CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	May 14, 2010
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA#	22-548
Applicant	Allergan, Inc.
Date of Submission	July 30, 2009
PDUFA Goal Date	May 30, 2010
Proprietary Name / Established (USAN) names	Zymaxid (gatifloxacin ophthalmic solution) 0.5%
Dosage forms / Strength	ophthalmic solution
Proposed Indication(s)	Treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms: *Haemophilus influenzae, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus mitis* group*, *Streptococcus oralis*, Streptococcus pneumoniae* *Efficacy for this organism was studied in fewer than 10 infections.
Recommended:	Approval

1. Introduction

Gatifloxacin is a fourth generation 8-methoxy fluoroquinolone that inhibits DNA gyrase and topoisomerase IV. Allergan's NDA 21-493 for Zymar (gatifloxacin ophthalmic solution) 0.3% was approved in March 2003 for the indication of bacterial conjunctivitis in adults and pediatric patients above the age of 1 year. In this NDA, Zymar (gatifloxacin ophthalmic solution) 0.3% has been reformulated with a higher concentration of gatifloxacin, 0.5%. The excipients are the same in both formulations. The formulation of Zymaxid is different from Zymar because it has an increased drug substance concentration, a small reduction in pH to insure adequate solubility of the drug substance and a slightly lower sodium chloride concentration for tonicity.

2. Background

Ophthalmic products currently approved for the treatment of bacterial conjunctivitis include azithromycin ophthalmic solution, ciprofloxacin ophthalmic solution, erythromycin

ophthalmic ointment, gatifloxacin ophthalmic solution, gentamicin ophthalmic ointment and solution, levofloxacin ophthalmic solution, moxifloxacin ophthalmic solution, norfloxacin ophthalmic solution, ofloxacin ophthalmic solution, and tobramycin ophthalmic ointment and solution.

In March 2003, gatifloxacin ophthalmic solution 0.3% was approved in Allergan's NDA 21-493 for Zymar. It is currently being marketed in the United States.

Zymaxid (gatifloxacin ophthalmic solution) 0.5% is not marketed in any other country.

Efficacy of the drug substance, gatifloxacin, has been demonstrated in multiple systemic indications in prior NDA submissions. Gatifloxacin ophthalmic solution 0.5% was studied in two adequate and well controlled studies submitted in this NDA. The clinical success results of gatifloxacin compared to vehicle in each of these studies were borderline statistically significant in the prespecified analyses. Sensitivity analyses demonstrated that the clinical success results to be convincingly statistically significant. Microbiological cure rates for gatifloxacin ophthalmic solution 0.5% were also superior to vehicle in both trials.

In Study 198782-004, the primary analysis was the Day 6 visit analysis in the modified Intent-to-Treat population. This analysis included all data collected for the day 6 visit including data collected in the defined window for day 6. The primary efficacy variable, clinical success defined as achievement of a score of zero for both conjunctival hyperemia and conjunctival discharge in the study eye, was borderline statistically significant when comparing the gatifloxacin and vehicle treatment groups. The Up-to-Day 6 visit sensitivity analysis was performed including all data collected up to and including day 6, but excluding any day 6 visit data that was collected after the day 6 time point. In this analysis, the primary efficacy variable, clinical success was convincingly statistically significant.

Prior to unblinding the data for Study 198782-005, the Applicant revised the primary efficacy analysis for Study 005 to correspond with the more successful Up-to-Day 6 visit analysis in Study 004. In Study 198782-005, the treatment group difference in the proportion of patients achieving clinical success was only borderline statistically significant in the Up to Day 6 visit analysis. The results in the Day 6 visit analysis for the primary efficacy variable, clinical success at day 6, were convincingly statistically significant in favor of gatifloxacin.

Dosing is recommended for 7 days which is the standard regimen recommended for ophthalmic anti-infectives to treat bacterial conjunctivitis. As noted in the clinical trials, efficacy has been determined based 5 days of dosing using a commonly used protocol to evaluate efficacy. Not all subjects were effectively treated with 5 days of treatment for bacterial conjunctivitis as measured by clinical resolution and bacterial eradication; these subjects would not routinely be cultured outside a clinical trial nor would they be scheduled for a follow-up visit. In this reviewer's opinion, there is an adequate safety margin to allow the use of gatifloxacin ophthalmic solution to be dosed every two hours in the affected eye(s) while awake, up to 8 times on Day 1 and two to four times daily in the affected eye(s) while awake on Days 2 through 7. Bacterial conjunctivitis is usually a self limited condition, but

without follow-up, an incomplete cure may not be recognized at day 5. One of the goals of therapy is to minimize the chances of infecting other individuals. Inadequately treated subjects with bacterial conjunctivitis may have the potential to infect others and produce resistant organisms.

Zymaxid (gatifloxacin ophthalmic solution) 0.5% when dosed twice daily on days 2 to 5 in clinical trials appears less effective than Zymar (gatifloxacin ophthalmic solution) 0.3% dosed four times daily on days 2 to 5 in clinical trials. There is adequate pharmacologic and pharmacokinetic information in the original Zymar NDA 21-493 to support the dosing of the Zymaxid product one drop two to four times daily in the affected eye(s) while awake on Days 2 through 7.

The recommended dosing of Zymaxid (gatifloxacin ophthalmic solution) 0.5% will be:

> Patients 1 year of age or older: Instill one drop every two hours in the affected eye(s) while awake, up to 8 times on Day 1. Instill one drop two to four times daily in the affected eye(s) while awake on Days 2 through 7.

3. CMC

From the CMC Reviews dated 4/1/2010, and 4/27/2010:

The drug substance, gatifloxacin (also referred to as AGN-198782), is a white to pale yellow (b) (4) Gatifloxacin has two pKa values of (b) (4) The chemical name is (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate. The molecular weight of gatifloxacin sesquihydrate is 402.4 g/mol. Gatifloxacin is the same drug substance as is currently used in Zymar (gatifloxacin ophthalmic solution) 0.3% in NDA 21-493. The drug substance is manufactured at Kyorin Pharmaceutical Co. Ltd., Noshiro Plant, Akita, Japan.

The drug product, gatifloxacin ophthalmic solution 0.5% is a clear, pale yellow, sterile, preserved aqueous solution containing gatifloxacin (0.5% w/v (b) (4)). The inactive ingredients include sodium chloride, edetate disodium, benzalkonium chloride and purified water. The pH of the bulk solution is adjusted using either (b) (4) sodium hydroxide or (b) (4) hydrochloric acid resulting in a final product release pH of (b) (4) The osmolality of the drug product is at 265 - 315 mOsm/kg at release. All excipients are tested to USP/NF. Except for sodium hydroxide and hydrochloric acid, all excipients are tested for endotoxin.

Gatifloxacin ophthalmic solution 0.5% will be filled in a 5-mL multiple-dose bottle with a tip manufactured of low density polyethylene (LDPE, (b) (4)) and a cap manufactured of high impact polystyrene (HIPS, (b) (4). The finished product is labeled with a pressure- sensitive label. The tamper evident security feature for the primary packaging container is a (b) (4) shrink seal surrounding the cap. The planned market

configurations include a 1 mL fill in a 5-mL bottle (physician sample), and a 2.5 mL fill in a 5-mL bottle. The secondary packaging consists of a unit cardboard carton and an insert.

The stability data is sufficient to support 24 month storage of gatifloxacin ophthalmic solution 0.5% in a 2.5 mL/5-mL (b) (4) and 12 months in the physician sample configuration (1-mL/5-mL). A storage statement of 'Store at 15°-25°C (59°-77°F). Protect from freezing.' is appropriate and justified by the stability data.

A recommendation from the Office of Compliance on the site acceptability was made on April 18, 2010; all sites were found "Acceptable" (See attachment 1, CMC review dated 4/27/10).

(b) (4)

DRUG PRODUCT COMPOSITION

Composition of Gatifloxacin Ophthalmic Solution 0.5%

Ingredient	Grade	Function	Concentration
Gatifloxacin Sesquihydrate (% w/v)	N/A	Active Ingredient	0.5
Benzalkonium Chloride (% w/v)	NF/Ph Eur	(b) (4)	
Edetate Disodium (% w/v)	USP/Ph Eur		
Sodium Chloride (% w/v)	USP/Ph Eur		

Hydrochloric Acid (b) (4) or Sodium Hydroxide (b) (4) (b) (4)		pH adjustment	5.2 – 5.7
Purified Water [a]	(b) (4)		q.s. ad (b) (4)

a Purified Water meets bacterial endotoxins specification for Water for Injection

DRUG PRODUCT FORMULATION COMPARISON

Product Comparison for ZYMAR and Gatifloxacin Ophthalmic Solution 0.5%

Ingredient	ZYMAR, % w/v	Gatifloxacin Ophthalmic Solution 0.5%, %w/v
Gatifloxacin Sesquihydrate	0.30	0.50
Sodium Chloride	(b) (4)	
Edetate Disodium		
Benzalkonium Chloride		
Hydrochloric Acid	(b) (4)	
Sodium Hydroxide		
Purified Water [a]	q.s (b) (4)	q.s (b) (4)

a Purified Water meets bacterial endotoxins specification for Water for Injection

(b) (4)

(b) (4)

[redacted]

The application is recommended for approval by the CMC Reviewer.

4. Nonclinical Pharmacology/Toxicology

From the Pharmacology/Toxicology Review dated 12/14/2009:

The applicant, Allergan, Inc. (Irvine, CA), has requested that the Division cross-reference the nonclinical data from approved NDA 21-493 for Zymar (gatifloxacin ophthalmic solution) 0.3% to the current NDA. The Zymar NDA contains data from nonclinical studies that support the higher concentration of gatifloxacin to be used in the new product. One month repeat dose ocular toxicity studies in the rabbit used gatifloxacin concentrations up to 1% and ocular toxicity studies up to 3 months duration in the dog used concentrations up to 0.5%. There were no adverse findings in the rabbits and the only finding in the dogs was mild, reversible conjunctival hyperemia that was not considered toxicologically significant by the reviewer, Dr. Zhou Chen. The only nonclinical study that the sponsor has submitted to the current NDA is a study conducted in-house entitled "Comparison of Ocular Pharmacokinetics

of Gatifloxacin in Dutch-Belted Rabbits Following 0.3% QID and 0.5% BID Dosing," Study No. PK-08-P029.

The application is recommended for approval by the Pharmacology/Toxicology Reviewer.

5. Clinical Pharmacology/Biopharmaceutics

From the Clinical Pharmacology Review dated 3/16/2010:

This NDA does not contain any new clinical pharmacology studies. Reference is made to the clinical pharmacology program conducted under NDA 21-493. Under the previous clinical pharmacology program, systemic concentrations were undetectable (< 5 ng/mL) following a total topical daily dose of 2.56 mg/day for three days.

A waiver of the requirement for submission of evidence of in vivo bioavailability for the drug product gatifloxacin ophthalmic solution 0.5% is granted under CFR 320.22 (e). Pharmacokinetic information from NDA 21-493 and from the previously marketed oral tablet of gatifloxacin supports this recommendation.

The application is recommended for approval by the Clinical Pharmacology Reviewer.

6. Sterility Assurance

From the Product Quality Microbiology Review dated 4/16/2010:

The drug product is an aqueous formulation containing benzalkonium chloride (b) (4) The drug product is formulated, (b) (4). Component plastic 5ml bottles and dropper tips are sterilized (b) (4). Caps (b) (4) The drug product (b) (4) to fill volumes of either 1 mL, 2.5 mL (b) (4).

Endotoxin Test Method Validation Results

Linear Regression	Acceptance Criteria	Result
Correlation Coefficient (r)	(b) (4)	- 0.996
Slope		- 0.250
Intercept		3.081
Control Standard Endotoxin (CSE) Standard Curve		Pass
% PPC Recovery	**Acceptance Criteria**	**Result**

[1] (b) (4) The 2.5 mL in 5 mL bottle commercial configuration contains adequate drug product for a course of therapy.

Lot 56874 Lot 56875 Lot 56876	(b) (4)		(b) (4)	
Endotoxin Test Results				
Bulk Lot 56874 Bulk Lot 56875 Bulk Lot 56876				

Although the bacterial endotoxin acceptance criterion of (b) (4) is greater than the Division's currently recommended level of (b) (4), the applicant has demonstrated sufficient control of the drug product manufacturing process to minimize endotoxin contamination. The raw materials and the container closure are controlled for endotoxins by application of individual internal limits. Except for the sodium hydroxide and hydrochloric acid used for pH adjustments during compounding, all formulation excipients are tested for bacterial endotoxins. The USP purified water used in formulation is also tested, and meets, the acceptance criterion for bacterial endotoxins in water for injection. The worst case maximum weighted contribution for endotoxin based on raw material and component internal limits is (b) (4). The applicant stated that, as more history and manufacturing experience with the drug product and raw materials are gained they intend to further evaluate the endotoxin levels in the raw materials and their contribution to the drug product.

7. Clinical/Statistical - Efficacy

From the Medical Officer Review dated May 14, 2010:

The Phase 3 clinical development program included two identically designed studies (198782-004 and 198782-005). The two studies only differ in the choice of including visits which occur after day 6 in the primary efficacy endpoint.

Analysis of Primary Endpoint(s) – Clinical Resolution

The primary statistical objective of the studies was to demonstrate that gatifloxacin ophthalmic solution 0.5% is more effective than vehicle in the treatment of bacterial conjunctivitis.
The primary efficacy variable was clinical success, defined as achievement of a score of zero for both conjunctival hyperemia and conjunctival discharge in the study eye.

The primary analysis for efficacy was the day 6 visit analysis for Study 198782-004, which included all data collected for the day 6 visit, including data that was collected during the pre-defined window for day 6. This was the analysis method defined in the statistical analysis plan. Up-to-Day 6 analyses, which included all data collected up to and including day 6 but excluding data collected after day 6, were conducted as sensitivity analyses for Study 198782-004.

The Up-to-Day 6 analysis is the primary efficacy analysis for Study 198782-005.[2] This analysis includes all data collected up to and including day 6, but excluding any day-6 visit data that was collected after the day 6 time point. The day 6 visit analysis includes all day 6 visit data within the predefined window for day 6. The day 6 visit analysis is considered secondary. The primary population used for all efficacy analyses for Study 198782-005 was the mITT population, which included all subjects who were culture positive at baseline.

As planned in the protocols, there were 4 analysis populations. The intent to treat (ITT) population included all randomized patients. The primary population for efficacy analysis was the modified intent to treat (mITT) population, which consisted of randomized patients who had a positive bacterial culture from the conjunctiva at baseline. The per protocol (PP) population included all mITT patients without major protocol violations who had at least 1 follow-up visit. The ITT and PP populations were secondary populations for efficacy analysis.

The safety population included all randomized and treated patients and was used for all safety analyses.

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[2] On January 14, 2009, Allergan notified the FDA of significant cGCP violations at a study site in India in Study 198782-005. The investigator at this site was Shanta Motwane, MD. At Site 13020 was found to have significant data integrity issues. This site enrolled 72 patients, of whom 31 were included in the mITT population. At Site 13020, the clinical success rates in both groups at the day 6 time point in the mITT population using the up to day 6 analysis method (84.6% [11/13] in the gatifloxacin group and 83.3% [15/18] in the vehicle group) were somewhat higher than at most other sites with comparable enrollment.

During monitoring of the site, significant cGCP violations were observed. These violations involved source documentation anomalies which in the sponsor's judgment did not adequately support the data in the Case Report Forms. In contrast to other study sites, this site reported no adverse events, concomitant medications, and/or medical/ophthalmic history for any randomized patients. As such Allergan was concerned the site was not sufficiently diligent in querying the patients for safety and history information and was concerned about the data quality at the site.

All efficacy analyses are presented with data from Site 13020 excluded.

Table 11–1 Clinical Success in the Study Eye by Population and Analysis Method 198782-004 [3]

	Day 6 Visit Analysis (Primary Analysis Method)			Up to Day 6 Analysis		
Population (Analysis) Time point	Gatifloxacin	Vehicle	P Value [a]	Gatifloxacin	Vehicle	P Value [a]
mITT (LOCF)						
Day 4 n/N (%)	56/167 (33.5)	33/158 (20.9)	0.011	56/167 (33.5)	33/158 (20.9%)	0.011
Day 6 n/N (%)	**125/167 (74.9)**	**103/158 (65.2)**	**0.057**	107/167 (64.1)	79/158 (50.0)	0.010
PP						
Day 4 n/N (%)	48/137 (35.0)	32/135 (23.7)	0.040	48/137 (35.0)	32/135 (23.7)	0.040
Day 6 n/N (%)	107/138 (77.5)	89/132 (67.4)	0.063	80/102 (78.4)	67/94 (71.3)	0.248
ITT (LOCF)						
Day 4 n/N (%)	105/287 (36.6)	88/291 (30.2)	0.106	105/287 (36.6)	88/291 (30.2)	0.106
Day 6 n/N (%)	220/287 (76.7)	199/291 (68.4)	0.026	190/287 (66.2)	160/291 (55.0)	0.006
mITT (As treated LOCF)						
Day 4 n/N (%)	55/168 (32.7)	34/157 (21.7)	0.025	55/168 (32.7)	34/157 (21.7)	0.025
Day 6 n/N (%)	126/168 (75.0)	102/157 (65.0)	0.048	106/168 (63.1)	80/157 (51.0)	0.027
ITT (As treated LOCF)						
Day 4 n/N (%)	104/288 (36.1)	89/289 (30.8)	0.176	104/288 (36.1)	89/289 (30.8)	0.176
Day 6 n/N (%)	221/288 (76.7)	198/289 (68.5)	0.027	189/288 (65.6)	161/289 (55.7)	0.015

ITT = intent to treat; LOCF = last observation carried forward; mITT = modified intent to treat; PP = per protocol
Bolding shows primary comparison.
a: P value is from Pearson's chi-square test, unless ≥ 25% of the cells had expected counts < 5, then Fisher's exact test was used.
Source: Table 14.2-1.1, 14.2-1.2, 14.2-1.3, 14.5-10.1, 14.5-10.2, 14.5-10.3, 14.5-17.1, 14.5-17.2, 14.5-20.1, 14.5-20.2

[3] Section 11.1.1.1, CSR 198782-004

In Study 198782-004, the primary analysis was the Day 6 visit analysis in the modified Intent-to-Treat population. This analysis included all data collected for the within the predefined window for the day 6 visit. The primary efficacy variable, clinical success defined as achievement of a score of zero for both conjunctival hyperemia and conjunctival discharge in the study eye, was borderline statistically significant at $p = 0.057$ when comparing the gatifloxacin and vehicle treatment groups.

The Up-to-Day 6 visit sensitivity analysis was performed including all data collected up to and including day 6, but excluding any day 6 visit data that was collected after day 6. In this analysis, the primary efficacy variable, clinical success was statistically significant at $p = 0.010$.

Table 11–1 Clinical Success in the Study Eye by Population and Analysis Method 198782-005 [4]

	Day 6 Visit Analysis			Up to Day 6 Analysis (Primary Analysis Method)		
Population (Analysis) Time point	Gatifloxacin	Vehicle	P Value [a]	Gatifloxacin	Vehicle	P Value [a]
mITT (LOCF)						
Day 4 n/N (%)	23/166 (13.9%)	17/167 (10.2%)	0.302	23/166 (13.9%)	17/167 (10.2%)	0.302
Day 6 n/N (%)	99/166 (59.6%)	78/167 (46.7%)	0.018	**86/166 (51.8%)**	**69/167 (41.3%)**	**0.055**
PP						
Day 4 n/N (%)	23/155 (14.8%)	16/148 (10.8%)	0.295	23/155 (14.8%)	16/148 (10.8%)	0.295
Day 6 n/N (%)	93/156 (59.6%)	72/146 (49.3%)	0.072	76/138 (55.1%)	61/134 (45.5%)	0.115
ITT (LOCF)						
Day 4 n/N (%)	65/394 (16.5%)	58/393 (14.8%)	0.502	65/394 (16.5%)	58/393 (14.8%)	0.502
Day 6 n/N (%)	226/394 (57.4%)	199/393 (50.6%)	0.058	200/394 (50.8%)	184/393 (46.8%)	0.269
mITT (As treated LOCF)						
Day 4 n/N (%)	23/166 (13.9%)	17/167 (10.2%)	0.302	23/166 (13.9%)	17/167 (10.2%)	0.302
Day 6 n/N (%)	96/166 (59.6%)	78/167 (46.7%)	0.018	86/166 (51.8%)	69/167 (41.3%)	0.055
ITT (As treated LOCF)						
Day 4 n/N (%)	65/393 (16.5%)	58/392 (14.8%)	0.502	65/393 (16.5%)	58/392 (14.8%)	0.502
Day 6 n/N (%)	226/393 (57.5%)	199/392 (50.8%)	0.058	200/393 (50.9%)	184/392 (46.9%)	0.268

ITT = intent-to-treat; LOCF = last observation carried forward; mITT = modified intent-to-treat; PP = per protocol
Note: Bolding shows primary comparison.
a: P value is from Pearson's chi-square test, unless ≥25% of the cells had expected counts <5, then Fisher's exact test was used.
Sources: Tables 14.2-1.1, 14.2-1.2, 14.2-1.3, 14.5-1.2, 14.5-3.1, 14.5-3.2, 14.5-4.1, 14.5-4.2, 14.5-4.3, 14.5-5.1, 14.5-5.2

[4] Section 11.1.1.1, CSR 198782-005

Prior to unblinding the data for Study 198782-005, the Applicant revised the primary efficacy analysis for Study 005 to correspond with the more successful Up-to-Day 6 visit analysis in Study 004.

In Study 198782-005, the treatment group difference in the proportion of patients achieving clinical success was only borderline statistically significant at p = 0.055 in the Up to Day 6 visit analysis. The results in the Day 6 visit analysis for the primary efficacy variable, clinical success at day 6, were convincingly statistically significant in favor of gatifloxacin with p = 0.018.

Analysis of Secondary Endpoints(s)

Microbiological Cure

A patient was considered to have microbiological cure if all bacterial species present at Day 1 (baseline) were eradicated.

Table 6.1.5-1 Microbiological Cure in the Study Eye
mITT Population 198782-004

	Day 6 Visit Analysis (Primary Analysis Method)		
Visit / Time point	**Gatifloxacin**	**Vehicle**	**p value [a]**
Day 4 n/N (%)	145/167 (86.8)	81/158 (51.3)	< 0.001
Day 6 n/N (%)	149/167 (89.2)	97/158 (61.4)	< 0.001

a P value is from Pearson's chi-square test, unless ≥ 25% of the cells had expected counts < 5, the Fisher's exact test was used.

The proportion of patients who achieved microbiological cure in the modified Intent-to-Treat population was numerically greater in the gatifloxacin group compared to the vehicle group. This difference was statistically significant as well.

Table 6.1.5-2 Microbiological Eradication in the Study Eye by Most Frequent Organisms at the Day 6 Time Point
mITT Population 198782-004

	Day 6 Visit Analysis (Primary Analysis Method)			
Organism	**Gatifloxacin (N=167)**		**Vehicle (N=158)**	
	No. of infections	**No. of eradications (%)**	**# of infections**	**# of eradications**
Haemophilus influenzae	62	60 (96.8%)	46	26 (56.5%)
Streptococcus pneumoniae	40	35 (87.5%)	40	25 (62.5%)

Organism	Day 6 Visit Analysis (Primary Analysis Method)			
	Gatifloxacin (N=167)		Vehicle (N=158)	
	No. of infections	No. of eradications (%)	# of infections	# of eradications
Staphylococcus aureus	23	20 (87.0%)	18	13 (72.2%)
Staphylococcus epidermidis	20	16 (80.0%)	25	17 (68.0%)
Streptococcus mitis group	10	10 (100.0%)	6	6 (100.0%)
Streptococcus oralis	7	7 (100.0%)	4	4 (100.0%)

The percentage of microbiological eradications was greater in the gatifloxacin group than in the vehicle group for Haemophilus influenzae, Streptococcus pneumoniae, Staphylococcus aureus, and Staphylococcus epidermidis.

Table 6.2.5-1 Microbiological Cure in the Study Eye mITT Population 198782-005

Visit / Time point	Up to Day 6 Visit Analysis (Primary Analysis Method)		
	Gatifloxacin	Vehicle	p value [a]
Day 4 n/N (%)	144/166 (88.0%)	123/167 (73.3%)	< 0.001
Day 6 n/N (%)	153/166 (92.2%)	134/167 (80.2%)	0.002

a P value is from Pearson's chi-square test, unless ≥ 25% of the cells had expected counts < 5, the Fisher's exact test was used.

The treatment group difference in microbiological cure in the study eye was statistically significant at the Day 6 time point.

Table 6.2.5-2 Microbiological Eradication in the Study Eye by Most Frequent Organisms at the Up-to-Day 6 Time Point mITT Population 198782-005

Organism	Up to Day 6 Visit Analysis (Primary Analysis Method)			
	Gatifloxacin (N=166)		Vehicle (N=167)	
	No. of infections	No. of eradications (%)	# of infections	# of eradications
Staphylococcus aureus	32	30 (93.8%)	20	15 (75.0%)
Staphylococcus epidermidis	26	24 (92.3%)	23	21 (91.3%)
Gram positive cocci, in clusters, isolated	7	4 (57.1%)	15	10 (66.7%)
Pseudomonas aeruginosa	6	6 (100.0%)	14	14 (100.0%)

Staphylococcus hominis	7	6 (85.7%)	14	14 (100.0%)

(b) (4)

(b) (4)

There was a higher percentage of microbiological eradications in the gatifloxacin group for each of the listed organisms except for Gram Positive cocci, in clusters, isolated and Staphylococcus hominis. There were less than 10 infections for each of these organisms in the gatifloxacin group.

198782-004 and 198782-004 Efficacy Conclusions

The primary analysis for efficacy for Study 198782-004 was the Day 6 visit analysis. The Up-to-Day 6 analysis is the primary efficacy analysis for Study 198782-005. This analysis includes all data collected up to and including day 6, but excluding day-6 visit data that was collected after day 6.

The two clinical trials 198782-004 and 198782-005 show marginal statistical significance in their specified primary efficacy endpoints; the sensitivity analyses for each trial are unquestionably statistically significant.

Clinical success by organism is displayed below:

Organism	Gatifloxacin		Vehicle	
	Clinical Success n/N (%)	Microbiological Cure n/N (%)	Clinical Success n/N (%)	Microbiological Cure n/N (%)
Haemophilus influenzae	38/43 (88%)	42/43 (98%)	19/45 (43%)	26/45 (58%)
				(b) (4)
Pseudomonas aeruginosa	2/7 (29%)	6/7 (86%)	4/10 (40%)	9/10 (90%)
Staphylococcus aureus	26/52 (50%)	45/52 (87%)	13/37 (35%)	22/37 (60%)
Staphylococcus epidermidis	21/35 (60%)	31/35 (89%)	14/27 (52%)	22/27 (82%)
				(b) (4)
Staphylococcus hominis	3/7 (43%)	7/7 (100%)	7/15 (47%)	15/15 (100%)
Staphylococcus warneri	5/11 (46%)	10/11 (91%)	1/2 (50%)	2/2 (100%)
				(b) (4)
Streptococcus pneumoniae	21/34 (62%)	30/34 (88%)	22/38 (58%)	24/38 (63%)
Streptococcus mitis group	8/9 (89%)	9/9 (100%)	3/4 (75%)	3/4 (75%)
Streptococcus oralis	7/12 (59%)	10/12 (83%)	1/6 (17%)	5/6 (83%)

The recommended labeling will state:

> In two randomized, double-masked, multicenter clinical trials, where patients 1-89 years of age were dosed for 5 days, **ZYMAXID™** solution was clinically superior to its vehicle on day 6 in patients with conjunctivitis and positive conjunctival cultures. Clinical outcomes for the trials demonstrated clinical success (resolution of conjunctival hyperaemia and conjunctival discharge) of 58% (193/333) for the gatifloxacin-treated groups versus 45% (148/325) for the vehicle-treated groups. Microbiological outcomes for the same clinical trials demonstrated a statistically superior eradication rate for causative pathogens of 90% (301/333) for gatifloxacin vs. 70% (228/325) for vehicle.

Zymar solution was superior to its vehicle on day 5-7 in patients with conjunctivitis and positive conjunctival cultures. Clinical outcomes for the trial demonstrated clinical cure of 77% (40/52) for the gatifloxacin treated group versus 58% (28/48) for the placebo treated group. Microbiological outcomes for the same clinical trial demonstrated a statistically superior eradication rate for causative pathogens of 92% (48/52) for gatifloxacin vs. 72% (34/48) for placebo.

Zymaxid (gatifloxacin ophthalmic solution) 0.5% when dosed twice daily on days 2 to 5 in clinical trials appears less effective than Zymar (gatifloxacin ophthalmic solution) 0.3% dosed four times daily on days 2 to 5 in clinical trials. There is adequate pharmacologic and pharmacokinetic information in the original Zymar NDA 21-493 to support the dosing of the Zymaxid product one drop two to four times daily in the affected eye(s) while awake on Days 2 through 7.

The recommended dosing of Zymaxid (gatifloxacin ophthalmic solution) 0.5% will be:

> Patients 1 year of age or older: Instill one drop every two hours in the affected eye(s) while awake, up to 8 times on Day 1. Instill one drop two to four times daily in the affected eye(s) while awake on Days 2 through 7.

8. Safety

From the Medical Officer Review dated May 14, 2010:

EXPOSURE

The safety database includes all randomized and treated patients, 717 patients treated with gatifloxacin 0.5% and 716 patients treated with vehicle.

Table 7.2.1-1 Overview of Exposure to Study Drug by Protocol

Study Number	Safety N	Gatifloxacin 0.5%	Vehicle
198782-004	577	288	289
198782-005	856	429	427

POSTMARKETING EXPERIENCE

Gatifloxacin ophthalmic solution 0.5% is not marketed in any country. Zymar (gatifloxacin ophthalmic solution, 0.3% was approved in the U.S. in 2003.

In the most recent annual Periodic Safety Update Report for Zymar (gatifloxacin ophthalmic solution) 0.3%, fifty-eight case reports involving 111 adverse event terms were reported worldwide associated with gatifloxacin. Thirty-five (35) were confirmed by healthcare professionals including 17 which were considered serious and 18 non-serious. The spontaneous postmarketing reports for gatifloxacin are consistent with its known safety profile. A review of the postmarketing reports does not raise concern that there is a new unknown safety risk associated with gatifloxacin.

ZYMAXID COMMON ADVERSE EVENTS

Adverse Events Occurring in ≥ 1% of Patients in Any Treatment Group
Study 198782-004 – Safety Population

Preferred Term [a]	Gatifloxacin (N=288)	Vehicle (N=289)	p value [b]
Conjunctivitis bacterial	14 (4.9%)	13 (4.5%)	0.837
Pyrexia	4 (1.4%)	1 (0.3%)	0.216 [c]
Pharyngolaryngeal pain	3 (1.0%)	1 (0.3%)	0.373 [c]
Conjunctivitis	2 (0.7%)	4 (1.4%)	0.686 [c]
Headache	2 (0.7%)	4 (1.4%)	0.686 [c]
Eyelid edema	2 (0.7%)	3 (1.0%)	>0.999 [c]
Eye pruritus	1 (0.3%)	4 (1.4%)	0.373 [c]
Lacrimation increased	1 (0.3%)	4 (1.4%)	0.373 [c]
Otitis media	0	3 (1.0%)	0.249 [c]

a MedDRA version 10.0
b Pearson's chi square unless otherwise specified
c Fisher's exact test

Adverse Events Occurring in ≥ 1% of Patients in Any Treatment Group
Study 198782-005 – Safety Population

Preferred Term [a]	Gatifloxacin (N=429)	Vehicle (N=427)	p value [b]
Eye irritation	14 (3.3%)	7 (1.6%)	0.125
Dysgeusia	8 (1.9%)	1 (0.2%)	0.038 [c]
Eye pain	6 (1.4%)	8 (1.9%)	0.584
Conjunctivitis bacterial	5 (1.2%)	19 (4.4%)	0.004
Instillation site irritation	5 (1.2%)	0 (0.0%)	0.062 [c]
Conjunctivitis	0 (0.0%)	5 (1.2%)	0.031 [c]

a MedDRA version 10.0
b Pearson's chi square unless otherwise specified
c Fisher's exact test

There were no significant treatment group differences in adverse events in Study 198782-004. The occurrence of dysgeusia in the gatifloxacin versus the vehicle treatment group in Study 198782-005 was statistically significant.

The occurrence of 'bacterial conjunctivitis' and 'conjunctivitis' was more frequent and statistically significant in the vehicle group compared to the gatifloxacin group. These events likely reflect the decreased efficacy of the vehicle compared to gatifloxacin.

Table 2.5.5–3 Adverse Events Occurring in ≥ 1% of Patients in Any Treatment Group (Pooled Safety Population)[5]

Preferred Term [a]	Primary SOC of PT [a]	Gatifloxacin (N= 717)	Vehicle (N= 716)
Overall	---	83 (11.6%)	95 (13.3%)
Conjunctivitis bacterial	Infections and Infestations	19 (2.6%)	32 (4.5%)
Eye irritation	Eye disorders	15 (2.1%)	8 (1.1%)
Dysgeusia	Nervous system disorders	8 (1.1%)	1 (0.1%)*
Eye pain	Eye disorders	7 (1.0%)	9 (1.3%)
Conjunctivitis	Eye disorders	2 (0.3%)	9 (1.3%)**

a: MedDRA 10.0
* $p < 0.05$, Fisher's exact test
** $p < 0.05$, Pearson's chi-square test
Source: Module 2.7.4 Table 2.7.4.2-2

The most frequent adverse event in both groups was conjunctivitis bacterial (19 patients in the gatifloxacin group and 32 patients in the vehicle group); mostly infection of the unqualified eye, which was then treated with study medication.

The recommended labeling for this drug product will state:

> Most common adverse reactions occurring in ≥ 1 % of patients included worsening of conjunctivitis, eye irritation, dysgeusia, and eye pain.

ZYMAXID DEATHS AND NONFATAL SERIOUS ADVERSE EVENTS

No deaths were reported in either Study 198782-004 or Study 198782-005.

Two patients experienced serious adverse events (1 in the gatifloxacin group and 1 in the vehicle group).

- In the vehicle group in Study 198782-004, patient 10006-1357 experienced congestive heart failure.

- In the gatifloxacin group in Study 198782-005, patient 10007-1727 was hospitalized for worsening depression and anxiety one day after beginning study medication. This patient had a history of depression and anxiety. Study medication was stopped and the patient was discontinued from the study.

[5] NDA 22-548 Section 2.5.5.5.1 All Adverse Events

ZYMAXID DROPOUTS AND/OR DISCONTINUATIONS

Table 7.3.3-1 Patient Discontinuations (Safety Population)

	Study 198782-004 N=577		Study 198782-005 N=856	
	Gatifloxacin 0.5%	Vehicle	Gatifloxacin 0.5%	Vehicle
Safety Population [a]	288	289	429	427
Completed, N (%)	277 (96.2%)	275 (95.2%)	402 (93.7%)	398 (93.2%)
Discontinued, N (%)	11 (3.8%)	14 (4.8%)	27 (6.3%)	39 (6.8%)
Adverse Events	2 (0.7%)	5 (1.7%)	6 (1.4%)	4 (0.9%)
-Ocular	2 (0.7%)	5 (1.7%)	4 (0.9%)	3 (0.7%)
-Non-ocular	0	0	2 (0.5%)	1 (0.2%)
Lack of efficacy	2 (0.7%)	2 (0.7%)	0	0
Pregnancy	0	0	0	0
Lost to follow-up	3 (1.0%)	0	18 (4.2%)	20 (4.7%)
Personal reasons	0	3 (1.0%)	2 (0.5%)	2 (0.5%)
Protocol violation	1 (0.3%)	0	0	0
Other [b, c]	3 (1.0%)	4 (1.4%)	1 (0.2%)	3 (0.7%)

a Safety population includes all randomized patients who received at least one dose of study medication. Patients are analyzed according to the medication actually received.
b Study 198782-004 - Other reasons were withdrawn consent (n=2) and visit schedule conflict (n=1) for the gatifloxacin group and patient withdrew consent (n=3) and non-compliance (n=1) for the vehicle group.
b Study 198782-005 - Other reasons were withdrawn consent (n=1) for the gatifloxacin group and withdrawn consent / lack of efficacy (n=2) and patient lost study medication (n=1) for the vehicle group.

A table of the adverse events associated with the discontinuations is presented below. Based on a review of the Case Report Forms, it does not appear that the other discontinuations were due to adverse events. The "lost to follow-up" is unusually high for a one week study.

Table 7.3.3-2 Adverse Events Leading to Study Discontinuation Safety Population

Adverse Event	Treatment	Center / Patient Number	Age	Sex	Day of Onset
Adverse event – worsening of bacterial conjunctivitis	Gatifloxacin 0.5%	10011 / 1514	49	M	4
Adverse event – worsening of bacterial conjunctivitis	Gatifloxacin 0.5%	10076 / 1617 [a]	88	M	1
Adverse event – Otitis media	Gatifloxacin 0.5%	10002 / 1769	6	M	3
Adverse event – Iritis	Gatifloxacin 0.5%	10007 / 1418	64	F	3
Adverse event – Worsening of anxiety and depression	Gatifloxacin 0.5%	10007 / 1727	48	F	2

Adverse Event	Treatment	Center / Patient Number	Age	Sex	Day of Onset
Adverse event – Corneal epithelium defect	Gatifloxacin 0.5%	13010 / 1095	13	M	4
Adverse event – Viral keratitis	Gatifloxacin 0.5%	13010 / 1504	62	F	1
Adverse event – Superficial punctate keratitis	Gatifloxacin 0.5%	13030 / 1471	38	F	3
Adverse event – Otitis media	Vehicle	10001 / 1677	11	F	3
Adverse event – Adenovirus infection	Vehicle	10007 / 1854	30	F	3
Adverse event – Corneal epithelial erosion	Vehicle	13010 / 1068	47	M	6
Adverse event – Hordeolum	Vehicle	13010 / 1605	70	M	2
Adverse event – worsening of bacterial conjunctivitis	Vehicle	10002 / 1310	4	F	4
Adverse event – worsening of bacterial conjunctivitis	Vehicle	10009 / 1097	61	M	2
Adverse event – Episcleritis	Vehicle	10012 / 1089	11	M	3
Adverse event – Dacryocystitis	Vehicle	10029 / 1508	37	F	3
Adverse event – Hyperopic shift	Vehicle	10048 / 1210	53	F	4
Adverse event – Periorbital cellulitis	Vehicle	10084 / 1314 [a]	10	F	4

a Both of patient's eyes were study eyes and experienced the adverse event. Both eyes were removed from treatment due to AE.

There were no significant treatment group differences in study discontinuations due to adverse events.

DEMOGRAPHICS OF TARGET POPULATIONS

Table 6.1.2-2 Demographic Data (mITT Population [c]) for Study 198782-004

	Gatifloxacin 0.5% N=167	Vehicle N=158	p-value
Age (years)			0.148 [a]
Mean	30.7	26.4	
SD	28.7	24.5	
Range	1-89	1-88	
No. Enrolled			
≥ 18 years	88	76	0.096
16-17 years	3	4	0.721
11-15 years	8	14	0.824
6-10 years	23	25	0.436
1-5 years	45	39	0.925
Sex, N (%)			0.605 [b]
Male	83 (49.7%)	74 (46.8%)	
Female	84 (50.3%)	84 (53.2%)	
Race, N (%)			0.605 [b]
Caucasian	84 (50.3)	84 (53.2)	
Non-Caucasian	83 (49.7)	74 (46.8)	

a One way analysis of variance **b** Pearson's chi-square test **c** Primary efficacy analysis population all randomized subjects who are culture positive at baseline

There were no significant differences in the treatment groups at baseline with regard to age or sex in either the ITT or mITT populations.

Table 6.2.2-2 Demographic Data (mITT Population Without Site 13020) for Study 198782-005

	Gatifloxacin 0.5% N=166	Vehicle N=167	p-value [a]
Age (years)			0.943
Mean	38.9	38.8	
SD	20.4	20.4	
Range	1-86	1-87	
Sex, N (%)			0.206
Male	88 (53.0%)	100 (59.9%)	
Female	78 (47.0%)	67 (40.1%)	
Race, N (%)			0.994
Caucasian	3 (1.8)	3 (1.8)	
Non-Caucasian	163 (98.2)	164 (98.2)	

a P-value for age from 1-way analysis of variance, and for sex and race from Pearson's chi-square test.

Significant data integrity issues were found at Site 13020 which enrolled 72 patients of whom 31 were included in the mITT population. There were no significant treatment group

differences in Demographic data in either the ITT or mITT populations whether Site 13020 is included or excluded.

9. Advisory Committee Meeting

No Advisory Committee Meeting was necessary for Zymaxid (gatifloxacin ophthalmic solution) 0.5%.

10. Pediatrics

Zymaxid has been demonstrated in clinical trials to be safe and effective for the treatment of bacterial conjunctivitis in pediatric patients one year or older. The Agency considers patients below one month of age with bacterial conjunctivits to be a different diagnostic condition (ophthalmia neonatorum).

Table 6.1.7-5 Clinical Success in the Study Eye - Day 6 Analysis [a]
mITT population (LOCF) for Study 198782-004

	Day 6 Visit Analysis		
Age Group Time point	**Gatifloxacin**	**Vehicle**	**p value [a]**
1 – 5 years			
Day 4 n/N (%)	17/45 (37.8)	8/39 (20.5)	
Day 6 n/N (%)	39/45 (86.7)	23/39 (59.0)	0.004
6 – 10 years			
Day 4 n/N (%)	6/23 (26.1)	7/25 (28.0)	
Day 6 n/N (%)	20/23 (87.0)	19/25 (76.0)	0.466 [b]
11 – 15 years			
Day 4 n/N (%)	4/8 (50.0)	3/14 (21.4)	
Day 6 n/N (%)	7/8 (87.5)	11/14 (78.6)	> 0.999 [b]
16 – 17 years			
Day 4 n/N (%)	1/3 (33.3)	0/4 (00.0)	
Day 6 n/N (%)	2/3 (66.7)	2/4 (50.0)	> 0.999 [b]
1 – 17 years			
Day 4 n/N (%)	28/79 (35.4)(33.3)	18/82 (22.0)	0.058
Day 6 n/N (%)	**68/79 (86.1)**	**55/82 (67.1)**	**0.005**

a Day 6 is the primary time point for the assessment of clinical success.
b P value is from Pearson's chi-square test, unless ≥ 25% of the cells had expected counts < 5, then Fisher's exact test was used.

Table 6.2.7-5 Clinical Success in the Study Eye – Up to Day 6 Analysis [c]
mITT population (LOCF) for Study 198782-004

	Up to Day 6 Visit Analysis		
Age Group Time point	**Gatifloxacin**	**Vehicle**	**p value [a]**
1 – 5 years			
Day 4 n/N (%)	5/6 (83.3)	5/12 (41.7)	
Day 6 n/N (%)	6/6 (100.0)	7/12 (58.3)	0.515 [b]
6 – 10 years			
Day 4 n/N (%)	3/7 (42.9)	0/3 (00.0)	
Day 6 n/N (%)	6/7 (85.7)	1/3 (33.3)	0.183 [b]
11 – 15 years			
Day 4 n/N (%)	0/3 (00.0)	0/3 (00.0)	
Day 6 n/N (%)	2/3 (66.7)	0/3 (00.0)	0.400 [b]
16 – 17 years			
Day 4 n/N (%)	0/2 (00.0)	0/2 (00.0)	
Day 6 n/N (%)	1/2 (50.0)	1/2 (50.0)	> 0.999 [b]
1 – 17 years			
Day 4 n/N (%)	8/18 (44.4)	5/20 (25.0)	
Day 6 n/N (%)	15/18 (83.31)	11/20 (55.0)	0.061

a P value is from Pearson's chi-square test, unless ≥ 25% of the cells had expected counts < 5, then Fisher's exact test was used.
b Fisher's exact is used.
c Day 6 is the primary time point for the assessment of clinical success. Up to Day 6 analysis excludes data collected after day 6.

The described treatment age groups (i.e., 1-5 years, 6 -10 years, 11-15 years or 16-17 years) were significantly underpowered to be able to determine significance.

Based on the review of the original NDA for Zymar (gatifloxacin ophthalmic solution, 0.3%), there is no evidence that the ophthalmic administration of gatifloxacin has any effect on weight bearing joints, even though oral administration of some quinolones has been shown to cause arthropathy in immature animals.

11. Other Relevant Regulatory Issues

Per the Statistical Review and Evaluation completed by the Office of Biostatistics on 3/26/2010, there were no major statistical issues for the studies.

In study 198782-004, for the pre-defined primary analysis of Day 6 analysis (including all data collected for the day 6), the clinical resolution rate for gatifloxacin 0.5% ophthalmic solution vs. Vehicle was 74.9% (125/167) vs. 65.2% (103/158), a 9.7% treatment difference with 95%

confidence interval of (-0.3%, 19.6%) (p-value = 0.057). The study result was statistically marginal and the p-value was slightly above the 0.05 significance level.

In study 198782-005, for the pre-defined primary analysis of up to Day 6 analysis (using only data collected up to and including day 6), the clinical resolution rate for gatifloxacin 0.5% ophthalmic solution vs. Vehicle was 51.8% (86/166) vs. 41.3% (69/167), a 10.5% treatment difference with 95% confidence interval of (-0.2%, 21.2%) (p-value = 0.055). The study result was also statistically marginal and the p-value was slightly above the 0.05 significance level.

A Division of Scientific Investigations (DSI) audit was requested. From the DSI review dated 4/23/2010, this was a routine audit request to assess data integrity and human subject protection for clinical trials submitted in support of this application. The sites requested for inspection were the centers with the largest numbers of enrolled subjects in the study. Dr Daniel Long's site was also selected due to high enrollment and inspectional history in 1988.

Name of CI, IRB, or Sponsor Location	**Protocol #: and # of Subjects:**	**Inspection Date**	**Field Classification/Final Classification**
Yasmin Rusi Bhagat, M.D. Head of Ophthalmology Department St. George's Hospital Fort, Mumbai , India	Protocol 198782-005 Site # 13008 84 Subjects	11/09/2009-11/11/2009	NAI/VAI
Nita Shanbhag, M.D. Omkar Eye Care Center 302/303 Koteshwar Plaza Junc of Jawaharlal Nehru road and RHB road, Mulund (West) Mumbai – 400080, India	Protocol 198782-005 Site # 13014 90 Subjects	11/16/2009-11/17/09	NAI/NAI
Daniel A. Long, MD Dr. Daniel A Long – A Professional Medical Corporation 120 Meadowcrest St. #330 Gretna, LA 70056	Protocol 198782-004 Site # 10008 50 Subjects	10/19/2009-10/21/2009	OAI/OAI-Untitled

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

In general, the studies appear to have been conducted adequately and the data in support of the NDA appear reliable. The final classification of the inspection for Dr. Shanbhag is NAI. The final classification of the Clinical Investigator inspection of Dr. Bhagat is VAI. Although regulatory violations were noted at Dr Bhagat's site, it is unlikely that they significantly affect overall data reliability from the site. The data from Dr. Long's clinical site documented several regulatory violations due to the clinical investigator's failure to conduct the study according to the signed investigator statement and the investigational plan. However, the violations are unlikely to affect overall data reliability from the site. The classification of the Clinical Investigator inspection of Dr. Long is OAI-Untitled, based on the conclusion that although there was a potential for these significant findings to impact subject safety and/or efficacy, review of the findings demonstrate that these findings did not result in adverse outcomes that would otherwise impact subject safety and/or efficacy. Dr. Long submitted a written response that provided adequate corrective actions for the violations noted during the inspection. The data in support of the application are considered reliable.

Allergan, Inc. 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 study were impacted by any financial payments.

A consult was requested from the Office of Surveillance and Epidemiology regarding a trade name review for the proposed name "Zymaxid." The results of the Proprietary Name Risk Assessment found that the proposed name, Zymaxid, is not vulnerable to name confusion that could lead to medication errors nor promotional. Thus, the Division of Medication Error Prevention and Analysis does not object to the use of the proprietary name, Zymaxid, for this product.

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the Agency's revised version of Allergan's proposed product labeling (PI) for this application on 4/10/2010. With one exception, their recommendations and suggestions were incorporated into the label. The DDMAC recommendation for the DOSAGE AND ADMINISTRATION section, "Please also consider including that Zymaxid is "*not for injection into the eye"* in this section," was not incorporated because there is no evidence that injection of Zymaxid (gatifloxacin ophthalmic solution) 0.5% into the eye presents a safety problem.

12. Labeling

NDA 22-548 is recommended for approval for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:

Haemophilus influenzae, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus mitis group*, *Streptococcus oralis*, *Streptococcus pneumoniae*

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

with the labeling submitted by Allergan, Inc. on 4/20/2010 and found in this Cross-Discipline Team Leader Review (see Appendix 1).

Two review team labeling meetings were held; the first was held on 3/26/2010, and the second was held on 4/5/2010. After the second labeling meeting, there was agreement from the review team on the proposed package insert, and it was sent to DDMAC for review (see above). After DDMAC review, the revised label was sent to the Allergan on 4/14/2010.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
NDA 22-548 is recommended for approval for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:

Haemophilus influenzae, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus mitis group*, *Streptococcus oralis, Streptococcus pneumoniae*

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

The labeling submitted by Allergan, Inc. on 4/20/10 and found in this Cross-Discipline Team Leader Review (see Appendix 1) is acceptable for approval.

There are no postmarketing agreements for this application.

RISK BENEFIT ASSESSMENT:
Efficacy of the drug substance, gatifloxacin, has been demonstrated in multiple systemic indications in prior NDA submissions. Gatifloxacin ophthalmic solution 0.5% was studied in two adequate and well controlled studies submitted in this NDA. The clinical efficacy of gatifloxacin was superior to vehicle in each of these studies. The most frequently reported adverse events were: worsening of the conjunctivitis, eye irritation, dysgeusia, eye pain, pyrexia, instillation site irritation, pharyngolaryngeal pain, headache and eye edema. No new safety concerns regarding the use of gatifloxacin for the treatment of bacterial conjunctivitis were raised in this NDA submission.

The benefit of gatifloxacin ophthalmic solution 0.5% in the treatment of bacterial conjunctivitis has been demonstrated in this NDA application. The risk for using this drug is mild and is consistent with the currently marketed Zymar. The risk/benefit profile has been adequately established. Clinical, CMC, Pharmacology/Toxicology, Product Quality Microbiology, Statistics, and Clinical Pharmacology have recommended approval for this application.

9 pages of draft labeling has been withheld in full immediately following this page as (B4) CCI/TS

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22548	ORIG-1	ALLERGAN	GATIFLOXACIN OPHTHALMIC SOLUTION 0.5%

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

/s/

WILLIAM M BOYD
05/17/2010

WILEY A CHAMBERS
05/17/2010