Medical Officer's Review of NDA 19-921 (b) (4)
Pediatric Supplement

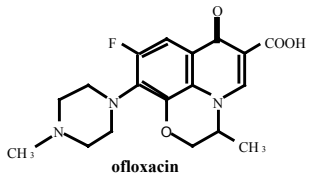
NDA 19-921 (b) (4)
Medical Officer's Review

Submission Date: December 19, 2002
Review Completed: April 29, 2003

Trademark: Ocuflox

Generic Name: ofloxacin ophthalmic solution 0.3%

Chemical Name:



ofloxacin

Mol Wt 361.37
ofloxacin $C_{17}H_{18}FN_3O_3 \bullet HCl \bullet H_2O$

(±)-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

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

Contact: Elizabeth Bancroft
800-347-4500

Pharmacologic Category: Anti-infective (fluoroquinolone)

Related INDs: IND
IND (b) (4)

Related NDAs: NDA 19-921

Table of Contents

Executive Summary

1 Recommendations

(b) (4)

1.2 Recommendation on Phase 4 Studies

No Phase 4 studies are recommended.

2 Summary of Clinical Findings

2.1 Brief Overview of Clinical Program

Ofloxacin is a fluoroquinolone anti-infective agent. Topical ofloxacin ophthalmic solution 0.3% is approved in the United States for the treatment of infections caused by susceptible microorganisms in conjunctivitis and corneal ulcers in patients above the age of one year.

There are currently no approved products to treat neonatal bacterial conjunctivitis (i.e. bacterial conjunctivitis in infants between birth to one month of age).

The sponsor conducted a 7-day multi-center, randomized, double-masked, parallel-group clinical trial that compared topical ofloxacin 0.3% ophthalmic solution (Ocuflox) to topical trimethoprim sulfate/polymyxin b sulfate combination ophthalmic solution (Polytrim) in neonates from birth to 31 days of age in response to an October 22, 1999 written request (amended on August 3, 2001 and September 6, 2002) from the agency for pediatric information on the safety and efficacy of ofloxacin ophthalmic solution (NDA 19-921).

2.3 Safety

The safety data contained in this submission is comparable to that reported for previously approved Ocuflox ophthalmic solution 0.3%, NDA 19-921.

2.4 Dosing

No change to the current dosing regimen is proposed in this submission.

2.5 Special Populations

No additional data on special populations was obtained.

Clinical Review

1 Introduction and Background

1.1 Trademark: Ocuflox ophthalmic solution, 0.3%

Generic Name: ofloxacin ophthalmic solution, 0.3%

NDA Drug Classification: 3P

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Dosage Form and Route of Administration: Ophthalmic solution for topical ocular administration

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1.2 There are currently no approved products to treat neonatal bacterial conjunctivitis.

1.3 There were no important milestones in the development of this product.

1.4 There are no safety or effectiveness concerns associated with agents in this pharmacologic class.

2 Significant Findings from Chemistry, Animal Pharmacology and Toxicology

Agree with Chemistry recommendations. See Chemistry Review for detailed comments.

No Pharmacology or Toxicology pre-clinical data was submitted in this supplement.

3 Human Pharmacokinetics and Pharmacodynamics

3.1 Pharmacokinetics

No Pharmacokinetic data was submitted in this supplement.

3.2 Pharmacodynamics

No Pharmacodynamic data was submitted in this supplement.

4 Description of Clinical Data and Sources

4.1 Included in this medical officer's review is an evaluation of a single clinical trial conducted in the United States, Mexico, and Brazil.

4.2 See Table 1 for a descriptive summary of the clinical trial.

Table 1 – Description of Data Sources

Protocol Number	190442-005
Study Design	Multi-Center, Randomized, Double-Masked, Parallel-Group
Treatment Duration	7 treatment days
Patient Population	Infants, from Birth to 31 Days of Age
Treatment Groups	• Ofloxacin 0.3% Ophthalmic Solution • Trimethoprim Sulfate/Polymyxin B Sulfate Combination Ophthalmic Solution
Dosing	1 drop every 2 to 4 hours for the first 2 days and then QID for 5 additional days
No. Sites	18
No. Subjects Enrolled/Randomized	173
Status	Completed

4.3 No new safety information from post-marketing experience was presented in this submission.

4.4 There are no data in the published literature pertinent to the review of this submission.

5 Clinical Review Methods

5.1 Included in this medical officer's review is the evaluation of one clinical trial conducted at 18 clinical centers located in the United States, Mexico, and Brazil.

5.2 The submission is provided in paper format. Electronic case-report forms and electronic data sets are provided. Both paper and electronic formats were utilized in the review of this application.

5.3 There is no evidence to indicate that the trials were not conducted in accordance with accepted ethical standards.

5.4 Financial disclosure statements are submitted. There is no evidence to indicate that participation of investigators who have financial arrangements with the applicant affected the integrity of the findings.

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Table 2 – List and Description of Investigators

Principal Investigators	ID Number	No. of Subjects Randomized
Manuel Rodriguez Almarez, M.D. Dr. Marquez No. 162 Col. Doctores Mexico, D.F.C.P 06720	3638	33
Mark M. Blatter, M.D. 1580 McLaughlin Run Road Pittsburg, PA 15241	3770	11
Bruce I. Bodner, M.D. 403 Medical Tower Norfolk, VA 23507	0562	1
Nilva Simeren Bueno de Moraes, M.D. Rua: Botucatu, 824-Vila Clementino CEP: 04023-062 Sao Paulo-SP Brazil	3876	2
Laura Campos Campos, M.D. Av. Vallejo Y Jacarandas Consultorio 149 ler. Piso Consulta Externa Col. La Raza, Mexico, D.F.	3799	11
Ralph Conti, M.D. Foothills Pediatrics 6301 Mountain Vista #205 Henderson, NV 89014	3830	38
David Dries, M.D. Pediatric Ophthalmology and Strabismus Scott and White Memorial Hospital and Clinic 2401 South 31st Street Temple, TX 76508	3812	2
Lee Friedman, M.D. Palm Beach Eye Foundation, Inc. 2889 10th Avenue North Lake Worth, FL 33461	3729	1
Bartlett H. Hayes, II, M.D. 417 State Street, Suite 230 Bangor, Maine 04401	3840	1

Table 2 – List and Description of Investigators – Continued

Principal Investigators	ID Number	No. of Subjects Randomized
Jeffrey A. Hirschfield, M.D. Clinical Research of West Florida 2147 NE Coachman Road Clearwater, FL 33765	3727	5
Barnett Lewis, M.D Central Kentucky Research Associate, Inc. 2801 Palumbo Drive, Suite 200 Lexington, KY 40509	3792	6
Jose Ricardo Rehdar, M.D. Faculdade de Medicina do ABC-Departmento De Oftalmologia Av. Principe de Gales. 821-1 andar Principe de Gales-Santo Andre-SP Brazil CEP 09060-650	3879	8
Victoria Sanchez-Bal, M.D. Center for Clincial Trials, LLC 16660 Paramount Blvd., Suite 301 Paramount., CA 90723	3769	39
Douglas W. Stewart, D.O. The Univ. of Oklahoma College of Medicine Department of Ophthalmology 4502 E. 41st Street Tulsa, OK 74135	3791	1
Michael Tepedino, M.D. Cornerstone Eye Care 307 North Lindssey St. High Point, NC 27262	3212	7
Charles A. Woods, M.D. Clinical Research Consultants, Inc. 15 Corporate Drive Trumbull, CT 06611	3775	1
Kenneth Wright, M.D. 8631 West Third Street, Suite 304-E Los Angeles, CA 90048	3810	1

Table 2 – List and Description of Investigators – Continued

Principal Investigators	ID Number	No. of Subjects Randomized
Richard W. Yee, M.D. 6411 Fannin, Jones Pavilion, 7th Floor Houston, TX 77030	2298	5

Reviewer's Comments:

It is preferable to have at least 10 patients per arm per center.

Study Design

This study was a 7-day, multi-center, randomized, double-masked, positive-controlled, parallel-group clinical trial evaluating the safety and efficacy of topical Ocuflox with that of topical Polytrim. It was planned that up to 234 patients (or up to 120 patients with positive cultures) were to be enrolled to ensure that at least 200 patients with a clinical diagnosis of bacterial conjunctivitis (or at least 100 patients with positive cultures) completed the study.

Assignment of qualified patients to treatment groups was in a 2:1 allocation (Ocuflox: Polytrim). The patient population included infants from birth to 31 days of age with bacterial conjunctivitis.

The duration of the treatment was 7 days to the qualified eye(s), with a slit lamp examination performed on the day 7 (or exit) visit. Any eye that had mild or greater conjunctival erythema and discharge at baseline was categorized as "qualified" and was treated. If necessary, nonqualified eyes were to be followed past the day 7 timepoint. At the discretion of the investigators, an unqualified eye may have been treated prophylactically. At follow-up, if an unqualified eye became infected, then the parent or LAR (legally authorized representative) was instructed to treat with masked study medication.

In considering the dosage of study medication for this double-masked study, the U.S. label-recommended dosage for Ocuflox (1 drop every 2 to 4 hours for the first 2 days and then QID for 5 additional days) was chosen, with the limitation of a maximum 8 doses per day for the first 2 days. The dosage of Ocuflox and the 7-day treatment period were considered safe for this population because of the drugs' minimal systemic absorption.

Study Medications

- Ocuflox (ofloxacin ophthalmic solution) 0.3% (Allergan formulation number 7651X, lot 11914; 10 mL bottle) contained 0.3% ofloxacin, sodium chloride, purified water, preserved with benzalkonium chloride; and contained hydrochloric acid and/or sodium hydroxide for pH adjustment.

- Polytrim (trimethoprim sulfate and polymyxin B sulfate ophthalmic solution) (Allergan Formulation number 8317X; lot 06861; 10 mL bottle) contained polymyxin B sulfate (10,000 units/mL), purified water, sodium hydroxide, sulfuric acid, sodium chloride, trimethoprim sulfate (0.1% solution) and benzalkonium chloride.

Inclusion Criteria

The following were requirements for entry into the study:

- Male or female infants, from birth to 31 days of age, in good general health.
- Signed informed consent form and, if appropriate, a signed Bill of Rights for Experimental Subjects obtained from the parent/LAR.
- Clinical diagnosis of bacterial conjunctivitis or blepharoconjunctivitis as defined by mild or greater conjunctival erythema and discharge.

Exclusion Criteria

The following were criteria for exclusion from study participation:

- Chemical or foreign body trauma to eye or ocular adnexa.
- Any evidence of orbital cellulitis.
- Corneal infiltrates or ulcer.
- Any current or prior enrollment in an investigational drug or device study.
- Sensitivity or poor tolerance to any component of the study medications.
- Patient has a situation or condition which in the investigator's opinion may have put the patient at a significant risk, may have confounded the study results, or may have interfered significantly with the patient's participation in the study.

Efficacy Variables

The primary efficacy variable, clinical cure was defined as the resolution of both conjunctival erythema and conjunctival discharge at day 7 within the population of patients who were culture positive at baseline.

Conjunctival Erythema
The investigator evaluated conjunctival erythema using a 4-point scale: None (0) = normal; Mild (+1) = slight localized injection; Moderate (+2) = pink color, confined to palpebral OR bulbar conjunctiva; Severe (+3) = red color of the palpebral OR bulbar conjunctiva.

Conjunctival Discharge
The investigator evaluated conjunctival discharge using a 4-point scale: None (0) = normal, no discharge; Mild (+1) = some discharge present on the inner portion of the eye but not on the lid or the skin of the eyelid; Moderate (+2) = discharge is abundant, easily observed, and has collected on the lid and around the skin of the eyelid;

Severe (+3) = discharge has been flowing over the eyelid so as to wet the skin substantially around the eye.

Microbial Improvement
For each qualified eye, a culture was taken and sent to a reference lab for analysis. Microbial evaluations were performed to determine the number of colony forming units/mL. Bacterial growth for each bacterial species was graded on a 4-point scale: 0 = no growth; +1 = less than 10 bacterial colonies; +2 = 10 to 100 bacterial colonies; and +3 = greater than 100 bacterial colonies. At baseline, the qualified eye must have shown evidence of at least 1 Gram (-) bacterial species isolated as grade +1 or more, or at least 1 Gram (+) bacterial species of +2 grade or more. Microbial outcomes were assessed for each bacterial species at the exit visit. Improvement was indicated as eradicated or reduced based on the criteria outlined in Table 3.

Table 3 – Microbial Improvement Grading

		Baseline Bacterial Colony Grade		
		+1	+2	+3
Exit Bacterial Colony Grade	0	**Eradicated**	**Eradicated**	**Eradicated**
	+1	*No Change*	**Reduced**	**Reduced**
	+2	Increased	*No Change*	**Reduced**
	+3	Increased	Increased	*No Change*

Reviewer's Comments:

The primary efficacy variable, clinical cure defined as the resolution of both conjunctival erythema and conjunctival discharge at day 7 within the population of patients who were culture positive at baseline, is acceptable.

The study population utilized in the review of this supplemental NDA is the modified intent-to-treat population.

The primary microbiological efficacy variable utilized in the review of this supplemental NDA is the assessment of microbial eradication at Day 7, not microbial improvement.

Safety Variables

The safety variables were adverse events (AEs), physical examination, ocular examinations (conjunctival erythema, edema and discharge; lid erythema, edema, and crusting; and corneal appearance), and vital signs (heart rate, temperature, and respiratory rate).

Table 4 – Schedule of Assessments

Visit	1[a]	2	3
Measurement	**Baseline Day 0**	**Day 3**	**Day 7 or exit[b]**
Obtain informed consent	X		
Medical history	X		
Physical examination[c]	X	X	X
Vital signs[d]	X	X	X
Ocular examination (pen light or slit lamp)[e]	X	X	
Ocular examination (slit lamp)[f]			X
Conjunctival bacterial culture/sensitivity[g]	X		X
Adverse events query	X	X	X
Study medication	dispense		collect

a A medical history, physical examination, and conjunctival swab for bacterial culture were obtained prior to dosing.

b The day 7 (or exit) visit occurred between 12 (minimum) to 48 (maximum) hours after the last dose.

c A physical examination, by body system, was performed for all visits. Weight and length were recorded at day 0.

d Vital signs included: heart rate, temperature, and respiratory rate.

e The ocular examination was performed with the aid of a pen light or a slit lamp on both eyes. If the slit lamp examination was performed, then it must have been done on both eyes by an ophthalmologist or optometrist.

f The slit lamp examination must have been performed on both eyes by an ophthalmologist or optometrist.

g The reference laboratory performed the susceptibility testing for each bacterial species using ofloxacin, polymyxin B sulfate, and trimethoprim.

Subject Disposition and Demographics

Table 5 – Subject Disposition

	Number of Subjects		
	Ocuflox N (%)	Polytrim N (%)	Total N (%)
Enrolled/Randomized	119	54	173
Safety Population [a]	119 (100)	54 (100)	173 (100)
Modified Intent-to-Treat Population [b]	93 (78)	42 (78)	135 (78)
Per-Protocol Population [c]	81 (68)	41 (76)	122 (71)

[a] Safety population includes all patients who received the study medication
[b] MITT population includes all randomized patients who are culture positive at Baseline
[c] PP population includes all randomized patients who are culture positive at Baseline with no major protocol violations

Table 6 – Discontinued Patients and Reasons

Invest.#	Pt#	Age/Sex/Race [a]	Tx	Reason	MITT	PP	Tx Exposure (days) [b]
3638	1132	8 F H	Ocuflox	Lost to F/U	Y	N	4
3638	1143	7 M H	Ocuflox	Lost to F/U	N	N	5
3638	1148	9 M H	Ocuflox	Lost to F/U	Y	N	1
3638	1163	8 M H	Ocuflox	Lost to F/U	Y	N	8
3638	1164	8 F H	Ocuflox	Lost to F/U	Y	N	8
3879	1233	2 M C	Ocuflox	Parent/LAR choice	N	N	1
3638	1129	8 F H	Polytrim	Parent/LAR choice	N	N	4
3799	1145	3 M H	Polytrim	Parent/LAR choice	N	N	3

[a] Age in Days. M=male. F=female. C=white. B=black. A=asian. H=hispanic. O=other.
[b] Number of days from the first dose of study medication (baseline) to the last medication date or exit date plus 1 day.

Reviewer's Comments:

A single Principle Investigator (Almarez, M.D. #3638) lost five of the eight Discontinued Patients *to follow-up.*

Table 7 – Summary of Demographics (Safety Population)

		Ocuflox N=119	Polytrim N=54	Total N=173	p-valve [a]
Age (days)	N	119	54	173	0.865
	Mean	14.2	14.0	14.2	
	SD	7.46	6.37	7.12	
	Median	13	12	13	
	Min	2	3	2	
	Max	32	31	32	
Sex	N	119	54	173	0.060
	Male	69 (58%)	23 (43%)	92 (53%)	
	Female	50 (42%)	31 (57.4%)	81 (47%)	
Race	N	119	54	173	
	Asian	3 (3%)	2 (4%)	5 (3%)	
	Black	5 (4%)	1 (2%)	6 (4%)	
	Hispanic	56 (47%)	25 (46%)	81 (47%)	
	Caucasian	50 (42%)	26 (48%)	76 (44%)	
	Other [b]	5 (4%)	0	5 (3%)	
	White	50 (42%)	26 (48%)	76 (44%)	0.451
	Non-white	69 (58%)	28 (52%)	97 (56%)	

[a] p-values analyzed by Pearson's Chi-square test
[b] Other race: caucasian/hispanic, black/asian, asian/caucasian

Reviewer's Comments:

For the safety population, there were no statistically significant differences between the 2 treatment groups for any of the demographic characteristics.

(b) (4)

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7 Integrated Review of Safety

7.1 The submitted study in this submission indicates that the safety profile of Ocuflox is similar to the currently approved and marketed product.

7.2 The safety database consists of safety data from one clinical trial, Protocol 190442-005.

7.3 Protocol 190442-005

For safety variables, the safety population included all enrolled patients who received treatment with patients analyzed by their actual treatment.

There was 1 serious adverse event, an episode of exacerbated bronchitis in the OCUFLOX group. The female infant (subject #2298-1082) was hospitalized on day 5, treated with inhaled albuterol, and discharged from the hospital on day 8 without further complications.

There were no deaths.

Table 13 – Number (%) of Patients with Adverse Events, Regardless of Causality, Reported by Patients In Each Treatment Group

BODY SYSTEM Preferred Term[a]	Ocuflox N = 119 n (%)	Polytrim N = 54 n (%)
BODY AS A WHOLE		
Abdominal pain	2 (1.7%)	0 (0.0%)
Infection	2 (1.7%)	0 (0.0%)
CARDIOVASCULAR		
Patent ductus arterious	1 (0.8%)	0 (0.0%)
DIGESTIVE		
Jaundice	1 (0.8%)	0 (0.0%)
Rectal disorder	1 (0.8%)	0 (0.0%)
Gastroenteritis	0 (0.0%)	1 (1.9%)
Vomiting	0 (0.0%)	1 (1.9%)
MUSCULOSKELETAL		
Joint disorder	0 (0.0%)	1 (1.9%)
RESPIRATORY		
Pharyngitis	2 (1.7%)	0 (0.0%)
Rhinitis	2 (1.7%)	1 (1.9%)
Bronchitis	1 (0.8%)	1 (1.9%)
Respiratory disorder	1 (0.8%)	0 (0.0%)
Cough increased	0 (0.0%)	1 (1.9%)
SKIN AND APPENDAGES		
Dermatitis	2 (1.7%)	0 (0.0%)
Sweating	2 (1.7%)	2 (3.7%)
Acne	1 (0.8%)	0 (0.0%)
Allergic contact dermatitis	1 (0.8%)	0 (0.0%)
Skin discharge	1 (0.8%)	0 (0.0%)
SPECIAL SENSES		
Conjunctival hemorrhage	1 (0.8%)	0 (0.0%)

Source: Tables 14.3-3 and 14.3-4.

a Adverse events presented in decreasing frequency of reports in the Ocuflox group. Within each preferred term, a patient was counted only once.

Ocular Signs

There were no statistically significant between-group differences in conjunctival edema, lid erythema, lid edema, lid crusting, or corneal appearance.

Physical Examination and Vital Signs

There were no statistically significant between-group differences in physical examination parameters, heart rate, temperature, or respiration.

8 Dosing, Regimen, and Administration Issues

No change in the dosing regimen is proposed in this submission.

9 Use in Special Populations

9.1 Applicant's analyses on the effects of gender, age, and ethnicity on efficacy and safety are adequate.

9.2 In response to the agency's pediatric written request, sponsor conducted Study 190442-005, (b) (4).

9.3 No additional data in other special populations are needed.

10 Conclusions, Recommendations, and Labeling

(b) (4)

The submitted study in this submission indicates that the safety profile of Ocuflox is similar to the currently approved and marketed product.

(b) (4)

William Boyd, M.D.
Clinical Team Leader

NDA 19-921 (b) (4)
HFD-550/Div Files
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William Boyd
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