day 7, an ocular exam of both eyes is required to be performed on the day of diagnosis.
f At Day 1 conjunctival swabs will be obtained from the qualified eye(s) (clinically diagnosed eye(s) with bacterial conjunctivitis on Day 1) and sent to the reference laboratory for bacteria and Chlamydia testing. On Day 7, a conjunctival swab for bacteria will be obtained from the qualified eye(s) and sent to the reference lab for testing.
g If an unqualified eye becomes clinically diagnosed with bacterial conjunctivitis after the Day 1 visit and prior to the Day 7 visit, a conjunctival swab of the unqualified eye will be obtained prior to the instillation of study medication in the unqualified eye. A follow-up conjunctival swab will be obtained at the final Unqualified Eye Follow-up visit.
h Prior to the first dose of study medication, a medical history, ocular exam, and conjunctival swab will be obtained and the subject will be assessed for study eligibility. The subject will be observed for adverse events over the 30-minute period following instillation of the first dose of study medication.
i A second (2nd) bottle will be dispensed for an unqualified eye that becomes clinically diagnosed with bacterial conjunctivitis after Day 1.

Efficacy Variable

The primary efficacy variable was the clinical success rate which is defined as the proportion of subjects in each treatment group whose study eye achieved a score of 0 for both conjunctival erythema and conjunctival discharge. Data will be collected at the Day 1, 3, and 7 (or early exit) visits. For the analyses on the primary efficacy variable, the method of last observation carried forward (LOCF) was applied to both the mITT and ITT populations. For the mITT population, missing values were to be imputed from the last post-baseline value if available. For the ITT population, missing values were to be imputed based on the last available observation, regardless of whether collected from a post-baseline visit.

Subjects Enrolled: Study 198782-003

(Enrolled/Culture Positive/Cure)

Site #	Investigator	Study Location	Gatifloxacin ophthalmic solution, 0.3%	Moxifloxacin ophthalmic solution, 0.5%
1003	Sanchez-Bal, Victoria, M.D.	Bellflower, CA 90706	11/9/6	5/5/5
1004	Hirschfield, Jeffrey, M.D.	St. Petersburgh, FL 33710	2/2/2	2/1/1
1007	Biag, Marita, M.D.	Sacramento, CA 958232	1/0/2	2/2/2
1008	Cruz, Marilou, M.D.	Downey, CA 90241	8/4/4	5/4/4
1009	De Leon, Liberation, M.D.	Paramonunt, CA 90723	8/8/6	16/14/13
1010	Duke, Anton, M.D.	Little, AR 72205	1/1/1	1/1/1
1011	Grossberg, Judith, M.D.	Midlothian, VA 23113	1/1/1	1/1/0

Site #	Investigator	Study Location	Gatifloxacin ophthalmic solution, 0.3%	Moxifloxacin ophthalmic solution, 0.5%
1015	Oca, Corazon, M.D.	Fountain Valley, CA 92708	2/0/0	4/4/4
1017	Rouse, Kevin, M.D.	Jonesboro, AR 72401	1/1/0	1/1/1
1018	Silas, Peter, M.D.	Layton, UT 84041	4/3/2	5/4/2
1019	Wilson-Phillips, Lynette, M.D.	Clarkston, GA 30021	1/0/0	1/1/1
1020	Levin, Michael, M.D.	Henderson, NV 89015	12/7/6	10/7/7
1021	Martin, Michael, M.D.	Vienna, VA 22189	3/2/1	1/1/1
1025	Hudson, Michael, M.D.	South Bend, IN 46601	3/2/1	0
1026	Peralta, Cynthia, M.D.	West Covina, 91790	4/4/4	5/3/2
1027	Silvey, Brentley, M.D.	Fayetteville, AR 72703	3/3/3	1/0/0
1028	Belcher, Barbar, M.D.	San Antonio, TX 78205	1/0/0	0
1029	Goswami, Umesh, M.D.	DeKalb, IL 60115	5/5/4	4/3/2
1032	Yeiser, Michael, M.D.	Owensboro, KY 42304	3/3/2	7/6/4
1033	Diehl, Michael, M.D.	Eugene, OR 97402	0	1/1/1
1038	Andres, Wilson, M.D.	Marietta, GA 30062	0	3/1/1
11303	Garfield, Hartley, M.D.	Toronto, Canada	4/2/2	5/4/4

6 Review of Efficacy

Efficacy Summary

6.1 Indication

6.1.1 Methods

The applicant conducted Study 198782-003, an adequate and well controlled clinical trial, to establish the safety and efficacy of the drug product in bacterial conjunctivitis in subjects from birth to 31 days of age.

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 an adequate and well-controlled, multi-center, independent trial of at least 7 days in duration. Independence refers to different investigators and different geographic locations.

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 infected patients who meet the inclusion criteria of the protocol. To demonstrate efficacy it is recommended that the drug product be statistically superior to a control (in study 198782-003

moxifloxacin was the control) or to the product's vehicle in the cure of the signs and symptoms of bacterial conjunctivitis. (b) (4)

6.1.2 Demographics

Demographic and Baseline Characteristics
Safety Population

Characteristic	Attribute	Gatifloxacin 0.3% (N= 85)	Moxofloxacin 0.5% (N=86)
Age, days	Mean	15.2	15.2
	SD	6.59	6.05
	Median	14.0	14.0
	Min, Max	3,31	5,31
Sex N (%)	Male	48 (56.5)	64 (74.4)
	Female	31 (43.5)	22(25.6)
Race, N (%)	Caucasian	43 (50.6)	36 (41.9)
	Black	3 (3.5)	4 (4.7)
	Asian	5 (5.9)	3 (3.5)
	Hispanic	32 (37.6)	40 (46.5)
	Other	2 (2.4)	3 (3.5)
Weight, kg	Mean	3.72	3.80
	SD	0.539	0.602
	Median	3.7	3.80
	Min, Max	2.5, 5.3	2.4, 6.3

6.1.3 Patient Disposition

A complete age range of subjects were enrolled from 3 days of age to 31 days old.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy variable is the clinical success rate defined as the proportion of subjects in each treatment group whose study eye achieves a score of 0 for both conjunctival erythema and conjunctival discharge at day 7 in the culture positive (modified intent to treat mITT) group.

Number (%) of Subjects with Clinical Success
mITT Population

Visit	Gatifloxacin 0.3% (N = 56)	Moxifloxacin 0.5% (N = 64)	P-value[a]	Difference, (95% CI)[b]
Day 3	17 (30.4)	28 (43.8)	0.131	-13.4 (-30.5, 3.7)
Day 7	44 (78.6)	54 (84.4)	0.412	-5.8 (-19.8, 8.1)

a P-value was derived from a 2-sided Pearson's chi-square test.
b 95% confidence interval (CI) for the treatment difference in the proportion of subjects with a score of 0 for both conjunctival erythema and conjunctival discharge was constructed using the normal approximation for binary variables.

(b) (4)

Number (%) of Subjects with Clinical Success
ITT Population

Visit	Gatifloxacin 0.3% (N = 85)	Moxifloxacin 0.5% (N = 86)	P-value[a]	Difference, (95% CI)[b]
Day 3	26 (30.6)	39 (45.3)	0.047	-0.148 (-0.291, -0.004)
Day 7	64 (75.3)	73 (84.9)	0.116	-0.096 (-0.215, 0.023)

a P-value was derived from a 2-sided Pearson's chi-square test.
b 95% confidence interval (CI) for the treatment difference in the proportion of subjects with a score of 0 for both conjunctival erythema and conjunctival discharge was constructed using the normal approximation for binary variables.

Results for the ITT population were similar to those for the mITT population. Subjects in both treatment groups experienced high rates of clinical success. However, a lower percentage of gatifloxacin subjects (75.3%) had clinical success at day 7 than moxifloxacin subjects (84.9%).

(b) (4)

Reviewer's comments:

(b) (4)

6.1.5 Analysis of Secondary Endpoints(s)

The secondary efficacy variable was microbiological improvement. Microbiological improvement was considered to have occurred if all bacterial species in the study eye at day 1 (baseline) were eradicated.

To determine the susceptibility of organisms to the drug product, organisms that are cultured above the clinically recognized thresholds from an eye with clinical signs and symptoms of bacterial conjunctivitis and treated with the drug product in a clinical trial in 10 or more cases with a $\geq$ 50% clinical cure rate are recommended to be included in the labeling. Organisms that are cultured above the clinically recognized thresholds from an eye with clinical signs and symptoms of bacterial conjunctivitis and treated with the drug product in a clinical trial in 5 to 9 cases with a $\geq$ 80% clinical cure rate can be considered for inclusion in the labeling with a notation describing the limited number of clinical cases.

Organisms that are cultured in less than 5 infections are not recommended to be listed in the labeling.

Microbiological Resolution by cultured organism at Day 7
(total eradicated/total organisms cultured at enrollment)

Organism	Gatifloxacin 0.3% (N= 56)	Moxifloxacin 0.5% (N=64)
Acinetobacter calcoaceticus	1/1	2/2
Chryseobacterium indologenes	1/1	1/1
Corynebacterium accolens	1/1	1/1
Corynebacterium group G	-	1/1
Corynebacterium macginleyi	1/1	1/1
Corynebacterium pseudodiphtheriticum	1/1	2/2
Corynebacterium species	-	1/1
Enterobacter cloacae	-	2/2
Entercocccus faecium	-	0/1
Gemella haemolysana	1/1	-
Gram negative bacillus	1/1	-
Haemophilus influenzae	2/2	5/6
Haemophilus parahaemolyticus	1/1	-
Haemophilus parainfluenzae	2/2	1/1
Kocuria varians	-	1/1
Lactococcus lactis spp. lactis	1/1	-
Moraxella catarrhalis	1/1	2/2
Neisseria cinerea	-	1/1
Serratia marcescens	3/3	-
Staphylococcus aureus	3/4	5/5
Staphylococcus capitis	1/1	-
Staphylococcus epidermidis	12/17	16/22
Staphylococcus haemolyticus	-	4/4
Staphylococcus hominis	2/2	4/4
Staphylococcus simulans	-	1/1
Staphylococcus warneri	-	1/1
Streptococcus agalactiae	1/1	-
Streptococcus mitis	6/7	7/7
Streptococcus mitis group	15/15	9/10
Streptococcus oralis	8/8	11/11
Streptococcu parasanguinis	2/2	1/1
Streptococcus pneumoniae	4/4	3/3
Streptococcus salivarius	2/2	3/3
Streptococcus sanguis	-	1/1
Streptococcus thermophilus	1/1	1/1
Streptococcus vestibularis	2/2	-
Coagulase negative staph	1/1	-
viridans Streptococcus	2/2	-

6.1.6 Other Endpoints

No other endpoints were used for the medical officer's review.

6.1.7 Subpopulations

The only population studied included pediatric patients of all races and gender from birth to age 31 days.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

There are no additional dosing recommendations.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

As with other anti-infectives, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If super-infection occurs, discontinue use and institute alternative therapy. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy, and, where appropriate, fluorescein staining.

6.1.10 Additional Efficacy Issues/Analyses

No additional endpoints were used to establish the efficacy of the drug product.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

The applicant conducted one study, Study 198782-003, an adequate and well controlled clinical trial to establish the safety (and efficacy) of the drug product in bacterial conjunctivitis in subjects from birth to 31 days of age.

A total of 171 subjects were enrolled into the study: 85 were randomized to the gatifloxacin 0.3% group and 86 were randomized to the moxifloxacin 0.5% group. These 171 subjects (ITT population / safety population) are the basis of the safety evaluation.

7.1.2 Adequacy of Data

A Division of Scientific Investigations (DSI) audit was requested on April 24, 2009. At the time of this review, the DSI report has not been completed. Refer to the Cross Discipline Team Leader Review.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Only one clinical trial was conducted: Study 198782-003.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Of 171 subjects enrolled in the safety population 84 gatifloxacin and 86 moxifloxacin received at least one dose of study medication and were included in the safety population.

Treatment Exposure – Safety Population
Cumulative Time Interval

Exposure (Days)	Gatifloxacin 0.3% (N = 84)	Moxifloxacin 0.5% (N = 86)
At least 1 Day	84 (100.0)	86 (100.0)
At least 2 Days	83 (98.8)	84 (97.7%)
At least 3 Days	82 (97.6%)	84 (97.7%)
At least 4 Days	82 (97.6%)	83 (96.5%)
At least 5 Days	82 (97.6%)	83 (96.5%)
At least 6 Days	82 (97.6%)	81 (94.2%)

In the safety population 163 subjects, 97.6% (82/84) in the gatifloxacin and 94.2% (81/86) in the moxifloxacin group had at least 6 days of treatment exposure.

Reviewer's comments:

(b) (4)

7.2.2 Explorations for Dose Response

The dose of gatifloxacin studied in the clinical trial was 0.3% which is the currently approved concentration in subjects 1 year or greater.

7.2.3 Special Animal and/or In Vitro Testing

As part of the original new drug application, a phase 1 pharmacokinetic study in healthy male subjects demonstrated no detectable serum levels of gatifloxacin following ophthalmic administration with concentrations as high as 0.5% (67% higher than used in this study) and administration as frequent as 2 drops given 8 times daily (ZYMAR NDA 21-493 submitted 29 May 2002).

Thus, due to the drug's minimal systemic absorption, the dosage of study medication and the 6 day treatment period were considered safe for this population.

7.2.4 Routine Clinical Testing

Vital sign and physical examination findings collected during Study 198782-003 were not clinically significant.

7.2.5 Metabolic, Clearance, and Interaction Workup

Vital sign and physical examination findings collected during Study 198782-003 were not clinically significant.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Ophthalmic anti-infectives are generally well tolerated and effective for bacterial conjunctivitis. There are no specific issues which warrant special attention.

In patients receiving **systemic** quinolones, including gatifloxacin, serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal, or facial edema), airway obstruction, dyspnea, urticaria, and itching. If an allergic reaction to gatifloxacin occurs, discontinue the drug. Serious acute hypersensitivity reactions may require immediate emergency treatment. Oxygen and airway management should be administered as clinically indicated.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in this study.

7.3.2 Nonfatal Serious Adverse Events

Only 1 subject in this study experienced a serious adverse event, which was moderate pyrexia in a moxifloxacin treated subject, starting on day 3 of the study. The subject was discontinued from the study and hospitalized. The adverse event lasted 5 days but resolved without sequelae.

7.3.3 Dropouts and/or Discontinuations

Of the 171 enrolled, 8 subjects discontinued from the study; 2 subjects from the gatifloxacin group and 6 subjects from the moxifloxacin group. Only 1 subject discontinued from the study due to an adverse event as reported in Section 7.3.2.

	Gatifloxacin 0.3%	Moxifloxacin 0.5%
Randomized (ITT/Safety)	85	86
Completed	83	80
Discontinued	2	6
Reason for Discontinuation		
Adverse Event	0	1
Lack of Efficacy	0	0
Lost to Follow-up	0	2
Personal reasons	2	0
Protocol Violation	0	3

7.3.4 Significant Adverse Events

Number (%) of Subjects with Adverse Events
Safety Population (ITT)

	Gatifloxacin 0.3% (N=84)	Moxifloxacin 0.5% (N=86)	P-value[a]
Overall	16 (19.0)	20 (23.3)	0.502
Conjunctivitis bacterial	7 (8.3)	5 (5.8)	0.521
Conjunctivitis	4 (4.8)	3 (3.5)	0.718
Umbilical granuloma	2 (2.4)	1 (1.2)	0.618
Acne infantile	1 (1.2)	0	0.494
Blepharitis	1 (1.2)	0	0.494
Cough	1 (1.2)	0	0.494
Dermatitis	1 (1.2)	0	0.494
Eye infection bacterial	1 (1.2)	0	0.494
Eyelid margin crusting	1 (1.2)	0	0.494
Rash papular	1 (1.2)	0	0.494

Candidiasis	0	1 (1.2)	0.494
Cardiac murmur	0	1 (1.2)	> 0.999
Conjunctivitis infective	0	1 (1.2)	> 0.999
Constipation	0	1 (1.2)	> 0.999
Dermatitis diaper	0	1 (1.2)	> 0.999
Erythema	0	1 (1.2)	> 0.999
Gastroenteritis	0	1 (1.2)	> 0.999
Heat rash	0	1 (1.2)	> 0.999
Irritability	0	1 (1.2)	> 0.999
Nasal congestion	0	1 (1.2)	> 0.999
Pyrexia	0	1 (1.2)	> 0.999

Reviewer's comments:

(b) (4)

7.3.5 Submission Specific Primary Safety Concerns

There are no specific primary safety concerns.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Refer to Section 7.3.4.

7.4.2 Laboratory Findings

Vital sign and physical examination findings collected during Study 198782-003 were not clinically significant.

7.4.3 Vital Signs

Vital sign and physical examination findings collected during Study 198782-003 were not clinically significant.

7.4.4 Electrocardiograms (ECGs)

Vital sign and physical examination findings collected during Study 198782-003 were not clinically significant.

7.4.5 Special Safety Studies

No special were required nor performed.

7.4.6 Immunogenicity

Gatofloxacin is not known to be immunogenic.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There were no dose dependency adverse events noted.

7.5.2 Time Dependency for Adverse Events

There were no time dependent adverse events noted.

7.5.3 Drug-Demographic Interactions

There were no drug-demographic interactions noted.

7.5.4 Drug-Disease Interactions

There were no drug-disease interactions noted.

7.5.5 Drug-Drug Interactions

There were no drug-drug interactions noted.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

No human carcinogenicity studies were performed in this neonatal population..

7.6.2 Human Reproduction and Pregnancy Data

Not applicable; study was in neonates only.

7.6.3 Pediatrics and Effect on Growth

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.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no abuse potential expected from topical ophthalmic drug products.

7.7 Additional Submissions

No additional submissions were submitted.

8 Postmarketing Experience

Following review of all cases in the postmarketing safety data base from 28 March 2003 through 30 September 2008, no significant safety issues were observed either in adults or in pediatric patients. Since initial marketing approval, a maximum exposure estimate for gatifloxacin (Zymar) of over (b) (4) patients has been documented. There have been no significant changes made to Zymar for safety reasons.

9 Appendices

9.1 Literature Review/References

Published information submitted supports the safety of topical ophthalmic quinolones in the treatment of bacterial conjunctivitis.

9.2 Labeling Recommendations

(b) (4)

9.3 Advisory Committee Meeting

An advisory committee was not required.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 21493	SUPPL 9	ALLERGAN INC	ZYMAR (GATIFLOXACIN) OPHTHALMIC SOLUTION

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARTIN P NEVITT
08/25/2009

WILLIAM M BOYD
08/25/2009