Deputy Division Director Review of NDA 19-992 Supplement 17

Date	January 17, 2017
From	Wiley A. Chambers, M.D.
NDA #	NDA 19-992 Supplement 17
Applicant	Alcon/Novartis
Date of Submission	October 14, 2002
Name	Ciprofloxacin ophthalmic solution, 0.3%
Dosage forms / Strength	Topical ophthalmic solution, 0.3%
Proposed Indication(s)	(b) (4)
Action:	Approval

1. Introduction

Ciprofloxacin ophthalmic solution, 0.3% is a fluoroquinolone anti-infective for the treatment of bacterial conjunctivitis. Its chemical name, 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline-carboxylic acid.

In the United States, Ciloxan was approved under NDA 19-992 on December 31, 1990. Ciloxan (ciprofloxacin ophthalmic solution) 0.3% is currently labeled for the treatment of bacterial conjunctivitis and corneal ulcers in subjects 1 year of age and older.

Active: Ciprofloxacin HCl 3.5 mg equivalent to 3 mg base; **Inactives:** benzalkonium chloride, sodium acetate, acetic acid, mannitol 4.6%, edetate disodium 0.05%, hydrochloric acid and/or sodium hydroxide (to adjust pH to 4.5) and purified water.

Indication:

Ciloxan is indicated for the treatment of infections caused by susceptible strains of the following organisms:

Corneal Ulcers: *Pseudomonas aeruginosa*
Serratia marcescens *
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus (Viridans Group) *

Conjunctivitis: *Haemophilus influenzae*
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumoniae

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

Dosing Regimen:

Corneal Ulcers: The recommended dosage regimen for the treatment of **corneal ulcers** is two drops into the affected eye every 15 minutes for the first six hours and then

two drops into the affected eye every 30 minutes for the remainder of the first day. On the second day, instill two drops in the affected eye hourly. On the third through the fourteenth day, place two drops in the affected eye every four hours. Treatment may be continued after 14 days if corneal re-epithelialization has not occurred.

Bacterial Conjunctivitis: The recommended dosage regimen for the treatment of **bacterial conjunctivitis** is one or two drops instilled into the conjunctival sac(s) every two hours while awake for two days and one or two drops every four hours while awake for the next five days.

2. Background

The treatment of ophthalmia neonatorum was previously considered a separate indication from bacterial conjunctivitis in older children and adults. The reasons for considering it a separate indication were: 1) there was the potential for neonates to be exposed to different bacterial organisms from the birth canal (as opposed to typical environmental contacts), 2) neonates routinely received a prophylactic dose of an anti-infective agent within minutes of birth, and 3) there was an expectation that the cure rate would be faster in neonates. For these reasons, the Agency specifically requested that ophthalmia neonatorum be studied in patients with bacterial conjunctivitis in patients under one month of age.

On October 22, 1999, a Written Request (with subsequent amendments on August 3, 2001, and September 6, 2002) was issued to conduct a clinical study to provide pediatric information on ciprofloxacin. The sponsor conducted a 9-day multicenter, randomized, double-masked, parallel group study that compared Ciloxan 0.3% dosed three times a day to moxifloxacin ophthalmic solution 0.5% dosed three times a day in neonates from birth to 31 days of age.

3. CMC

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

4. Nonclinical Pharmacology/Toxicology

There were no additional Pharmacology/Toxicology studies submitted.

5. Clinical Pharmacology/Biopharmaceutics

No clinical pharmacology studies were performed or considered necessary to support the proposed dosing regimen in neonates aged 0 to 31 days.

6. Clinical/Statistical - Efficacy

See also the original Medical Officer Review finalized April 14, 2003.

The applicant conducted multicenter, randomized, well controlled clinical trial (Study C-01-34) in subjects less than 1 month of age (birth to 31 days old) for the treatment of bacterial conjunctivitis. The study compared Moxifloxicin ophthalmic solution, 0.5% versus Ciprofloxacin Ophthalmic Solution, 0.3%; each were dosed three times a day for four days. The patients were evaluated at on Days 1 (Screening), 2, 3, 4, 5 (end-of-therapy), and 9 (test-of-cure).

Summary of Clinical Cure and Microbial Eradication by Study Day

Study Day Modified Per Protocol (MPP[c])	Outcome	MOXFX	Ciloxan	Confidence Interval	P-value[a]
Day 2	Clinical cure	24% (16/66)	19% (13/70)	-8% to 19%	0.4470
Day 3	Clinical cure	36% (24/67)	27 (19/70)	-7% to 24%	0.2739
Day 4	Clinical cure	48% (32/67)	49% (34/70)	-18% to 16%	0.9244
Day 5 (end-of-therapy)	Clinical cure	53% (35/66)	61 (43/70)	-25% to 8 %	0.3223
Day 9/Exit (test-of-cure)	Clinical cure	80% (52/75)	80 (55/69)	-13% to 14%	0.9667

To provide a prospective of the expected clinical resolution rate for individuals with bacterial conjunctivitis, the clinical studies supporting the approval of a number of different products is presented below. This data was collected from the respective Medical Officer Reviews (except for one study which was collected from the Original Study Report. These clinical studies included either a vehicle arm or another anti-infective comparator. The data below was then used to establish a historical clinical cure rate both for active treatments and for vehicle treatments.

Levo-Child/Adult	N21199	MO Page 16
Oflox-Child/Adult	N21199	MO Page 16
Levo-Child/Adult	N21199	MO Page 23
Veh-Child/Adult	N21199	MO Page 23
Moxi-Child/Adult	N21598	MO Page 19
Veh-Child/Adult	N21598	MO Page 19
Moxi-Child/Adult	N21598	MO Page 25
Oflox-Child/Adult	N21598	MO Page 25
Gati-Child/Adult	N22548	MO Page 39
Veh-Child/Adult	N22548	MO Page 39
Gati-Child/Adult	N22548	MO Page 53
Veh-Child/Adult	N22548	MO Page 53
Gati-Child/Adult	N21493	MO Page 21
Veh-Child/Adult	N21493	MO Page 21
Gati-Child/Adult	N21493	MO Page 31
Oflox-Child/Adult	N21493	MO Page 31
Moxi-Child/Adult	N22428	MO Page 24
Veh-Child/Adult	N22428	MO Page 24
Moxi-Child/Adult	N22428	MO Page 25
Moxi-Child/Adult	N22428	MO Page 25
Moxi-Child/Adult	N22428R	MO Page 23
Veh-Child/Adult	N22428R	MO Page 23
Besi-Child/Adult	N22308	MO Page 26
Veh-Child/Adult	N22308	MO Page 26
Besi-Child/Adult	N22308	MO Page 26
Veh-Child/Adult	N22308	MO Page 26
Besi-Child/Adult	N22308	MO Page 26
Moxi-Child/Adult	N22308	MO Page 26
Besi-Child/Adult	N22308	Study Report Page 57
Veh-Child/Adult	N22308	Study Report Page 57

MO Page# refers to the Page Number of the Medical Officer's Original Review
Study Report Page# refers to the Page Number of the Original Study Report

Table of Treatment Arm Cure Rates from Studies in Children and Adults Supporting the Approval of Ophthalmic Fluoroquinolones Products followed by Treatment Arm Cure Rates from Studies in Neonates

Treatment Arms	%cure	# Cure	# Stu	#Cur	# Studied		# Cure	# Studi	#Cure	# Studied		# Cure	# Studi	#Cure	# Studied		# Cure	# Studie	#Cure	# Studied		# Cure	# Studi	#Cure	# Studied		# Cure	# Studie	#Cure	# Studied		# C
Children & Adults	Day 2	Day 3					Day 4					Day 5					Day 6					Day 7					Day 8					Da
Levo-Child/Adult		25%=27/106	27	106																		79%=81/103	81	103								
Oflox-Child/Adult		26%=24/94	24	94																		81%=75/93	75	93								
Levo-Child/Adult		27%=16/59	16	59																		78%=46/59	46	59								
Veh-Child/Adult		24%=13/55			13	55																61%=34/56			34	56						
Moxi-Child/Adult		27%=38/143	38	143								66%=95/143	95	143																		83
Veh-Child/Adult		15%=22/144			22	144						51%=74/144			74	144																74
Moxi-Child/Adult		21%=36/176	36	176								69%=122/176	122	176																		87
Oflox-Child/Adult		20%=34/168	34	168								68%=114/168	114	168																		84
Gati-Child/Adult							34%=56/167	56	167								75%=125/167	125	167													
Veh-Child/Adult							21%=33/158			33	158						65%=103/158			103	158											
Gati-Child/Adult							14%=23/166	23	166								52%=86/166	86	166													
Veh-Child/Adult							10%=17/167			17	167						41%=69/167			69	167											
Gati-Child/Adult		20%=9/45	9	45													77%=40/52	40	52													
Veh-Child/Adult		14%=6/42			6	42											58%=28/48			28	48											
Gati-Child/Adult		16%=12/73	12	73													82%=64/78	64	78													
Oflox-Child/Adult		24%=16/66	16	66													75%=52/69	52	69													
Moxi-Child/Adult							58%=104/178	104	178													72%=129/178	129	178								
Veh-Child/Adult							47%=78/167			78	167											68%=113/167			113	167						
Moxi-Child/Adult							58%=109/189	109	189													80%=152/189	152	189								
Moxi-Child/Adult							65%=125/193	125	193													84%=163/193	163	193								
Moxi-Child/Adult		17%=71/424	71	424			63%=265/424	265	424																							
Veh-Child/Adult		13%=56/423			56	423	51%=214/423			214	423																					
Besi-Child/Adult							23%=14/60	14	60																		62%=37/60	37	60			
Veh-Child/Adult							14%=8/56			8	56																36%=20/56			20	56	
Besi-Child/Adult												46%=90/195	90	195													87%=171/197	171	197			
Veh-Child/Adult												35%=63/179			63	179											72%=132/183			132	183	
Besi-Child/Adult												59%=149/251	149	251													89%=223/251	223	251			
Moxi-Child/Adult												60%=165/274	165	274													85%=232/274	232	274			
Besi-Child/Adult																											54%=112/206	112	206			
Veh-Child/Adult																											55%=46/83			46	83	
	Day 2	Day 3			0 188	0 232	Day 4			0 479	0 532	Day 5			0 581	0 636	Day 6			0 649	0 728	Day 7			0 763	0 82	Day 8			0 757	0 809	Da
Summary-Drug		21%	283	1354			51%	696	1377			61%	735	1207			69%	367	532			79%	646	815			78%	775	988			
Summary-Vehicle		15%			97	664	36%			350	971	42%			137	323	54%			200	373	66%			147	223	61%			198	322	
					0 121	0 176				0 331	0 392				0 371	0 48				0 485	0 587				0 595	0 72				0 56	0 668	
Neonates	Day 2	Day 3					Day 4					Day 5					Day 6					Day 7					Day 8					Da
Oflox-Neonate		29%=27/93	27	93																		60%=56/93	56	93								
Polytrim-Neonate		19%=8/42	8	42																		48%=20/42	20	42								
Moxi-Neonate	24%=16/66	36%=24/67	24	67			48%=32/67	32	67			53%=35/66	35	66																		80
Cipro-Neonate	19%=13/70	27%=19/70	19	70			49%=34/70	34	70			61%=43/70	43	70																		80
Gati-Neonate		30%=17/56	17	56																		79%=44/56	44	56								
Moxi-Neonate		44%=28/64	28	64																		84%=54/64	54	64								

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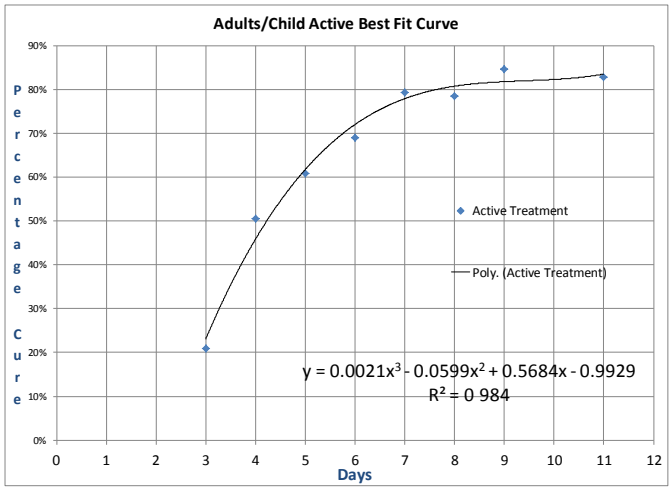
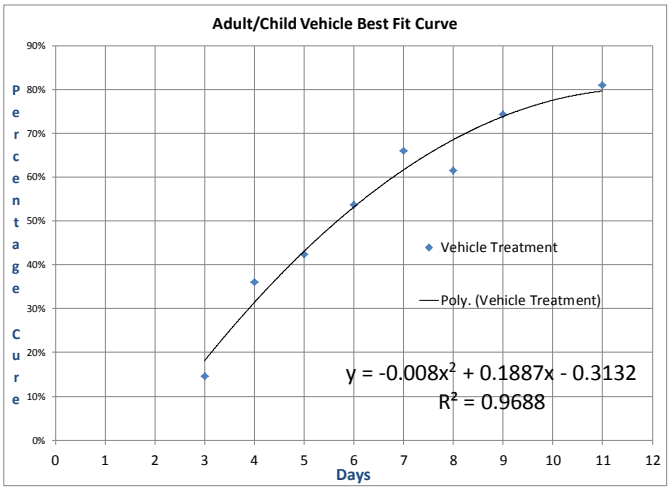
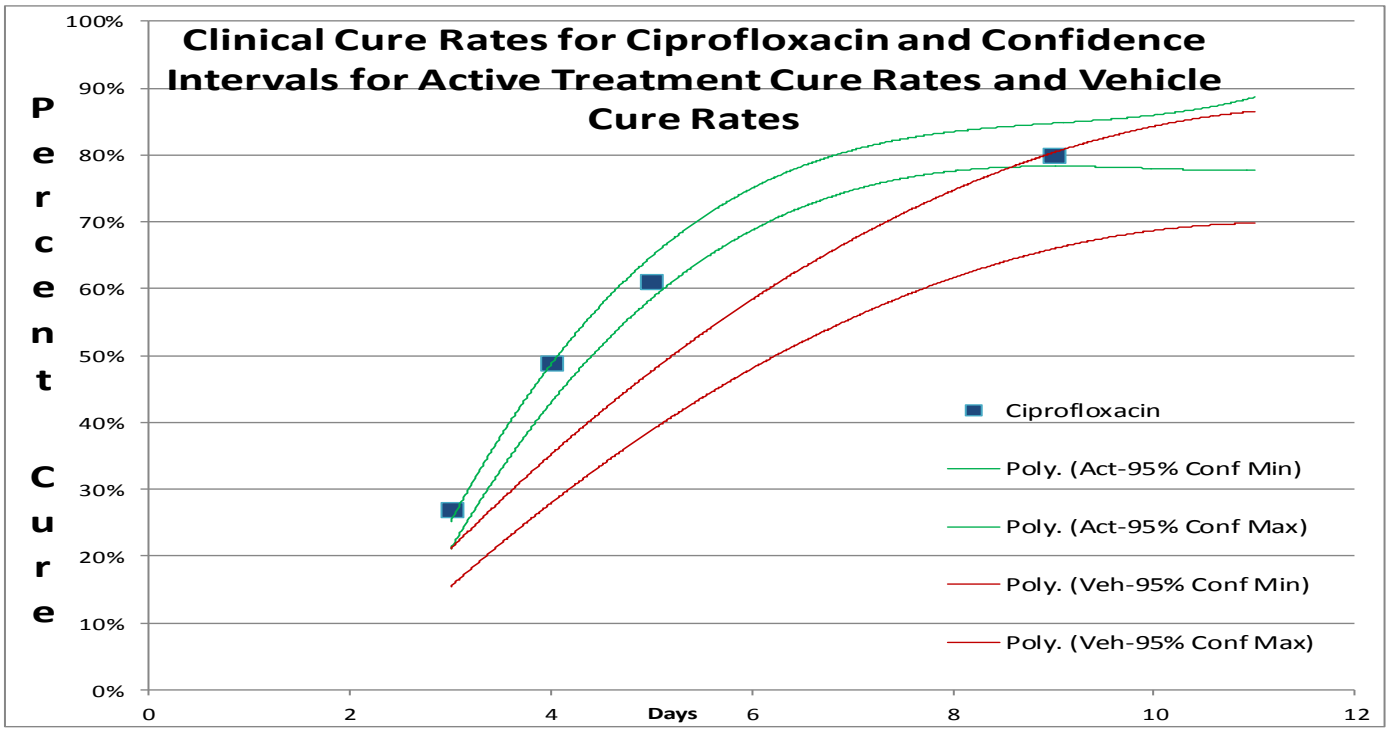
Best Fit Polynomials







The graph above displays the 95% confidence intervals for the best fit Clinical Cure Rates Curves which supported the approval of the treatments of bacterial conjunctivitis and the Clinical Cure Rates for the vehicles used in the corresponding clinical trials. There is separation between active treatments and vehicle rates from Days 4-8. In this clinical trial Ciprofloxacin Ophthalmic Solution was considered effective because the group demonstrated efficacy greater than the expected vehicle control rate at Day 4 and Day 5.

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

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

Microbial Eradication Rates from Baseline to Final by Organism

Organism	Moxifloxacin	Ciloxan
GRAM-POSITIVE BACTERIA		
Staphylococcus epidermidis	100% (29/29)	97% (32/33)
Staphylococcus aureus	100% (4/4)	100 % (3/3)
Staphylococcus simulans	100% (1/1)	
Streptococcus "schlechii"	100% (1/1)	
Staphylococcus haemolyticus	100% (2/2)	
Streptococcus pneumoniae	67% (2/3)	100% (3/3)
Streptococcus mitis	100% (3/3)	100% (4/4)
Streptococcus "schlechii"	100% (1/1)	
Bacillus sp. nov. 3	100% (1/1)	
Corynebacterium amycolatum	100% (1/1)	
Micrococcus luteus	100% (1/1)	
Staphylococcus capitis	100% (1/1)	100% (1/1)
Staphylococcus warneri	100% (1/1)	100% (1/1)
Staphylococcus hominis		100% (1/1)
Streptococcus salivarius	100% (1/1)	
Streptococcus viridans group sp. nov. J	100% (1/1)	
Viridans Streptococcus	100% (1/1)	100% (3/3)
GRAM-NEGATIVE BACTERIA		
Haemophilus influenzae	100% (2/2)	100% (3/3)
Haemophilus parainfluenzae	100% (1/1)	
Acinetobacter baumanii	100% (1/1)	
Klebsiella pneumoniae	100% (1/1)	
Moraxella catarrhalis	100% (1/1)	100% (3/3)
Acinetobacter johnsonii		100% (1/1)
Enterobacter aerogenes		100% (1/1)
Enterobacter hormaechei		100% (1/1)
Escherichia coli		100% (1/1)
Haemophilus "alconae"		100% (1/1)
Klebsiella oxytoca		100% (1/1)
Stenotrophomonas maltophila		100% (1/1)

The organisms cultured at Day 1 are consistent with the organisms cultured at Day 1 in conjunctivitis clinical trials of older children and adults. Both moxifloxacin and gatifloxacin were effective against the vast majority of organisms cultured. The initial assumptions of differences between ophthalmia neonatorum and bacterial conjunctivitis in older children and adults appear to be incorrect.

7. Safety

There was no significantly new safety information in this application.

8. Labeling

As required by the Best Pharmaceuticals for Children Act (BPCA) (21 U.S.C. 355a), data submitted in response to a Written Request under the BPCA and assessments submitted in response to a PREA study requirement must be described in labeling whether findings are positive, negative, or inconclusive (sections 505A(j) and 505B(g)(2) of the FD&C Act). These pediatric data should be placed in the labeling as required by regulation (21 CFR 201.57(c)(9)(iv)). The data submitted in this supplement was submitted in response to a Written Request under the BPCA.

Current Labeling:

"Pediatric Use
Safety and effectiveness in pediatric patients below the age of 1 year have not been established. Although ciprofloxacin and other quinolones cause arthropathy in immature animals after oral administration, topical ocular administration of ciprofloxacin to immature animals did not cause any arthropathy and there is no evidence that the ophthalmic dosage form has any effect on the weight bearing joints.

…

CLINICAL STUDIES
Following therapy with CILOXAN Ophthalmic Solution, 76% of the patients with corneal ulcers and positive bacterial cultures were clinically cured and complete re-epithelialization occurred in about 92% of the ulcers.

In 3 and 7 day multicenter clinical trials, 52% of the patients with conjunctivitis and positive conjunctival cultures were clinically cured and 70-80% had all causative pathogens eradicated by the end of treatment."

Recommended Labeling Revision:

Pediatric Use

The safety and effectiveness of Ciloxan (cipofloxacin ophthalmic solution) 0.3% have been established in all ages. Use of Ciloxan is supported by evidence from adequate and well controlled studies of Ciloxan in adults, children and neonates *[see Clinical Studies]*.

…

CLINICAL STUDIES
Following therapy with CILOXAN Ophthalmic Solution, 76% of the patients with corneal ulcers and positive bacterial cultures were clinically cured and complete re-epithelialization occurred in about 92% of the ulcers.

In 3 and 7 day multicenter clinical trials, 52% of the patients with conjunctivitis and positive conjunctival cultures were clinically cured and 70-80% had all causative pathogens eradicated by the end of treatment. (b) (4)

In a randomized, double-masked, multicenter clinical trial of pediatric patients with bacterial conjunctivitis between birth and 31 days of age, patients were dosed with Ciloxan or another anti-infective agent. Clinical outcomes for the trial demonstrated clinical cure of 80% (b) (4) at Day 9."

9. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
The labeling of NDA 19-992, Ciloxan (ciprofloxacin ophthalmic solution) 0.3% should be revised. The labeling of the product should continue to include the treatment of bacterial conjunctivitis and corneal ulcers and the restrictions of the treatment age should be removed. The clinical results of the study conducted in response to the Agency's written request letter should be included in the labeling.

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/s/

WILEY A CHAMBERS
01/23/2017

WILLIAM M BOYD
01/23/2017