CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-493

MEDICAL REVIEW

Medical Officer's Review of NDA 21-493
Labeling and Financial Disclosure Review

NDA 21-493	Submission:	3/24/03
Labeling and Financial Disclosure Review	Received:	3/24/03
	Review Completed:	3/26/03

Proposed Tradename:	Zymar
Generic Name:	Gatifloxacin Ophthalmic Solution 0.3%
Sponsor:	Allergan 2525 Dupont Drive P.O. Box 19534 Irvine, California 92623-9534
Pharmacologic Category:	Anti-infective
Proposed Indication:	Treatment of Bacterial Conjunctivitis
Dosage Form and Route of Administration:	topical
Submitted:	Revised labeling based on Agency's draft labeling dated 3/20/03

This review incorporates labeling comments received from the sponsor on 3/24/03.
Recommended additions are shown by underlining and recommended deletions are shown by strikethrough lines.
In addition, a review of the financial disclosure for the NDA submission is included at the end of the labeling review.

ZYMAR™

(gatifloxacin ophthalmic solution) 0.3%
Sterile

ALLERGAN

DESCRIPTION

5 Page(s) Withheld

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✓ § 552(b)(5) Draft Labeling

Financial Disclosure

The primary source of efficacy for this NDA submission was from two phase 3 trials, SPCL-GFLX 3/01 and SPCL-GFLX 3/02. None of the investigators involved in these two trials had any financial arrangements with either Allergan

Recommendation:

Original conclusions concerning the efficacy of Gatifloxacin remain unchanged based on the review of the financial disclosure. The proposed draft labeling is considered acceptable.

Jennifer D. Harris, M.D.
Medical Officer

NDA 21-493
HFD-550/Div Files
HFD-550/MO/Harris
HFD-550/SMO/Chambers
HFD-550/Div Dir/Simon
HFD-880/Biopharm/Bashaw
HFD-725/Biostats/Rahman
HFD-550/Chem/Rodriquez
HFD-550/PharmTox/ChenZ
HFD-550/PM/Gorski

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/s/

Jennifer Harris
3/27/03 04:18:13 PM
MEDICAL OFFICER

Wiley Chambers
3/27/03 05:22:50 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

Medical Officer's Review of NDA 21-493
Labeling Review

NDA 21-493	Submission: 3/12/03
Labeling Review	Received: 3/12/03
	Review Completed: 3/20/03

Proposed Tradename:	Zymar
Generic Name:	Gatifloxacin Ophthalmic Solution 0.3%
Sponsor:	Allergan 2525 Dupont Drive P.O. Box 19534 Irvine, California 92623-9534
Pharmacologic Category:	Anti-infective
Proposed Indication:	Treatment of Bacterial Conjunctivitis
Dosage Form and Route of Administration:	topical
Submitted:	Revised labeling based on Agency's draft labeling dated 3/13/03

Reviewer's Comments:
This review incorporates comments received from the sponsor and those received from DDMAC in a memo dated 3/14/03. Recommended additions are shown by underlining and recommended deletions are shown by strikethrough lines.

ZYMAR™

(gatifloxacin ophthalmic solution) 0.3% ALLERGAN
Sterile

DESCRIPTION

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Jennifer Harris
3/21/03 12:48:26 PM
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Wiley Chambers
3/25/03 12:46:03 PM
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APPEARS THIS WAY
ON ORIGINAL

Medical Officer's Review of NDA 21-493
Original Review #3

NDA 21-493	Submission: 10/11/02
Medical Officer's Review #3	Review Completed: 10/25/02

Proposed Tradename: ~~~~

Generic Name: Gatifloxacin Ophthalmic Solution 0.3%

Sponsor: Allergan
2525 Dupont Drive
P.O. Box 19534
Irvine, California 92623-9534

Pharmacologic Category: Anti-infective

Proposed Indication: Treatment of Bacterial Conjunctivitis

Dosage Form and Route of Administration: topical

Submitted: Response to request from medical reviewer for addition information/clarification of items in original NDA submission. The list of concerns were as follows:

1. Both studies 3/01 and 3/02 have errors in the data tables that were carried forward in all of the analyses in the NDA. The sponsor must submit the corrected data tables along with the correct analysis for review.

2. Significant treatment by center interaction was found in study 3/01. This was not adequately addressed by the sponsor. Study 3/01 showed a statistically significant difference (0.034) in the treatment-by-investigator analysis for the per protocol population (N=100). This was addressed by defining a new per protocol population (N=106) and re-running the analysis which found the p-value to be 0.167. The sponsor should provide the division with the rationale for adding the additional 6 patients to the per-protocol population and if this population is to be used, the efficacy and safety data throughout the submission needs to be corrected reflecting

this change. Alternatively, the sponsor should submit a sensitivity analysis to further investigate this interaction.

Response to item #1:

Table 1- Efficacy Analyses (per protocol) – Protocol 3/01

Visit	Clinical Cure (a)	0.3% GFLX (n=52)	Vehicle (n=48)	P-value (b)	Difference CI (c)
Day 3		n=45	n=42		
	Success	9 (20.0%)	6 (14.3%)	0.573	0.057 (-0.101,0.215)
	Failure	36 (80.0%)	36 (85.7%)		
Day 6		n=52	n=48		
	Success	40 (76.9%)	28 (58.3%)	0.050	0.186 (0.004,0.368)
	Failure	12 (23.1%)	20 (41.7%)		

(a) success is achieved when the scores for mucopurulent discharge and bulbar conjunctival erythema are equal to 0 (none).

(b) P-value from cochran-mantel-haenszel test stratified for age group (≤12, >12).

(c) Difference (GFLX-vehicle) and confidence interval for difference in success rates: The confidence level is 95% for day 3, and 95.2% for day 6.

Reviewer's Comments: *There is no impact on the clinical cure rate when these errors are accounted for.*

Table 2- Eradication rates (per protocol) at day 6 - Study 3/01

	0.3% GFLX	**vehicle**
Bacterial Classification		
All organisms	92.9% (65/70)	*78.8% (52/66)*
Gram positive bacteria	92.7% (51/55)	*71.4% (35/49)*
Gram negative bacteria	93.3% (14/15)	100% (17/17)

Reviewer's comments:
The eradication rates affected by correcting the data errors are italicized. There is no effect on the original conclusions about the efficacy of gatifloxacin.

Table 3- Efficacy Analyses (per protocol) – Protocol 3/02

Visit	Clinical Cure (a)	0.3% GFLX (n=77)	0.3%OFLX (n=69)	P-value (b)	Difference CI (c)
Day 3		n=72	n=66		
	Success	12 (16.7%)	16 (24.2%)	0.221	-0.076 (-0.210,0.059)
	Failure	60 (83.3%)	50 (75.8%)		
Day 6		n=77	n=69		
	Success	63 (81.8%)	52 (75.4%)	0.352	0.065 (-0.070,0.199)
	Failure	14 (18.2%)	17 (24.6%)		

(a) success is achieved when the scores for mucopurulent discharge and bulbar conjunctival erythema are equal to 0 (none)

(b) P-value from cochran-mantel-haenszel test stratified for age group (<12, >12)

(c) Difference (GFLX-OFLX) and confidence interval for difference in success rates. The confidence level is 95% for day 3, and 95.2% for day 6.

Reviewers Comments:

The efficacy rates affected by correcting the data errors are italicized. There is no effect on the original conclusions about the efficacy of gatifloxacin.

Table 4- Eradication rates at day 6 - Study 3/02

	0.3% GFLX	0.3% OFLX
Bacterial Classification		
All organisms	*86.6% (84/97)*	88.6% (78/88)
Gram positive bacteria	*81.5% (53/65)*	86.6% (58/67)
Gram negative bacteria	96.9% (31/32)	95.2% (20/21)

Reviewer's comments:

The eradication rates affected by correcting the data errors are italicized. There is no effect of the original conclusions about the efficacy of gatifloxacin.

Response to item #2:

Study 3/01 was conducted at 22 investigator sites; 18 sites contributed to the PP population clinical cure success rates at day 6 for each investigator site are shown in the following table:

Clinical Cure Success Rates at Day 6 per Investigator Site (PP Population)

Investigator Site	Gatifloxacin (N=52)	Placebo (N=48)	Difference[a]
101	1/2(50.0%)	0	NA
103	3/3 (100%)	1/2 (50.0%)	50.0%
108	0	2/3 (66/7%)	NA
111	1/1 (100.0%)	0	NA
116	1/1 (100%)	0/1 (0%)	100%
117	3/3 (100%)	0/4 (0%)	100%
118	2/3 (66.7%)	2/3 (66.7%)	0%
119	1/4 (25.0%)	1/6 (16/7%)	8.3%
121	**5/8 (62.5%)**	**9/10 (90.0%)**	**-27.5%**
123	1/2 (50.0%)	0	NA
125	4/6 (66.7%)	3/3 (100.0%)	-33.3%
128	9/10 (90.0%)	3/3 (100.0%)	-10.0%
129	1/1 (100.0%)	1/3 (33.3%)	66.7%
131	5/5 (100.0%)	2/4 (50.0%)	50.0%
136	0	2/2 (100.0%)	NA
138	0	0/1 (0%)	NA
144	1/1 (100.0%)	2/2 (100.0%)	0.0%
149	2/2 (100.0%)	0/1 (0%)	100.0%

[a] gatifloxacin – placebo difference in clinical cure success rates

The treatment-by-investigator site interaction was statistically significant in the PP population, p=0.034. A sensitivity analysis was performed to investigate the observed treatment-by-investigator site interaction by removing each of the 3 investigator sites (121, 125, and 128) where the clinical cure success rate with placebo was greater than with gatifloxacin.

Clinical Cure Success Rates at Day 6[a] Excluding Sites Where the Success Rate was Higher with Placebo (PP Population)

Analysis Population	Clinical Cure Success at Day 6		Difference	Treatment P-value[a]	Interaction P-value[b]
	Gatifloxacin	Placebo			
PP all sites	40/52 (76.9%)	28/48 (58.3%)	18.6%	0.050	0.034
Exclude site 121	35/44 (79.5%)	19/38 (50.0%)	29.5%	0.005	0.121
Exclude site 125	36/46 (78.3%)	25/45 (55.6%)	22.7%	0.023	0.045
Exclude site 128	31/42 (73.8%)	25/45 (55.6%)	18.3%	0.082	0.026

[a] P-value from Cochran-Mantel-Haenszel test stratified for age group (≤12 years and >12 years)
[b] P-value from Breslow-Day test for treatment-by-investigator site interaction

The analyses indicated that investigator site 121 was the potential cause of the significant interaction. When this site is excluded, the treatment-by-site interaction term was non-significant.

P-values for Breslow-Day Test for Interaction at Day 6 Excluding Center 121 (per-protocol population)

	P-value
Treatment-by-Investigator Site	0.121
Treatment-by-Age Group [a]	0.413

[a] Age group is (≤12 and >12)

The demographics and baseline characteristics of the PP population for site 121 were reviewed for possible explanations of the observed difference in clinical success rates. In general, site 121 was similar to other study sites in terms of sex, race, iris color, number of organisms above threshold at baseline, reference eye and duration of current episode. Two notable differences were that the PP population at site 121 included only patients > 12 years of age and only patients with unilateral infections.

Clinical Cure Success Rates at Day 6[a] by Age and Infection subgroups with and without Site 121 (PP Population)

Baseline Variable	Category	All Sites		Investigator Site 121		All Sites Excluding 121	
		Gatiflox (N=52)	Placebo (N=48)	Gatiflox (N=8)	Placebo (N=10)	Gatiflox (N=44)	Placebo (N=38)
Age Group	≤12 years	13/14 (92.9%)	7/12 (58.3%)	0	0	13/14 (92.9%)	7/12 (58.3%)
	>12 - <65	18/26 (69.2%)	16/28 (57.1%)	2/4 (50.0%)	5/5 (100%)	16/22 (72.7%)	11/23 (47.8%)
	≥65	9/12 (75.0%)	5/8 (62.5%)	3/4 (75.0%)	4/5 (80.0%)	6/8 (75.0%)	1/3 (33.3%)
Infection	unilateral	22/29 (75.9%)	17/26 (65.4%)	5/8 (62.5%)	9/10 (90.0%)	17/21 (81.0%)	8/18 (50.0%)
	bilateral	18/23 (78.3%)	11/22 (50.0%)	0	0	18/23 (78.3%)	11/22 (50.0%)

The analyses indicated that across all sites, gatifloxacin-treated patients had a higher rate of clinical success than placebo-treated patients in each of the 3 age subgroups of the PP population. Patients in the youngest subgroup (≤12 years) showed the greatest benefit from gatifloxacin. However as gatifloxacin was also effective in older patients, the lack

of younger patients at investigator site 121 would not explain why the overall treatment effect was reversed at that center.

Reviewer's Comments:

Investigator 121 is the most likely cause of the significant interaction for study 3/01. This investigator has the highest number of per protocol patients in the study (18 total) and the treatment effect was reversed at this center (i.e. results favoring the placebo group). This accounts for 18% of the total per protocol population.

The majority of centers in this study (7vs 3) and the results of the overall study favor gatifloxacin over vehicle.

Conclusions:

The sponsor has adequately addressed the points of clarification requested based on the original NDA review. The submitted data in conjunction with the original NDA support the use of gatifloxacin in the treatment of bacterial conjunctivitis for patients above the age of 1 years old.

Jennifer D. Harris, M.D.
Medical Officer

NDA 21-493
HFD-550/Div Files
HFD-550/MO/Harris
HFD-550/SMO/Chambers
HFD-550/ Div Dir/Simon
HFD-880/Biopharm/Bashaw
HFD-725/Biostats/Rahman
HFD-550/Chem/Rodriquez
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S/

Jennifer Harris
2/12/03 02:45:05 PM
MEDICAL OFFICER

Wiley Chambers
2/13/03 11:18:30 AM
MEDICAL OFFICER

Medical Officer's Review of NDA 21-493
120-Day Safety Update

NDA 21-493	Submission: 10/4/02
Medical Officer's Review	Received: 10/7/02
	Review Completed: 10/18/02

Proposed Tradename: [redacted]

Generic Name: Gatifloxacin Ophthalmic Solution 0.3%

Sponsor:
Allergan
2525 Dupont Drive
P.O. Box 19534
Irvine, California 92623-9534

Pharmacologic Category: Anti-infective

Proposed Indication: Treatment of Bacterial Conjunctivitis

Dosage Form and Route of Administration: topical

Submitted:

1. Safety data for 4 phase 3 trials conducted by Senju Pharmaceutical in Japan

2. Proposed Labeling Change (*This change includes additional in-vitro data. This will be addressed in a separate labeling review*)

Safety data from the following trials are included in this review:

SJC 7001/3-01	A Phase 3 Multicenter, Randomized, Double-Masked, Parallel Study to Compare the Efficacy and Safety of 0.3% Gatifloxacin Ophthalmic Solution with that of 0.3% Ofloxacin Ophthalmic Solution in the Treatment of Bacterial Conjunctivitis
SJC 7001/3-02	A Phase 3 Multicenter, Open Labeled Study to Examine the Efficacy and Safety of 0.3% Gatifloxacin Ophthalmic Solution in the Treatment of Bacterial Hordeolum, Tarsadenitis, Blepharitis and Dacryocystitis
SJC 7001/3-03	A Phase 3 Multicenter, Open Labeled Study to Examine the Efficacy and Safety of 0.3% Gatifloxacin Ophthalmic Solution in the Treatment of Bacterial Keratitis
SJC 7001/3-04	Phase 3 Multicenter, Open Labeled Study to Examine the Efficacy and Safety of 0.3% Gatifloxacin Ophthalmic Solution in the Ophthalmic Preoperative Asepsis

Table 1 – Incidence of Adverse Events Reported by ≥ 1% of Patients Treatment Group Pooled Data

Preferred Term	0.3% GFLX N=359
Eye disorders	
Conjunctival hyperemia	3(0.84%)
Eye discharge	3(0.84%)
Hordeolum	3(0.84%)
Intraocular pressure increased	5(1.4%)
Iritis	3(0.84%)
General disorders and administration site conditions	
Application site irritation	12(3.3%)
Application site pruritus	12(3.3%)
Infections and infestations	
Conjunctivitis bacterial NOS	3(0.84%)
Nasopharyngitis	5(1.4%)
Musculoskeletal and connective tissue disorders	

Preferred Term	0.3% GFLX N=359
Back pain	3(0.84%)
Nervous system disorders	
Headache NOS	5(1.4%)
Gastrointestinal disorders	
Constipation	10(2.8%)

One serious event was reported for study SJC-7001/3-04. This was for a 68 y.o. male who developed cough, bloody sputum and fever and was diagnosed with tuberculosis one month after starting gatifloxacin. The patient was successfully treated with anti-tuberculosis drugs.

Reviewer's Conclusions

1) *Original conclusions regarding the safety of gatifloxacin 0.3% are unaltered*

2) *No changes to the label are warranted based on this safety database.*

Jennifer D Harris, M.D.
Medical Officer

NDA 21-493
HFD-550/Div Files
HFD-550/MO/Harris
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/s/

Jennifer Harris
11/27/02 01:54:18 PM
MEDICAL OFFICER

Tables revised, conclusion corrected

Wiley Chambers
12/5/02 03:08:57 PM
MEDICAL OFFICER

Medical Officer's Review of NDA 21-493

Drug:	**Gatifloxacin ophthalmic solution 0.3%**
Proposed Tradename:	**ZYMAR**
Sponsor:	**Allergan 2525 Dupont Drive** **P.O. Box 19534** **Irvine, California 92623** Elizabeth Bancroft (714) 246-4391
Proposed Indication:	**Treatment of Bacterial Conjunctivitis**
Date of Submission:	May 30, 2002
Date of Review	September 16, 2002

Table of Contents

Executive Summary

I. Recommendatons

The submitted studies show that gatifloxacin 0.3% potentially may have efficacy in the treatment of bacterial conjunctivitis. It is recommended that this NDA be granted an approvable status at this time. The sponsor must address the following issues before a final determination can be made:

- Both studies 3/01 and 3/02 have errors in the data tables which were carried forward in all of the analysis in the NDA. The sponsor must submit the corrected data tables along with the correct analysis for review.

- Significant treatment by center interaction was found in study 3/01. This was not adequately addressed by the sponsor. Study 3/01 showed a statistically significant difference (0.034) in the treatment-by-investigator analysis for the per protocol population (N=100). This was addressed by defining a new per protocol population (N=106) and re-running the analysis which found the p-value to be 0.167. The sponsor should provide the division with the rationale for adding the additional 6 patients to the per-protocol population and if this population is to be used, the efficacy and safety data throughout the submission needs to be corrected reflecting this change. Alternatively, the sponsor should submit a sensitivity analysis to further investigate this interaction.

- Study 3/02 had a significant number of patients "lost to follow-up." The sponsor should describe the methods used to locate these patients and provide an exploratory analysis of the potential impact on the study results.

II. Summary of Clinical Findings

A. Overview of clinical program

The primary sources of efficacy and safety data for the use of gatifloxacin 0.3% ophthalmic solution were two phase 3 studies; SPCL-GFLX 3/01 and SPCL-GFLX 3/02. These studies enrolled a total of 724 patients of which 364 were exposed to the study drug. Study 3/01 was a vehicle control design while 3/02 was and active control design. The primary efficacy variable for each study was the clinical cure of bacterial conjunctivitis at the conclusion of the trial. A patient was classified as a success for clinical cure if two ophthalmic signs (mucopurulent discharge and bulbar conjunctival erythema) were scored at 0=none at day 6±1 of the trial.

The criteria necessary to prove efficacy of gatifloxacin was to demonstrate superiority to vehicle in study 3/01 and equivalence to ofloxacin 0.3% ophthalmic solution (an approved drug for bacterial conjunctivitis within the same class) in study 3/02

The equivalence criteria for the active-control study was defined based on a 2-sided 95% confidence interval (CI) for the difference in success rates. If the control cure rate (p_c) is greater than 90%, the CI must be within ± 0.1. If p_c is between 80% and 90%, the CI must be within ± (1-p_c). If p_c is less than 80%, the CI must be within ± 0.2.

B. Efficacy

The submitted studies show that gatifloxacin 0.3% appears to be efficacious in the treatment of bacterial conjunctivitis for patients above the age of 1 years old. Its overall efficacy is similar to currently marketed floroquinolones used in the treatment of bacterial conjunctivitis. The sponsor must address the issues raised in the recommendations section before a final determination can be made.

C. Safety

There are no new concerns raised in this NDA submission concerning the use of gatifloxacin for bacterial conjunctivitis. The adverse events reported during the phase 3 studies were similar to those listed in the package inserts of the currently marketed fluoroquinolone ophthalmic solutions. No clinically significant differences were found between gatifloxacin and the active control ofloxacin or vehicle in the frequency, or type of adverse events.

D. Dosing

The recommended duration of treatment for bacterial conjunctivitis is 7 days. The dosing schedule based on the clinical trials submitted is one drop instilled in the affected eye every 2 hours while awake for the first 2 days, and then 4 times daily every 4 hours. This is the recommended dosing schedule for maximum efficacy in both the adult and

pediatric population. This is consistent with other marketed drugs in this class for the treatment of bacterial conjunctivitis.

E. Special Populations

The phase 3 studies included adult and pediatric patients (≥1 to ≤12 years of age). There was no indication of a differential effect in children versus adults, and no safety concerns were identified for younger patients. There were no notable differences between the adverse event profile for gatifloxacin in males and females, Caucasians and non-Caucasians, or patients with light and dark irides.

Clinical Review

I. Introduction and Background

A. Proposed Trade Name and Drug Class

Proposed Tradename:	(Zymar) Gatifloxacin ophthalmic solution 0.3%
Sponsor:	Allergan 2525 Dupont Drive P.O. Box 19534 Irvine, California 92623
Pharmacologic Category:	Antimicrobial
Proposed Indication:	Treatment of Bacterial Conjunctivitis
Dosage Form and Route of Administration:	Ophthalmic solution for topical ocular administration

B. Clinical Background

One of the most common eye diseases worldwide is conjunctivitis, an inflammation of the conjunctiva which may be of bacterial, viral, allergic, fungal, or traumatic etiology. *Streptococcus pneumoniae* and *Haemophilus influenzae* are responsible for most cases of bacterial conjunctivitis in children and *Staphylococcus* species are the predominant organisms causing conjunctivitis in adults (Friedlander, 1995). Acute bacterial conjunctivitis may be self-limiting. Untreated, it may last 10 to 14 days. With proper treatment, bacterial conjunctivitis can be limited to 1 to 3 days (Schwab and Dawson, 1992).

In the last decade, 4 fluoroquinolone anti-infectives have been approved for ophthalmic applications and are available in the United States and Europe: norfloxacin, ofloxacin, and ciprofloxacin as 0.3% ophthalmic solutions, and most recently, levofloxacin as 0.5% ophthalmic solution.

C. Important Milestones in Product Development

- EOP2 meeting (11/1/99) and follow-up teleconference (11/22/99)
- *IND 59,408 transferred from Senju Pharmaceutical Company Limited to Allergan, Inc on 19 February 2001*
- Pre-NDA Meeting (11/26/01)

D. Foreign Marketing

Gatifloxacin is currently marketed in oral and intravenous formulations as shown in the following countries. It has not been withdrawn from marketing in any country for any reason.

Table 1 - Countries where Gatifloxacin is Marketed

Country	Product	Approval Date
Mexico	Tequin tablets and injection	22 June 1999
United Stated	Tequin™ tablets and injection	17 December 1999 (NDAs 21-061 and 21-062)
Brazil	Tequin tablets Tequin injection	20 December 1999 25 May 2000
Puerto Rico	Tequin tablets Tequin injection	21 December 1999 31 January 2000
Argentina	Tequin tablets Tequin injection	12 January 2000 17 May 2000
Singapore	Tequin tablets and injection	29 May 2000
Thailand	Tequin tablets and injection	19 June 2000
Philippines	Tequin tablets and injection	11 September 2000
Canada	Tequin tablets and injection	9 January 2001
South Africa	Tequin tablets and injection	13 February 2001
Australia	Tequin tablets and injection	15 February 2001
Indonesia	Tequin tablets and injection	9 April 2001
Aruba	Tequin tablets and injection	07 May 2001
Malaysia	Tequin tablets and injection	12 July 2001
Germany	Bonoq tablets	22 October 2001

II. Clinically Relevant Finding from Microbiology Review

Based on *in-vitro* data from this NDA in conjunction with *in-vitro* data provided in the tablet and intravenous NDA submissions for gatifloxacin, the microbiology reviewer has recommended the following changes to the proposed microbiology section of the package insert. Recommended deletions are shown with a strike-through. The justification is shown in parenthesis.

AEROBES, GRAM-POSITIVE:

3 Page(s) Withheld

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✓ § 552(b)(5) Draft Labeling

IV. Description of Clinical Data Sources

Table 2 - Clinical Data Sources

Protocol	Study dates	Study Design	Treatment Groups	Number of Patients	Dosing	Age, Sex, Race	Duration of Treatment
SPCL-GFLX 3/01	Initiation date 08 March 2000 Completion date 18 July 2001	Multicenter double-masked randomized parallel group	Gatifloxacin 0.3% Vehicle	134 131	Approximately every 2 hours while awake on days 1 and 2; 4 times daily approximately every 4 hours while awake on days 3 to 5 ±1	**Mean age** 38.4 **Sex** Male 34.7% (92/265) Female 65.3% (173/265) **Race** Caucasian 80.8% (214/265) African-American 10.9% (29/265) Asian/Pacific island 0.4% (1/265) Hispanic 7.2% (19/265) Other 0.8% (2/265)	5±1
SPCL-GFLX 3/02	Initiation date 23 February 2000 Completion date 05 December 2001	Multicenter double-masked randomized parallel group	Gatifloxacin 0.3% Ofloxacin 0.3%	230 229	Approximately every 2 hours while awake on days 1 and 2; 4 times daily approximately every 4 hours while awake on days 3 to 5 ±1	**Mean age** 39.3 **Sex** Male 37.0% (170/459) Female 63.0% (289/459) **Race** Caucasian 69.7% (320/459) African-American 10.7% (49/459) Asian/Pacific island 0.9% (4/459) Hispanic 17.2% (79/459) Native American/Alaskan 0.4%(2/459) Other 1.1% (5/459)	5±1

V. Clinical Review Methods

A. Overall approach

The primary sources of efficacy and safety data for the use of gatifloxacin 0.3% ophthalmic solution were two phase 3 studies; SPCL-GFLX 3/01 and SPCL-GFLX 3/02. Study 3/01 was a vehicle control design while 3/02 was an active control design. The primary efficacy variable for each study was the clinical cure of bacterial conjunctivitis at the conclusion of the trial. A patient was classified as a success for clinical cure if two ophthalmic signs (mucopurulent discharge and bulbar conjunctival erythema) were scored at 0=none at day 6±1 of the trial.

The criteria necessary to prove efficacy of gatifloxacin was to demonstrate superiority to vehicle in study 3/01 and equivalence to ofloxacin 0.3% ophthalmic solution in study 3/02

The equivalence criteria for the active-control study was defined based on a 2-sided 95% confidence interval (CI) for the difference in success rates. If the control cure rate (p_c) is greater than 90%, the CI must be within ± 0.1. If p_c is between 80% and 90%, the CI must be within ± (1 - p_c). If p_c is less than 80%, the CI must be within ± 0.2.

B. Financial Disclosure

Allergan has certified that no investigators in the two phase 3 trials submitted had any financial arrangement with the sponsor; hand no proprietary interest in gatafloxocin or significant equity interest in Allergan and was not the recipient of significant payments of other sorts.

VI. Integrated Review of Efficacy

Study 1 – Protocol SPCL-GFLX 3/01

Title: A Phase III Multicenter Randomized, Double-Masked, Parallel Study to compare the Safety and Efficacy of 0.3% Gatifloxacin Ophthalmic Solution with that of Placebo in the Treatment of Acute Bacterial Conjunctivitis

Objectives:

The goal of this study was to demonstrate that gatifloxacin 0.3% ophthalmic solution was superior to vehicle in the treatment of bacterial conjunctivitis in patients ≥ 1 year of age.

Study Design:

The study used a double-masked, vehicle-control, parallel-group design to evaluate the efficacy and safety of gatifloxacin versus vehicle in the treatment of acute bacterial conjunctivitis. Multiple sites enrolled patients who were 1 year of age or older, had a clinical diagnosis of acute bacterial conjunctivitis, and were eligible based on the other

study entry criteria. Patients were randomly allocated to treatments using a central stratified simple randomization scheme, which included stratification by age (≤ 12 years and >12 years).

Clinical Sites – Study 3/01

Principle Investigator (Center Number)	Location	Number of Subjects Enrolled
KF Archer, MD (101)	Corpus Christi,TX	5
A Carraby, MD (149)	Torrance, California	12
P Dawson, MD (103)	Houston, Texas	10
L Ericson, MD (111)	Salt Lake City, Utah	2
BR Friedland, MD (108)	Durham, North Carolina	13
M Gooch, MD (111)	Salt Lake City, Utah	0
ST Jackson, MD (136)	Sandy, Utah	9
GR John, MD (115)	Louisville, Kentucky	3
DL Kilpatrick, MD (116)	Scottsdale, Arizona	7
B Kissack, OD (117)	Honeoye Falls, New York	13
JH Krug, Jr, MD (118)	Charlotte, North Carolina	11
D Lorenz, DO (131)	Las Vegas, Nevada	18
AI Mandell, MD (119)	Memphis, Tennessee	20
ML Monica, MD, PhD (121)	New Orleans, Louisiana	30
J Orellana, MD, MS, FACS (132)	Cary, North Carolina	1
MH Rotberg, MD (123)	Charlotte, North Carolina	9
Sk Sethi, MD (144)	Greensboro, North Carolina	6
JP Shovlin, OD (124)	Scranton, Pennsylvania	2
LT Smith, MD (138)	Richmond, Virginia	5
SS Spector, MD (125)	West Palm Beach, Florida	43
OD Stevenson, MD (150)	New Orleans, Louisiana	2
ME Tepedino, MD (128)	High Point, North Carolina	37
TR Walters, MD (129)	Austin, Texas	7

Reviewer's Comments:
The agency prefers patients to be randomized with at least ten patients per arm per center in multicenter trials so that interaction between centers can be evaluated.

The agency requires that principle investigators be qualified by training and experience as appropriate experts in the field of ophthalmology. Investigators 117 and 124 do meet this criteria.

Study Population – Inclusion and Exclusion Criteria

Inclusion Criteria

To be eligible for the study, each patient must have met the following criteria:

1) The patient or his/her legal guardian signed the informed consent or assent document.
2) The patient was male or female, ≥1 year of age.
3) The patient had a clinical diagnosis of acute bacterial conjunctivitis at baseline. The average of 2 key signs (mucopurulent discharge and bulbar conjunctival erythema) should have been 2 or greater (eg, 1 and 3, 2 and 3, 3 and 3, or 2 and 2).
4) The patient and/or his/her legal guardian was capable of understanding and complying with the protocol.
5) The patient was in general good health, with the exception of signs and/or symptoms related to acute bacterial conjunctivitis, as assessed by the investigator.
6) Females who had reached menarche, were not surgically sterile, and were not more than 1 year postmenopausal must have had a negative urine pregnancy test at visit 1.

Exclusion Criteria

Patients were excluded from study participation for any of the following reasons:

1) The patient had signs and/or symptoms of conjunctivitis for more than 4 days.
2) The patient had conjunctivitis signs and/or symptoms that were suggestive of a viral etiology.
3) The patient had signs and/or symptoms typical of chlamydial or fungal infections, or inflammation of allergic etiology.
4) The patient had a clinical diagnosis of keratitis or corneal ulcers, based on slit-lamp examination and positive fluorescein staining.
5) The patient had a clinical diagnosis of *Staphylococcal* blepharitis.
6) The patient had a clinical diagnosis of hyperacute bacterial conjunctivitis (eg, gonococcal conjunctivitis), or any other infectious conditions that, in the opinion of the investigator, had the potential to lead to visual loss if left untreated.
7) The patient had any serious current systemic infection.
8) The patient was known to have renal insufficiency by history.
9) The patient was known to have current clinically significant hepatic disease by history.
10) The patient was known to be immunosuppressed.
11) The patient had a history of hypersensitivity to nalidixic acid or any quinolone.
12) The patient was pregnant, lactating, or was of childbearing potential, but was not using clinically adequate contraceptive methods. For this study, adequate contraceptive methods included abstinence; oral, injected, or implantable contraceptive therapy; use of a diaphragm in association with use of spermicide; intrauterine devices; or surgical sterility. Use of condoms or spermicide, or surgical sterility of the sexual partner were not considered to be adequate contraceptive methods.
13) The patient had been treated with ophthalmic antimicrobial agents or corticosteroids during the previous 2 weeks.
14) The patient was currently receiving systemic antimicrobial therapy.

15) The patient had participated in an investigational new drug study within 30 days prior to visit 1.

Study Medications

Gatifloxacin sesquihydrate, (+/-)-1-cyclopropyl-6-fluoro-1, 4-dihydro-8-methoxy-7- (3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate, was the active ingredient in the ophthalmic solution used in the study. This aqueous 0.3% ophthalmic solution was a sterile, clear, pale yellow solution that was instilled into the eye via drops. It contained gatifloxacin at a concentration of 0.3 g/100 mL, [redacted], sodium chloride, [redacted] disodium edetate, 0.005 g/100 mL benzalkonium chloride, water for injection, hydrochloric acid or sodium hydroxide, adjusted to a pH of [redacted]

The vehicle comparator was a clear colorless solution containing [redacted] sodium chloride, [redacted], disodium edetate, 0.005 g/100 mL benzalkonium chloride, water for injection, hydrochloric acid or sodium hydroxide, adjusted to a pH of [redacted]

The container system used for both gatifloxacin and vehicle consisted of a [redacted] white opaque LDPE bottle with tamper-evident overcap, a white low-density polyethylene tip, and a white high-density polyethylene screw cap. Clinical trial material was to be stored at controlled room temperatures of 20 to 25°C. The lot numbers for the gatifloxacin and vehicle used in the study were as follows:

- gatifloxacin 0.3% ophthalmic solution - Lot No. 02599D [redacted]
- vehicle ophthalmic solution - Lot No. 02599F [redacted]

Study Dosing

Each patient was to receive their randomly assigned study drug for a total of 5±1 days. For the first 2 days, patients were instructed to instill 1 to 2 drops of study medication to the conjunctival sac of each affected eye approximately every 2 hours (Q2H) while awake. On day 1, patients were to receive a minimum of 4 applications per 24 hours, to a maximum of 8 applications per 24 hours. On day 2, patients were to receive a minimum of 6 applications per 24 hours, to a maximum of 8 applications per 24 hours. For the remainder of the treatment days, patients were instructed to instill medication 4 times daily (QID) approximately every 4 hours (Q4H) while awake.

Study Masking

This was a double-masked study. All personnel responsible for clinical patient management, the laboratory that performed microbiological testing, and personnel involved in the administrative management of the study were strictly masked to the randomized treatment assignment of each patient throughout the study. An interim analysis for the purpose of sample size re-evaluation was conducted midway through the

study by a statistician at [redacted] who was not involved in the conduct of the study then, or at any time in the future. All paper and electronic copies of unmasked materials were stored in a secure area; only another randomization statistician and the computer system administrator had access. The specific results of the interim analysis were not revealed to personnel at investigator sites and those individuals at [redacted] and the Sponsor involved in the study. The results of the interim analysis indicated that no sample size adjustment was required. The final significance level was set at [redacted] to account for the interim analysis.

One part of the 3-part label on each container of study medication contained the treatment assignment, which could be accessed by scratching the surface of the label. These labels were to be opened only in the case of an emergency, when knowledge of the study drug identity was necessary for urgent treatment of the patient.

Efficacy Variable

Efficacy was evaluated based on microbiological cultures and the clinical assessment of the severity of 4 key ophthalmic signs and symptoms. The ophthalmic signs evaluated were mucopurulent discharge, and bulbar conjunctival erythema. The ophthalmic symptoms evaluated were ocular discomfort (including foreign body sensation and/or itching and/or photophobia) and tearing. At each of the 3 study visits, the severity of each sign and symptom was rated on a 4-point scale from 0 = none to 3 = severe. To provide continuity and minimize variability, the severity assessments for a given patient were performed by the same evaluator when possible.

For the primary efficacy analysis, a patient was classified as a success for clinical cure if the 2 key signs (mucopurulent discharge and bulbar conjunctival erythema) were scored a 0 = none at day 6±1. Clinical improvement was evaluated as a secondary efficacy endpoint, and was achieved if the average score of the 2 key signs was =1.5, with neither sign equal to 3, and neither sign scored greater than baseline.

At each of the 3 visits, a swab of the conjunctival sac of each affected eye was obtained and sent to the central laboratory for analysis. Any bacterial growth was quantified and if it exceeded the pathological threshold (defined in terms of colony forming units [CFU] per mL), the organisms were then tested for antibiotic susceptibility. The conjunctival swab samples taken at visits 2 and 3 were to be collected from 4 to 12 hours and from 12 to 24 hours, respectively, after the last administration of study drug. If necessary, the patient or the patient's legal guardian was advised to adjust the timing of the last administration of study drug prior to the visit in order to accommodate the timing of the conjunctival swab sampling.

Microbiological success was defined as eradication relative to the microbiological status determined from the conjunctival culture swab sample taken prior to the administration of the first dose of study drug. A 4-point classification was used to record bacterial culture data as follows:

eradication - pathogen originally present above threshold at baseline is absent in follow-up culture
reduction – pathogen originally present above threshold at baseline is reduced to a count below threshold in follow-up culture
persistence - pathogen originally present above threshold at baseline is reduced to a count below or equal to the baseline count, but is above or equal to threshold in follow-up culture
proliferation - pathogen originally present above threshold at baseline is increased to a count above baseline level in follow-up culture

Organisms above the pathological threshold were tested in vitro for susceptibility to gatifloxacin, ciprofloxacin, levofloxacin, and ofloxacin. Susceptibility was reported as susceptible, intermediate, or resistant based on minimum inhibitory concentration (MIC) breakpoints. "Not applicable" indicated that the given species did not have interpretation reference ranges for the given antibiotic in the M100 S-100 National Committee for Clinical Laboratory Standards (NCCLS) guidelines. "Inadequate growth" indicated that the given species was present above threshold at a visit, but MIC testing could not be performed due to inadequate growth of the culture.

Safety Variable

Safety variables included adverse events (AEs), ophthalmic examinations, and visual acuity assessments. An ophthalmic examination was performed at each visit and included a slit-lamp examination with fluorescein staining and a gross inspection of the affected external eye(s). The lids, conjunctiva, cornea, and anterior chamber of the eye were examined for the presence of erythema, edema, follicles, papillae, punctate keratitis, endothelial changes, cells, flare, and lens/cataract. The presence and/or severity of any of these findings were graded on a 4-point scale from 0 = none to 3 = severe.

Table 3 - Schedule of Assessments

	Visit 1 (day 1)	Visit 2 (day 3±1)	Visit 3 (day 6±1)
Informed Consent	X		
Complete Ocular History	X		
General Medical History[a]	X		
Ophthalmic Examination[b]	X	X	X
Clinical Assessment[c]	X	X	X
Conjunctival Swab Sample for Culture and Sensitivity[d]	X	X	X
Urine Pregnancy Test[e]	X		
Randomization	X		
Distribution of the Patient Diary[f]	X		
Distribution of Study Drug	X		

	Visit 1 (day 1)	Visit 2 (day 3±1)	Visit 3 (day 6±1)
Administration of the First Dose[g]	X		
Review of Adverse Events	X	X	X
Drug Instillation (times/day)	Q2H[h] while awake	QID[i] while awake	
Review Concomitant Medications		X	X
Patient Diary Review		X	X
Collection of the Patient Diary			X
Collection of Unused Study Drug			X

a included documentation of all medications taken during the previous 30 days
b included inspection of the external eye, slit-lamp examination, fluorescein staining, and visual acuity
c severity of 2 key signs and 2 key symptoms of ophthalmic infection graded
d sampling from 4 to 12 hours and from 12 to 24 hours, respectively, after study drug at visits 2 and 3
e for females who had reached menarche, were not surgically sterile, or were not =1 year postmenopausal
f recorded date and number of times study drug was administered per day
g administered at the investigator site by patient or legal guardian under the supervision of a staff person
h instilled in the affected eye(s) approximately every 2 hours (Q2H) while awake (maximum 8/day)
i instilled in the affected eye(s) 4 times daily (QID) approximately every 4 hours (Q4H)while awake; study drug was to be stopped after day 5 unless it was necessary to schedule visit 3 for day 5 or day 7 in which case study drug was to be stopped after day 4 or day 6, respectively

Subject Disposition and Demographics

Table 4- Subject disposition (safety population) – Study 3/01

	0.3% GFLX (n=134)	Vehicle (n=131)	Total (n=265)
Number Completed	123 (91.8%)	124 (94.7%)	247 (93.2%)
Number discontinued	11 (8.2%)	7 (5.3%)	18 (6.8%)

	0.3% GFLX	Vehicle	Total
Safety Population *	134	131	265
Per Protocol Population **	52	48	100
Modified intent-to-treat***	133	128	261

* all enrolled patients
**all enrolled patients who had a positive bacteriological culture that was above the pathological threshold at baseline and who did not have any significant protocol deviations
***all enrolled patients who received study drug and had at least one post baseline efficacy measure

Table 5- Discontinued Patients and Reason – Study 3/01

Patient	Age	Treatment	Reason
121-1192	31	gatifloxacin	Lost to follow-up
121-1219	70	gatifloxacin	Personal reasons - family illness
123-1263	63	gatifloxacin	Treatment failure
125-1048	68	gatifloxacin	Withdrew consent
128-1323	2	gatifloxacin	Adverse event – facial rash
131-1209	54	gatifloxacin	Treatment failure
131-1231	2	gatifloxacin	Adverse event – hives
131-1429	6	gatifloxacin	Adverse event – phlectenules, edema and keratitis OD
144-1150	2	gatifloxacin	Protocol violation - patient started antibiotics after randomization
149-1217	2	gatifloxacin	Personal reasons – parents request
149-1408	39	gatifloxacin	Lost to follow-up
118-1023	55	vehicle	Improper entry – systemic antibiotics
123-1255	63	vehicle	Treatment failure
125-1220	49	vehicle	Personal reasons – leaving town
128-1289	1	vehicle	Lost to follow-up
128-1362	3	vehicle	Bilateral otitis media
131-1170	7	vehicle	Treatment failure
131-1287	3	vehicle	Treatment failure

Reviewers Comments:

The number of discontinued patients is significantly higher (9/18) in the pediatric population (defined as ≤ 12). Eighteen (18%) of the pediatric population was discontinued versus four (4%) of the adult population.

Demographics

Table 6- Demographics - Study 3/01

		0.3% GFLX (n=134)	Vehicle (n=131)	p-value [a]
Age	**Mean**	40.4	36.5	0.178
	Median	39	37	
	Min	1	1	
	Max	90	90	
	≤ 12	25 (18.7%)	25 (19.1%)	
	> 12	109 (81.3%)	106 (80.9%)	
Sex				
Male		47 (35.1%)	45 (34.4%)	1.00
Female		87 (64.9%)	86 (65.6%)	
Race				
Caucasian		106 (79.1%)	108 (82.4%)	0.643
African America		16 (11.9%)	13 (9.9%)	
Asian/Pacific islander		1 (0.7%)	0	
Hispanic		9 (6.7%)	10 (7.6%)	
Native American/Alaskan		0	0	
Other		2 (1.5%)	0	
Infection				
Unilateral		88 (65.7%)	87 (66.4%)	1.0
Bilateral		46 (34.3%)	44 (33.6%)	
Number of Organisms Above Pathological threshold in Reference Eye				
0		62 (46.3%)	69 (52.7%)	0.140
1		57 (42.5%)	40 (30.5%)	
2		8 (6.0%)	15 (11.5%)	
3 or more		7 (5.2%)	7 (5.3%)	

[a] p-value for age from F test from an ANOVA model containing term for treatment. P-values for sex, race, infection, number of organisms from Fisher exact test.

Reviewers Comments:

There were no statistically significant differences in demographics between the treatment groups.

Efficacy Analysis

Reviewers Comments:

Two errors are present in the data tables for this study and were not corrected by the sponsor before submission of the NDA. One patient was incorrectly identified as belonging to the >12 year old group when in actuality the patient was 12. Another patient was misrandomized but was not identified as such in the protocol deviations. Neither is expected to have a significant impact on the final efficacy analysis, however the sponsor is required to submit the accurate data tables and study reports so that any impact can be evaluated.

Table 7- Baseline (Day 1) Efficacy Scores (per protocol) - Protocol 3/01

	0.3% GFLX (n=52)	Vehicle (n=48)
Mucopurulent Discharge		
Mean (SD)	2.2 (0.58)	2.1 (0.41)
Median	2.0	2.0
(min, max)	1,3	1,3
Bulbar Conjunctival Erythema		
Mean (SD)	2.4 (0.5)	2.1 (0.42)
Median	2.0	2.0
(min, max)	2,3	1,3

Table 8- Efficacy Analyses (per protocol) – Protocol 3/01

Visit	Clinical Cure (a)	0.3% GFLX (n=52)	Vehicle (n=48)	P-value (b)	Difference CI (c)
Day 3		n=45	n=42		
	Success	9 (20.0%)	6 (14.3%)	0.573	0.057 (-0.101,0.215)
	Failure	36 (80.0%)	36 (85.7%)		
Day 6		n=52	n=48		
	Success	40 (76.9%)	28 (58.3%)	0.050	0.186 (0.004,0.368)
	Failure	12 (23.1%)	20 (41.7%)		

(a) success is achieved when the scores for mucopurulent discharge and bulbar conjunctival erythema are equal to 0 (none).

(b) P-value from cochran-mantel-haenszel test stratified for age group (≤12, >12).

(c) Difference (GFLX-vehicle) and confidence interval for difference in success rates: The confidence level is 95% for day 3, and 95.2% for day 6.

Reviewers Comments: An interim analysis was conducted to check the validity of the assumptions made in the sample size and power calculations. The sample size did not require any adjustment. The alpha was set at [redacted] to account for this interim analysis. The difference between Gatifloxacin and vehicle does not reach statistical significance.

In review of the two phase 3 trials, it is noted that Tepedino is an investigator in both trials with the majority of enrolled patients (investigator 128 in study 3/01 and investigator number 243 in study 3/02). Efficacy results for clinical cure at day 6 were run for study 3/01 excluding this investigator. The difference between gatifloxacin and placebo at day 6 in not significant with this investigators results removed from the trial The p-value is 0.08 (-0.37, 0.019. However, the overall percentages for success rate at day 6 remain consistent (76.9% for gatifloxacin and 58% for vehicle). The lack of statistical significance is likely attributed to the small sample size.

Table 9- Baseline (Day 1) Efficacy Scores (safety population) - Protocol 3/01

	0.3% GFLX (n=134)	Vehicle (n=131)
Mucopurulent Discharge		
Mean (SD)	2.1 (0.50)	2.1 (0.51)
Median	2.0	2.0
(min, max)	1,3	1,3
Bulbar Conjunctival Erythema		
Mean (SD)	2.3 (0.47)	2.2 (0.50)
Median	2.0	2.0
(min, max)	2,3	1,3

Table 10- Efficacy Analyses (modified intent-to-treat) – Protocol 3/01

Visit	Clinical Cure (a)	0.3% GFLX (n=133)	Vehicle (n=128)	P-value (b)	Difference CI (c)
Day 3		n=133	n=128		
	Success	22 (16.5%)	16 (12.5%)	0.328	0.040 (-0.045,0.126)
	Failure	111(83.5%)	112 (87.5%)		
Day 6		n=133	n=128		
	Success	79 (59.4%)	65 (50.8%)	0.152	0.086 (-0.035,0.208)
	Failure	54 (40.6%)	63 (49.2%)		

(a) success is achieved when the scores for mucopurulent discharge and bulbar conjunctival erythema are equal to 0 (none).

(b) P-value from cochran-mantel-haenszel test stratified for age group (≤12, >12).

(c) Difference (GFLX-vehicle) and confidence interval for difference in success rates: The confidence level is 95% for day 3, and 95.2% for day 6.

Reviewers Comments: *There is no difference in efficacy between Gatifloxacin and vehicle for this population. This is an expected finding. This analysis addresses the concern of gatifloxacin potentially leading to disease progression in patients misdiagnosed with viral or other non-bacterial conjunctival inflammatory conditions. Treatment of non-bacterial conjunctivitis is common in clinical practice since patients are not routinely cultured.*

Table 11- Eradication rates (per protocol) at day 6 - Study 3/01

	0.3% GFLX	vehicle
Bacterial Classification		
All organisms	92.9% (65/70)	79.1% (32/67)
Gram positive bacteria	92.7% (51/55)	72.0% (36/50)
Gram negative bacteria	93.3% (14/15)	100% (17/17)

Reviewer's comments:
While this table is accurate, it is misleading. Of the 37 organisms isolated in the study, the majority were seen in only 1 infection. This is not sufficient information to draw conclusions about efficacy for any organisms besides those listed in table 12.

Table 12- Organism Eradication rates at day 6 for organisms present in ≥ 5 infections in patients treated with 0.3%GFLX. Study 3/01

	0.3% GFLX		vehicle	
Organism	**# of infections**	**Eradication rate (%)**	**# of infections**	**Eradication rate (%)**
Haemophilus influenzae	10	100	13	100
Staphylococcus aureus	13	100	8	62.5
Staphylococcus epidermidis	9	88.9	15	53.3
Streptococcus mitis	5	100	1	100
Streptococcus pneumoniae	10	90	8	50

Reviewers Comments:
Microorganisms listed in this table are those that will be recommended for inclusion in the indicaitions section of the labeling are based on the following criteria:

- *Organism has been cultured from an eye with conjunctivitis and treated with gatifloxacin in a clinical trial in 5 or more cases with a ≥ 80% eradication rate.*
- *Organisms that are cultured in less than 5 infections are not listed in the label.*

Table 13- P-values for Breslow-Day Test for Interaction at Day 6 (Per Protocol Population)

	P-value
Treatment-by-investigator	0.034
Treatment-by-age group (a)	0.178

(a) age group is ≤ 12 and > 12.

Reviewers Comments:

There is a statistically significant difference (0.034) found in the treatment-by-investigator analysis for the per protocol population (N=100). This was addressed by the sponsor by defining a new per protocol population (N=106) and re-running the analysis which found the p-value to be 0.167. This is not acceptable to the agency. The sponsor should provide the rationale for adding the additional 6 patients to the per-protocol population and if this population is to be used, the efficacy and safety data throughout the submission needs to be corrected reflecting this change. Alternatively, a sensitivity analysis on the original population (n=100) needs to be performed to identify which investigator site(s) affect the interaction.

Adverse Events

Table 14- Number (%) of Patients with Adverse Events Reported by ≥1% of Patients in Either Treatment Group (Safety Population) – Study 3/01

System Organ Class Preferred Term	Gatifloxacin (N=134)	Vehicle (N=131)	P-value[a]
Eye Disorders			
Conjunctivitis NEC	17 (12.7%)	13 (9.9%)	0.562
Ketatitis NEC	9 (6.7%)	4 (3.1%)	0.255
Lacrimation increased	7 (5.2%)	5 (3.8%)	0.769
Conjunctivitis papillary	6 (4.5%)	2 (1.5%)	0.282
Conjunctival disorder NOS	5 (3.7%)	5 (3.8%)	1.0
Eye irritation	5 (3.7%)	3 (2.3%)	0.722
Eyelid edema	5 (3.7%)	3 (2.3%)	0.722

System Organ Class Preferred Term	Gatifloxacin (N=134)	Vehicle (N=131)	P-value[a]
Eye pain	4 (3.0%)	5 (3.8%)	0.747
Dry eye NEC	3 (2.2%)	0	0.247
Corneal dystrophy	2 (1.5%)	1 (0.8%)	1.0
Red eye	2 (1.5%)	4 (3.1%)	0.443
Visual acuity reduced	2 (1.5%)	3 (2.3%)	0.682
Skin & Subcutaneous Tissue Disorders			
Erythema NEC	4 (3.0%)	3 (2.3%)	1.0
Nervous System Disorders			
Headache NOS	3 (2.2%)	3 (2.3%)	1.0
Gastrointestinal Disorders			
Taste disturbance	3 (2.2%)	0	0.247
Immune System Disorders			
Seasonal allergy	2 (1.5%)	0	0.498
Respiratory, Thoracic and Mediastinal Disorders			
Influenza	0	2 (1.5%)	0.243

[a] between-group p-value based on the Fisher exact test
NEC = not elsewhere classified
NOS = not otherwise specified

Reviewers comments:
There were no significant differences in the rates of adverse reactions between Gatifloxacin and vehicle in this study.

Study 2 – Protocol SPCL-GFLX 3/02

Title: A Phase III Multicenter Randomized, Double-Masked, Parallel Study to compare the Safety and Efficacy of 0.3% Gatifloxacin Ophthalmic Solution with that of 0.3% Ofloxacin Ophthalmic Solution in the Treatment of Acute Bacterial Conjunctivitis

Objectives:

The goal of this study was to demonstrate that gatifloxacin 0.3% ophthalmic solution was at least as effective as ofloxacin 0.3% ophthlamic solution in the treatment of bacterial conjunctivitis in patients ≥ 1 year of age.

Study Design:

The study used a double-masked, active-control, parallel-group design to evaluate the efficacy and safety of gatifloxacin versus ofloxacin in the treatment of acute bacterial conjunctivitis. Multiple sites enrolled patients who were 1 year of age or older, had a clinical diagnosis of acute bacterial conjunctivitis, and were eligible based on the other study entry criteria. Patients were randomly allocated to treatments using a central stratified simple randomization scheme, which included stratification by age (≤ 12 years and >12 years).

Clinical Sites – Study 3/02

Principle Investigator (Center Number)	**Location**	**Number of Subjects Enrolled**
A. Alpar, OD (201)	Amarillo, Texas	30
M. Bernstein, MD (203)	Birmingham, Alabama	2
B. Bodner, MD (204)	Norfolk, Virginia	41
J. Bokosky, MD (205)	San Diego, California	10
G. Corbin, OD (207)	Wyomissing, Pennsylvania	22
T. Coronado, MD (208)	San Antonio, Texas	55
V. Crandall, MD (209)	Fort Myers, Florida	1
J. Foley, Jr, MD (212)	Exmore, Virginia	13
F. Grady, MD, PhD (214).	Lake Jackson, Texas	5
R. Hayhurst, MD (215)	Austin, Texas	1
H. Katz, MD (217)	Baltimore, Maryland	14
S. Luo, MD (219)	Pottsville, Pennsylvania	8
N.R. Melton, OD (222)	Charlotte, North Carolina	3
K. O'Brien, MD (223)	Fall River, Massachusetts	5
K. Olander, MD, PhD (224)	Maryville, Tennessee	21
B. Perez, MD (225)	Tampa, Florida	23
B. Pogue, MD (227)	Boise, Idaho	1
F. Shanks, OD (228)	Nashville, Tennessee	8

J. Sutphin, MD (230)	Iowa City, Iowa	1
J. Fishburn, MD (234)	Boise, Idaho	13
V. deLuise, MD (239)	Waterbury, Connecticut	3
J. Rubin, MD (240)	San Antonio, Texas	3
R. Williams, MD (242)	Louisville, Kentucky	13
M. Tepedino, MD (243)	High Point, North Carolina	90
Y. Au, MD (244)	Bossier City, Louisiana	9
N. Levy, MD (245)	Gainesville, Florida	30
J. Yoakum, OD (254)	Greensboro, North Carolina	5
J. Rowsey, MD (256)	Tarpon Springs, Florida	2
D. Wry, MD (257)	Norfolk, Virginia	1
J. Maher, MD (259)	Fullerton, California	24
H. Kaufman, MD (260)	New Orleans, Louisiana	2

Reviewers comments:

The agency prefers patients to be randomized with at least ten patients per arm per center in multicenter trials so that interaction between centers can be evaluated.

The agency requires that principle investigators be qualified by training and experience as appropriate experts in the field of ophthalmology. Investigators 201, 207, 222, 228, and 254 do meet this criteria.

Study Population – Inclusion and Exclusion Criteria
Same as Protocol SPCL-GFLX 3/01

Study Medications

Gatifloxacin sesquihydrate; same as Protocol SPCL-GFLX 3/01.

Ofloxacin, (+/-)-9-fluoro-2, 3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4 benzoxazine-6-carboxylic acid, was the active ingredient in the comparator product for this study. This aqueous 0.3% ophthalmic solution was a sterile, clear, pale to light yellow solution that was instilled in the eyes via drops. It contained ofloxacin at a concentration of 0.3 g/100 mL, 0.005 g/100 mL benzalkonium chloride, sodium chloride, and purified water. The solution may also have contained hydrochloric acid or sodium hydroxide to adjust to a pH of

The container system used for both gatifloxacin and ofloxacin consisted of a white opaque LDPE bottle with tamper evident overcap, a white low density polyethylene tip, and a white high density polyethylene screw cap. Clinical trial material was to be stored at controlled room temperatures of 20 to 25°C.

The lot numbers for the gatifloxacin and ofloxacin used in the study were as follows:

- gatifloxacin 0.3% ophthalmic solution - Lot No. 02599D
- ofloxacin 0.3% ophthalmic solution - Lot No. 02599E

Study Dosing
Same as Protocol SPCL-GFLX 3/01

Study Masking
See Protocol SPCL-GFLX 3/01
An interim analysis for the purpose of sample size re-evaluation was conducted midway through the study by a statistician at who was not involved in the conduct of the study then, or at any time in the future. The results of the interim analysis indicated that although the overall response rate was 75.5% (comparable to the 75% assumed in the original sample size calculation), the evaluability rate was lower than expected and thus the total enrollment was increased to 458 patients, 229 patients per treatment group. The final significance level was set at to account for the interim analysis.

Efficacy Variable
Same as Protocol SPCL-GFLX 3/01

Safety Variable
Same as Protocol SPCL-GFLX 3/01

Table - Schedule of Assessments
Same as Protocol SPCL-GFLX 3/01

Subject Disposition and Demographics

Table 15- Subject disposition (safety population) – Study 3/02

	0.3% GFLX (n=230)	OFLX (n=229)
Number Completed	220 (95.7%)	215 (93.9%)
Number discontinued	10 (4.3%)	14 (6.1%)

	0.3% GFLX	OFLX (n=229)
Safety Population *	230	229
Per Protocol Population **	78	69
Modified Intent-to-treat population***	220	222

* all enrolled patients
**all enrolled patients who had a positive bacteriological culture that was above the pathological threshold at baseline and who did not have any significant protocol deviations
***all enrolled patients who received study drug and had at least one post baseline efficacy measure

Table 16- Discontinued Patients and Reason – Study 3/02

Patient	Age	Treatment	Reason
204-2435	78	Gatifloxacin	Adverse event – pituitary adenoma
205-2213	46	Gatifloxacin	Protocol violation – antibacterial use
207-2236	9	Gatifloxacin	Adverse event-preauricular adenopathy
208-2033	15	Gatifloxacin	Lost to follow up
208-2135	3	Gatifloxacin	Lost to follow up
208-2285	10	Gatifloxacin	Lost to follow up
219-2380	80	Gatifloxacin	Protocol violation prohibited medication
240-2134	67	Gatifloxacin	Lost to follow up
243-2095	43	Gatifloxacin	Adverse event-marginal corneal infiltrates
245-2326	26	Gatifloxacin	Lost to follow up
201-2224	3	Ofloxacin	Lost to follow up
201-2518	39	Ofloxacin	Lost to follow up
207-2355	55	Ofloxacin	Adverse event-left ear drainage
208-2130	1	Ofloxacin	Lost to follow up
208-2323	1	Ofloxacin	Adverse event-ear infection
212-2577	24	Ofloxacin	Adverse event-facial swelling
217-2034	36	Ofloxacin	Symptoms on visit 2 suggest viral conjunc.
217-2463	24	Ofloxacin	Lost to follow up
224-2300	28	Ofloxacin	Lost to follow up
225-2447	68	Ofloxacin	Adverse event-acanthamoeba keratitis
225-2465	64	Ofloxacin	Investigator withdrew patient
242-2448	33	Ofloxacin	Lost to follow up
243-2117	69	Ofloxacin	Adverse event-ocular discomfort/follicular rxn
243-2428	49	Ofloxacin	Adverse event-viral conjunctivitis

Reviewers Comments:
There are a large number of patients discontinued due to "lost to follow-up". The sponsor should describe the methods used to locate these patients.

Demographics

Table 17- Demographics - Study 3/02

		0.3% GFLX (n=230)	0.3%OFLX (n=229)	p-value [a]
Age	Mean	38.9	39.7	0.710

		0.3% GFLX (n=230)	0.3%OFLX (n=229)	p-value [a]
	Median	37	36	
	Min	1	1	
	Max	95	99	
	≤ 12	36 (15.7%)	38 (16.6%	
	> 12	194 (84.3%)	191 (83.4%)	
Sex				
Male		92 (40.0%)	78 (34.1%)	0.209
Female		138 (60.0%)	151 (65.9%)	
Race				
Caucasian		167 (72.6%)	153 (66.8%)	0.328
African America		26 (11.3%)	23 (10.0%)	
Asian Pacific islander		2 (0.9%)	2 (0.9%)	
Hispanic		32 (13.9%)	47 (20.5%)	
Native American/Alaskan		0	2 (0.9%)	
Other		3 (1.3%)	2 (0.9%)	
Infection				
Unilateral		145 (63.0%)	149 (65.1%)	0.697
Bilateral		85 (37.0%)	80 (34.9%)	
Number of Organisms Above Pathological threshold in Reference Eye				
0		121 (52.6%)	126 (55.0%)	0.227
1		88 (38.3%)	74 (32.3%)	
2		13 (5.7%)	23 (10.0%)	
3 or more		8 (3.5%)	6 (2.6%)	

[a] p-value for age from F test from an ANOVA model containing term for treatment. P-values for sex, race, infection, number of organisms from Fisher exact test.

Reviewers Comments:

There were no statistically significant differences in demographics between the treatment groups.

Efficacy Analysis

Reviewers Comments:

An error is present in the data table for this study and was not corrected by the sponsor before submission of the NDA. One of the study patients was incorrectly identified as belonging to the per protocol population. The patient was included in the primary efficacy analysis as a clinical cure success in the gatifloxacin group. This will have an

impact on the results of the primary analysis. The sponsor is required to submit the accurate data tables and study reports so that any impact can be evaluated.

Table 18- Baseline (Day 1) Efficacy Scores (per protocol) - Protocol 3/02

	0.3% GFLX (n=78)	0.3%OFLX (n=69)
Mucopurulent Discharge		
Mean (SD)	2.3 (0.59)	2.1 (0.46)
Median	2.0	2.0
(min, max)	1,3	1,3
Bulbar Conjunctival Erythema		
Mean (SD)	2.2 (0.56)	2.3 (0.50)
Median	2.0	2.0
(min, max)	1,3	1,3

Table 19- Efficacy Analyses (per protocol) – Protocol 3/02

Visit	Clinical Cure (a)	0.3% GFLX (n=78)	0.3%OFLX (n=69)	P-value (b)	Difference CI (c)
Day 3		n=73	n=66		
	Success	12 (16.4%)	16 (24.2%)	0.208	-0.078 (-0.212,0.056)
	Failure	61 (83.6%)	50 (75.8%)		
Day 6		n=78	n=69		
	Success	64 (82.1%)	52 (75.4%)	0.325	0.067 (-0.067,0.201)
	Failure	14 (17.9%)	17 (24.6%)		

(a) success is achieved when the scores for mucopurulent discharge and bulbar conjunctival erythema are equal to 0 (none).
(b) P-value from cochran-mantel-haenszel test stratified for age group (≤12, >12).
(c) Difference (GFLX-OFLX) and confidence interval for difference in success rates: The confidence level is 95% for day 3, and 95.2% for day 6.

Reviewers Comments:
The equivalence criteria for this study was defined based on a 2-sided 95% confidence interval (CI) for the difference in success rates. The control cure rate (p_c) for ofloxacin less than 80% therefore, the CI is required to be within ± 0.2 to meet the equivalence criteria. Gatifloxacin is equivalent to Ofloxacin in the clinical cure of bacterial conjunctivitis in this study.

In review of the two phase 3 trials, it is noted that Tepedino is an investigator in both trials with the majority of enrolled patients (investigator 128 in study 3/01 and

investigator number 243 in study 3/02). Efficacy results for equivalence at day 6 between gatifloxacin and ofloxacin were run for study 3/02 excluding this investigator. The equivalence criteria is not met with this investigators results removed from the trial. The p-value is 0.28 and the 95% confidence interval is (-0.0661, 0.2433)

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ON ORIGINAL

Table 20- Baseline (Day 1) Efficacy Scores (safety population) - Protocol 3/02

	0.3% GFLX (n=230)	0.3%OFLX (n=229)
Mucopurulent Discharge		
Mean (SD)	2.1 (0.64)	2.1 (0.60)
Median	2.0	2.0
(min, max)	1,3	1,3
Bulbar Conjunctival Erythema		
Mean (SD)	2.4 (0.55)	2.4 (0.54)
Median	2.0	2.0
(min, max)	1,3	1,3

Table 21- Efficacy Analyses (modified intent-to-treat) – Protocol 3/02

Visit	Clinical Cure (a)	0.3% GFLX (n=220)	0.3%OFLX (n=222)	P-value (b)	Difference CI (c)
Day 3		n=220	n=222		
	Success	36 (16.4%)	52 (23.4%)	0.057	-0.071 (-0.145,0.004)
	Failure	184 (83.6%)	170 (76.6%)		
Day 6		n=220	n=222		
	Success	159 (72.3%)	141 (63.5%)	0.049	0.088 (0.000,0.175)
	Failure	61 (27.7%)	81 (36.5%)		

(a) success is achieved when the scores for mucopurulent discharge and bulbar conjunctival erythema are equal to 0 (none).

(b) P-value from cochran-mantel-haenszel test stratified for age group (≤12, >12).

(c) Difference (GFLX-OFLX) and confidence interval for difference in success rates: The confidence level is 95% for day 3, and 95.2% for day 6.

Table 22- Eradication rates at day 6 - Study 3/02

	0.3% GFLX	0.3% OFLX
Bacterial Classification		
All organisms	86.7% (85/98)	88.6% (78/88)
Gram positive bacteria	81.8% (54/66)	86.6% (58/67)
Gram negative bacteria	96.9% (31/32)	95.2% (20/21)

Reviewer's comments:

While this table is accurate, it is misleading. Of the 30 organisms isolated in the study, the majority were seen in only 1 infection. This is not sufficient information to draw conclusions about efficacy for any organisms besides those listed in table 23.

Table 23- Organism Eradication rates at day 6 for organisms present in ≥ 5 infections in patients treated with 0.3%GFLX.

	0.3% GFLX		0.3% OFLX	
Organism	**# of infections**	**Eradication rate (%)**	**# of infections**	**Eradication rate (%)**
Haemophilus influenzae	26	96.2	14	100
Staphylococcus aureus	9	100	14	78.6
Staphylococcus epidermidis	17	70.6	19	84.2
Streptococcus pneumoniae	20	70.0	19	84.2

Reviewers Comments:
Microorganisms listed in this table are those that will be recommended for inclusion in the indications section of the labeling are based on the following criteria:

- *Organism has been cultured from an eye with conjunctivitis and treated with gatifloxacin in a clinical trial in 5 or more cases with a ≥ 80% eradication rate.*
- *Organisms that are cultured in less than 5 infections are not listed in the label.*

In a pooled analysis of study 3/01 and 3/02 it is noted that Cornebacterium propinquum was cultured in 5 infections with and eradication rate of 100%.

Adverse Events

Table 24- Number (%) of Patients with Adverse Events Reported by ≥1% of Patients in Either Treatment Group (Safety Population) – Study 3/02

System Organ Class Preferred Term	**Gatifloxacin (N=230)**	**Ofloxacin (N=229)**	**P-value[a]**
Eye Disorders			
Conjunctivitis NEC	22 (9.6%)	25 (10.9%)	0.648
Conjunctivitis papillary	13 (5.7%)	15 (6.6%)	0.702
Keratitis NEC	12 (5.2%)	20 (8.7%)	0.147
Conjunctival disorder NOS	10 (4.3%)	17 (7.4%)	0.171
Lacrimation increased	10 (4.3%)	6 (2.6%)	0.446
Red eye	9 (3.9%)	6 (2.6%)	0.601
Visual acuity reduced	9 (3.9%)	12 (5.2%)	0.513

System Organ Class Preferred Term	Gatifloxacin (N=230)	Ofloxacin (N=229)	P-value[a]
Eyelid edema	8 (3.5%)	10 (4.4%)	0.641
Conjunctival hemorrhage	5 (2.2%)	4 (1.7%)	1.0
Eye discharge	5 (2.2%)	7 (3.1%)	0.575
Eye irritation	4 (1.7%)	2 (0.9%)	0.685
Eye pain	4 (1.7%)	9 (3.9%)	0.173
Dry eye NEC	3 (1.3%)	1 (0.4%)	0.623
Chemosis	2 (0.9%)	3 (1.3%)	0.685
Skin & Subcutaneous Tissue Disorders			
Erythema NEC	6 (2.6%)	3 (1.3%)	0.503
Nervous System Disorders			
Headache NOS	2 (0.9%)	8 (3.5%)	0.062
General Disorders and Administration Site conditions			
Pyrexia	0 (0.0%)	3 (1.3%)	0.123

[a] between-group p-value based on the Fisher exact test
NEC = not elsewhere classified
NOS = not otherwise specified

Reviewers comments:
There were no significant differences in the rates of adverse reactions between Gatifloxacin and Ofloxacin in this study.

VII. Integrated Review of Safety

One or more adverse events were reported for 41.2% (150/364) of patients in the gatifloxacin group, 46.3% (106/229) of patients in the ofloxacin group, and 32.8% (43/131) of patients in the vehicle group. The majority of adverse events reported in each treatment group were mild in severity

Table 25 - Number (%) of Patients with Adverse Events Reported by ≥ 1% of Patients in Any Treatment Group (Phase 3 Studies)

SYSTEM ORGAN CLASS Preferred Term[a]	Gatifloxacin N = 364	Ofloxacin N = 229	Vehicle N = 131
EYE DISORDERS			
conjunctivitis NEC[b]	39 (10.7%)	25 (10.9%)	13 (9.9%)
keratitis[c]	21 (5.8%)	20 (8.7%)	4 (3.1%)
conjunctivitis papillary	19 (5.2%)	15 (6.6%)	2 (1.5%)
lacrimation increased	17 (4.7%)	6 (2.6%)	5 (3.8%)
conjunctival disorder NOS[b]	15 (4.1%)	17 (7.4%)	5 (3.8%)
eyelid oedema	13 (3.6%)	10 (4.4%)	3 (2.3%)
visual acuity reduced	11 (3.0%)	12 (5.2%)	3 (2.3%)
red eye	11 (3.0%)	6 (2.6%)	4 (3.1%)
eye irritation	9 (2.5%)	2 (0.9%)	3 (2.3%)
eye pain	8 (2.2%)	9 (3.9%)	5 (3.8%)
eye discharge	6 (1.6%)	7 (3.1%)	1 (0.8%)
dry eye NEC[b]	6 (1.6%)	1 (0.4%)	0 (0.0%)
conjunctival haemorrhage	5 (1.4%)	4 (1.7%)	0 (0.0%)
chemosis	3 (0.8%)	3 (1.3%)	0 (0.0%)
SKIN & SUBCUTANEOUS TISSUE DISORDERS			
erythema NEC[b]	10 (2.7%)	3 (1.3%)	3 (2.3%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
influenza	0 (0.0%)	0 (0.0%)	2 (1.5%)
GASTROINTESTINAL DISORDERS			
taste disturbance	5 (1.4%)	0 (0.0%)	0 (0.0%)
NERVOUS SYSTEM DISORDERS			
headache NOS[b]	5 (1.4%)	8 (3.5%)	3 (2.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
pyrexia	0 (0.0%)	3 (1.3%)	1 (0.8%)

a body system organ class and preferred terms from MedDRA, version 2.4
b NEC = not elsewhere classified, NOS = not otherwise specified
c combination of preferred terms keratitis NEC and corneal disorder NOS based on verbatim text

Of the 77 patients with conjunctivitis reported as an adverse event, 11 patients had bilateral disease at baseline which worsened during the study. This is considered treatment failure rather than an adverse event. The other 66 patients had unilateral

disease at baseline which spread to the contralateral (untreated) eye. This is considered progression of the disease rather than an adverse event.

Adverse events led to the discontinuation from the phase 3 studies for 1.6% (6/364) of patients in the gatifloxacin group, 2.6% (6/229) of patients in the ofloxacin group, and 0.8% (1/131) of patients in the vehicle group.

Serious adverse events were reported for 0.5% (2/364) of patients in the gatifloxacin group, 0.9% (2/229) of patients in the ofloxacin group, and no patients in the vehicle group.

Patient 125-1048 (gatifloxacin) was a 68-year-old Caucasian male who experienced moderate **hallucinations** and resolved without treatment.

Patient 204-2435 (gatifloxacin) was a 78-year-old male who was admitted to hospital due to ongoing symptoms of headache, diplopia and right eye pain, later diagnosed as a **pituitary adenoma**. The tumor was resected with no complications.

Patient 212-2577 (ofloxacin) was a 24-year-old woman who was hospitalized and diagnosed with **facial cellulitis**. The study drug was discontinued and the patient was exited from the study.

Patient 225-2447 (ofloxacin) was a 68-year-old woman who was diagnosed with **acanthamoeba keratitis**. The study drug was discontinued and the patient was exited from the study.

Corrected visual acuity was assessed at every visit and reported in Snellen equivalent units. In each phase 3 study, more than 90% of patients in each treatment group showed "no change" in visual acuity, defined as less than a 2-line difference from baseline. In study 3/01, there was a decrease of ≥ 2lines (worsening) for 0.8% (1/126) of gatifloxacin patients and 2.4% (3/124) of vehicle patients, and an increase of ≥ 2 lines (improvement) for 6.3% (8/126) of gatifloxacin patients and 5.6% (7/124) of vehicle patients (p=0.628). In study 3/02, worsening was found for 2.3% (5/221) of gatifloxacin patients and 3.7% (8/217) of ofloxacin patients, while an improvement was found for 4.1% (9/221) of gatifloxacin patients and 4.6% (10/217) of ofloxacin patients (p=0.637).

General Safety Conclusions

The adverse events reported during the phase 3 studies were similar to those listed in the package inserts of the currently marketed fluoroquinolone ophthalmic solutions. No clinically or statistically significant differences were found between gatifloxacin and the active control ofloxacin or vehicle in the frequency, type, severity, or causality of adverse events. Ophthalmic examinations and visual acuity were also similar between the active and vehicle patients.

VIII. Dosing, Regimen, and Administration Issues

The dosing regimen used in the two phase 3 efficacy trials was as follows: Gatifloxacin was dosed for a total of 5±1 days. For the first 2 days, patients were dosed every 2 hours (Q2H) while awake. On day 1, patients received a minimum of 4 applications per 24 hours, to a maximum of 8 applications per 24 hours. On day 2, patients received a minimum of 6 applications per 24 hours, to a maximum of 8 applications per 24 hours. For the remainder of the treatment days, patients were dosed 4 times daily (QID) approximately every 4 hours (Q4H) while awake.

The recommended dosing schedule in both the adult and pediatric population will be for seven days of treatment. This is consistent with other marketed drugs in this class for the treatment of bacterial conjunctivitis.

IX. Use in Special Populations

The phase 3 studies included adult and pediatric patients (≥1 to ≤12 years of age). There was no indication of a differential effect in children versus adults, and no safety concerns were identified for younger patients. There were no notable differences between the adverse event profile for gatifloxacin in males and females, Caucasians and non-Caucasians, or patients with light and dark irides.

X. Labeling

Reviewer's Comments:
Recommended additions are shown by underlining and recommended deletions are shown by strikethrough lines.

ZYMAR™

(gatifloxacin ophthalmic solution) 0.3% ALLERGAN
Sterile

DESCRIPTION

[redacted]

Structural Formula:

10 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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/s/

Jennifer Harris
2/28/03 11:47:48 AM
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Wiley Chambers
3/3/03 11:43:32 AM
MEDICAL OFFICER

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Labeling Review of NDA 21-493

NDA 21-493

Submission Date: 3/25/03
Review Date: 3/27/03

Applicant:

Allergan, Inc.
P.O. Box 19534
2525 Dupont Drive
Irvine, CA 92713-9534

Applicant's Representative:

Elizabeth Bancroft
Senior Director, Regulatory Affairs
714-246-4391 Phone
714-246-4272 Fax

Drug:

Zymar™ (gatifloxacin ophthalmic solution) 0.3%

Pharmacologic Category:

Anti-infective

Submitted:

Draft Carton and container labels for NDA 21-493

Recommendations:

The draft carton and container labels may be approved provided the applicant agrees to the following at the next printing of the labels:

1. *The [redacted] must be removed from the proprietary name.*
2. *The word [redacted]' should be replaced with "approximately" in the carton label.*
3. *The phrase [redacted] should be eliminated from the label.*
4. *The [redacted] should be replaced with "between" in the storage note on the carton.*
5. *The prominence of the trademark should be more similar to the prominence of the established name.*

Lisa M. Hubbard, R.Ph.

Wiley Chambers, M.D.

cc:
NDA 21-493
HFD-550/Div. files
HFD-550/Clin Rev/Hubbard
HFD-550/MO/Harris
HFD-550/Dep Dir/Chambers
HFD-550/PM/Gorski

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/s/

Lisa Hubbard
3/27/03 04:34:16 PM
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Jennifer Harris
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MEDICAL OFFICER

Wiley Chambers
3/27/03 05:18:04 PM
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