Deputy Division Director Review of NDA 21-598 & (b) (4) (b) (4)

Date	January 17, 2017
From	Wiley A. Chambers, M.D.
NDA #	NDA 21-598 & (b) (4) (b) (4)
Applicant	Allergan, Inc.
Date of Submission	October 14, 2002
Name	Vigamox (moxifloxacin ophthalmic solution) 0.5%
Dosage forms / Strength	Topical ophthalmic solution, 0.5%
Proposed Indication(s)	Treatment of bacterial conjunctivitis in patients less than 1 year of age
Action:	Approval

1. Introduction

Vigamox (moxifloxacin ophthalmic solution) 0.5% is an 8-methoxy fluoroquinolone anti-infective for the treatment of bacterial conjunctivitis. Its chemical name is1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolol[3,4-b]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid.

In the United States, VIGAMOX was approved under NDA 21-598 on April 15, 2003. (b) (4) .

VIGAMOX (moxifloxacin ophthalmic solution) 0.5% is currently labeled in the US for the treatment of bacterial conjunctivitis in subjects 1 year of age and older.

Active: moxifloxacin 0.5% (5 mg/mL); **Inactives:** boric acid, sodium chloride, and purified water. May contain hydrochloric acid and/or sodium hydroxide to adjust pH to approximately 6.8.

Indication:

Vigamox is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:

Corynebacterium species*
*Micrococcus luteus**
Staphylococcus aureus
Staphylococcus epidermidis
Staphylococcus haemolyticus
Staphylococcus hominis
*Staphylococcus warneri**
Streptococcus pneumoniae
Streptococcus viridans group
*Acinetobacter lwoffii**
Haemophilus influenzae
*Haemophilus parainfluenzae**
Chlamydia trachomatis

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

Dosing Regimen: Instill one drop 3 times a day

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 June 26, 2000, a Written Request (with a subsequent amendment on September 6, 2002) was issued to conduct a clinical study to provide pediatric information on moxifloxacin. The sponsor conducted 9-day multi-center, randomized, double-masked, parallel-group clinical trial that compared VIGAMOX (moxifloxicin ophthalmic solution, 0.5% versus Ciloxan (ciprofloxacin ophthalmic solution) 0.3%; each were dosed three times a day for four days in neonates from birth to 31 days of age.

3. CMC

There were no proposed changes to the Chemistry and Manufacturing Controls for Vigamox 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
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Veh-Child/Adult	N21598	MO Page 19
Moxi-Child/Adult	N21598	MO Page 25
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Gati-Child/Adult	N22548	MO Page 39
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Gati-Child/Adult	N22548	MO Page 53
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Gati-Child/Adult	N21493	MO Page 21
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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
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Moxi-Child/Adult	N22308	MO Page 26
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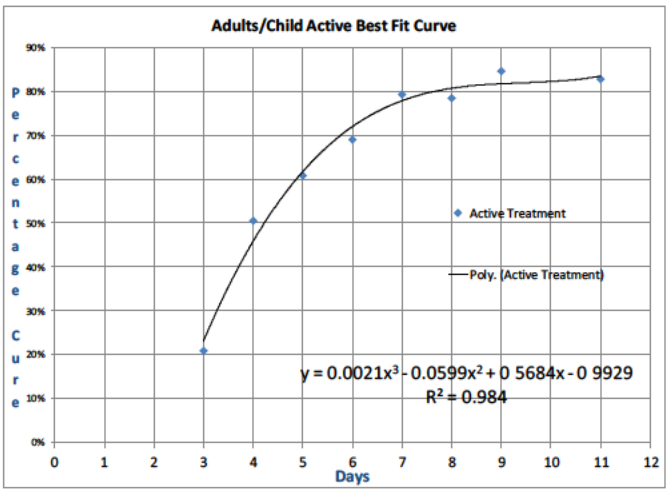
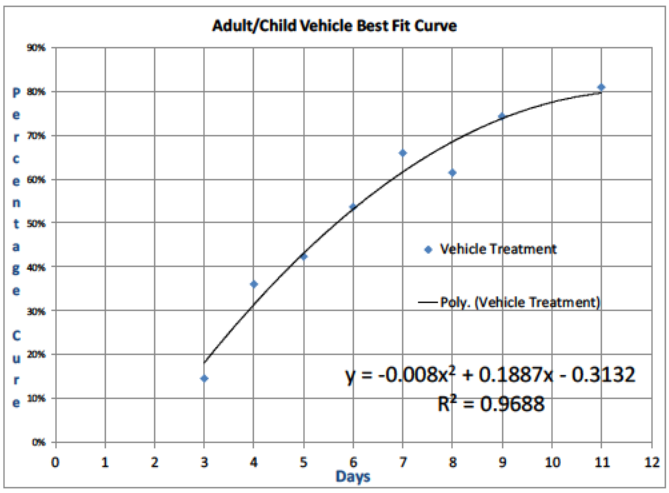
MO Page# refers to the Page Number of the Medical Officer's Original Review
Study Report Page# refers to the Page Number of the Original Study Report

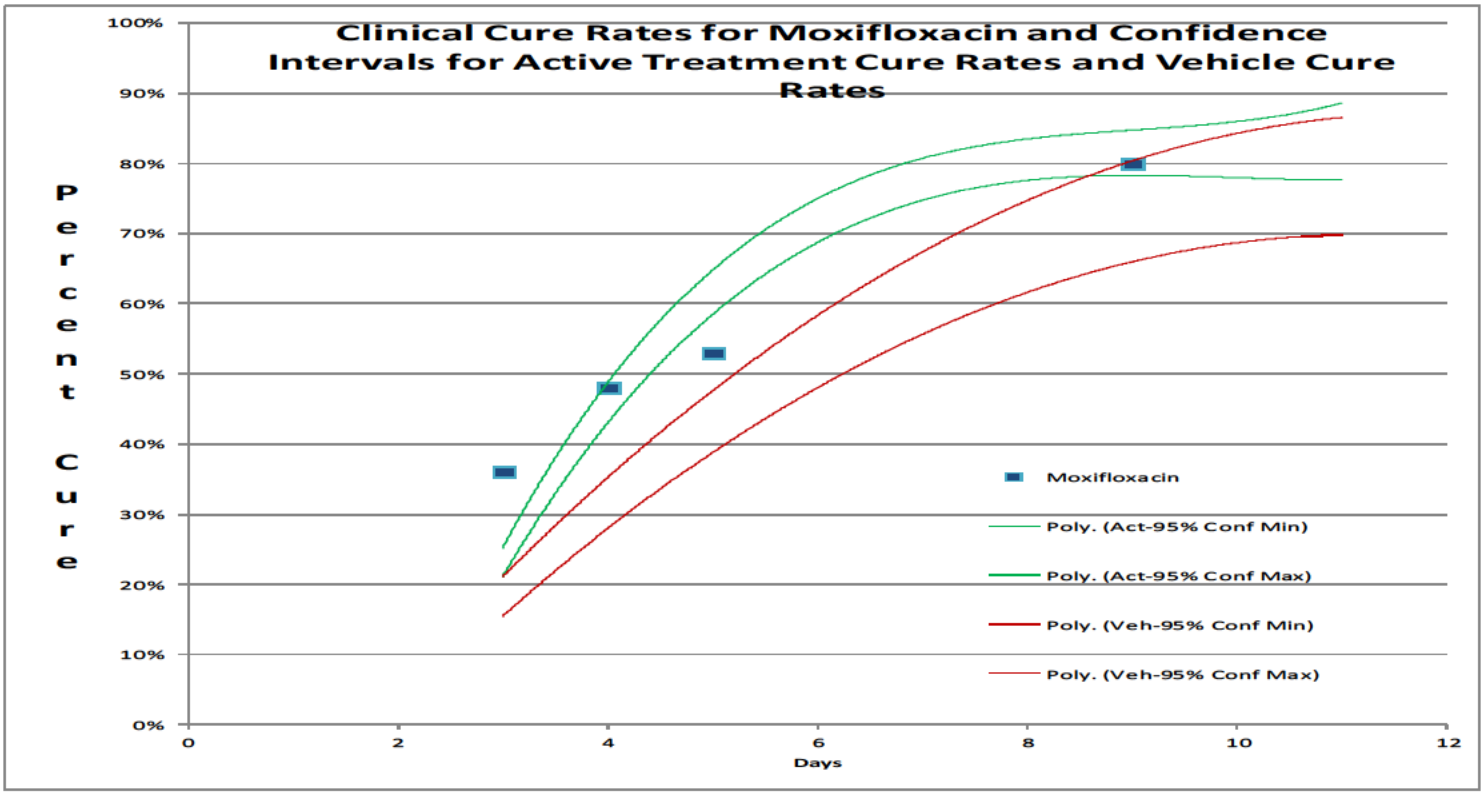
Table of Treatment Arm Cure Rates from Studies in Children and Adults Supporting the Approval of Ophthalmic Fluoroquinolones Products followed by Treatment Arm Cure Rates from Studies in Neonates

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								

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 Moxifloxacin Ophthalmic Solution was considered effective because the group demonstrated efficacy greater than the expected vehicle control rate at Day 4. The decrease in efficacy at Day 5 suggests that therapy should be continued past day 4 as recommended in the labeling.

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
(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:

"8.4 Pediatric Use
The safety and effectiveness of VIGAMOX® solution in infants below 1 year of age have not been established.

There is no evidence that the ophthalmic administration of VIGAMOX® solution has any effect on weight bearing joints, even though oral administration of some quinolones has been shown to cause arthropathy in immature animals.

…

14 CLINICAL STUDIES
In two randomized, double-masked, multicenter, controlled clinical trials in which patients were dosed 3 times a day for 4 days, VIGAMOX® solution produced clinical cures on day 5-6 in 66% to 69% of patients treated for bacterial conjunctivitis. Microbiological success rates for the eradication of baseline pathogens ranged from 84% to 94%. Please note that microbiologic eradication does not always correlate with clinical outcome in anti-infective trials."

Recommended Labeling Revision:

"8.4 Pediatric Use

The safety and effectiveness of ZYMAR (gatifloxacin ophthalmic solution) 0.3% have been established in all ages. Use of ZYMAR is supported by evidence from adequate and well controlled studies of ZYMAR in adults, children and neonates [*see Clinical Studies (14)]*.

…

14 CLINICAL STUDIES

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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 or another anti-infective agent. Clinical outcomes for the trial demonstrated clinical cure of 80% (52/75) at Day 9."

9. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:

The labeling of NDA 21-598, VIGAMOX (moxifloxacin ophthalmic solution) 0.5% should be revised. The labeling of the product should continue to include the treatment of bacterial conjunctivitis, 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