Deputy Division Director Review of NDA 21-493/S-009

Date	January 17, 2017
From	Wiley A. Chambers, M.D.
NDA #	21-493 SE5 S-009
Applicant	Allergan, Inc.
Date of Submission	March 30, 2009
Name	Zymar (gatifloxacin ophthalmic solution) 0.3%
Dosage forms / Strength	Topical ophthalmic solution, 0.3%
Proposed Indication(s)	Treatment of bacterial conjunctivitis in patients less than 1 year of age
Action:	Approval

1. Introduction

Zymar (gatifloxacin ophthalmic solution) 0.3% is an 8-methoxy fluoroquinolone anti-infective for the treatment of bacterial conjunctivitis. Its chemical name is (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate. Its molecular formula is $C_{19}H_{22}FN_3O_4 \cdot 1.5\ H_2O$, and its molecular weight is 402.42.

Active: gatifloxacin 0.3% (3 mg/mL); **Inactives:** benzalkonium chloride 0.005%; edetate disodium; purified water; and sodium chloride. May contain hydrochloric acid and/or sodium hydroxide to adjust pH to approximately 6.

In the United States, Zymar was approved under NDA 21-493 on March 28, 2003. Zymar (gatifloxacin ophthalmic solution) 0.3% is currently labeled in the US for the treatment of bacterial conjunctivitis in subjects 1 year of age and older. Zymar (gatifloxacin ophthalmic solution) 0.3% is currently registered for marketing in 29 countries and marketed in 23 countries.

Indication:

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

Aerobic Gram-Positive Bacteria:
*Corynebacterium propinquum**; *Staphylococcus aureus; Staphylococcus epidermidis; Streptococcus mitis**; *Streptococcus pneumoniae*

Aerobic Gram-Negative Bacteria: *Haemophilus influenzae*

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

Proposed Dosing Regimen: (b) (4)

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 4, 2001, a Written Request (with subsequent amendment (b) (4) July 13, 2007) was issued to conduct a clinical study to provide pediatric information on gatifloxacin. Additionally, a type C meeting was held on October 30, 2006. Agreement with the FDA was obtained from the pediatric written request to conduct studies in neonates (birth to 31 days of age). One clinical study, 198782-003, was designed and conducted according to the criteria specified in the written request to assess the safety and efficacy of Zymar in this age group. Based on the conductance of pediatric study 198782-003, pediatric exclusivity was granted May 19, 2009.

3. CMC

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

4. Nonclinical Pharmacology/Toxicology

There were no additional Pharmacology/Toxicology studies submitted to this supplement that changed the conclusions from the original application.

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 August 25, 2009.

The applicant conducted a single adequate and well controlled clinical trial (Study 198782-003) in subjects less than 1 month of age (birth to 31 days old) for the treatment of bacterial conjunctivitis. Study 198782-003 compared Zymar (gatifloxacin ophthalmic solution) 0.3% versus Vigamox (moxifloxacin ophthalmic solution) 0.5%; each were dosed three times a day for six days.

The primary efficacy variable was the clinical success rate at day 7, which is defined as the proportion of subjects in each treatment group whose study eye achieved a score of 0 for both conjunctival erythema and conjunctival discharge. Data was collected at the Day 1, 3, and 7 (or early exit) visits. For the analyses on the primary efficacy variable, the method of last observation carried forward (LOCF) was applied to both the mITT and ITT populations. For the mITT population, missing values were to be imputed from the last post-baseline value if available. For the ITT population, missing values were to be imputed based on the last available observation, regardless of whether collected from a post-baseline visit.

Number (%) of Subjects with Clinical Success- mITT Population

Visit	Gatifloxacin 0.3% (N = 56)	Moxifloxacin 0.5% (N = 64)	P-value[a]	Difference, (95% CI)[b]
Day 3	17 (30.4)	28 (43.8)	0.131	-13.4 (-30.5, 3.7)
Day 7	44 (78.6)	54 (84.4)	0.412	-5.8 (-19.8, 8.1)

a p-value was derived from a 2-sided Pearson's chi-square test.

b 95% confidence interval (CI) for the treatment difference in the proportion of subjects with a score of 0 for both conjunctival erythema and conjunctival discharge was constructed using the normal approximation for binary variables.

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
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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
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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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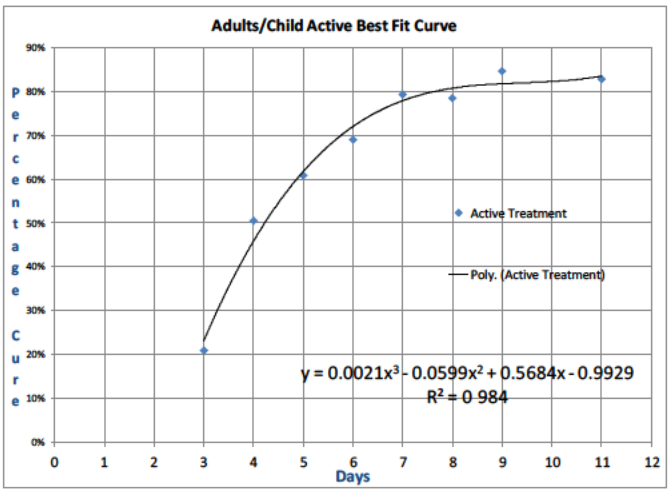
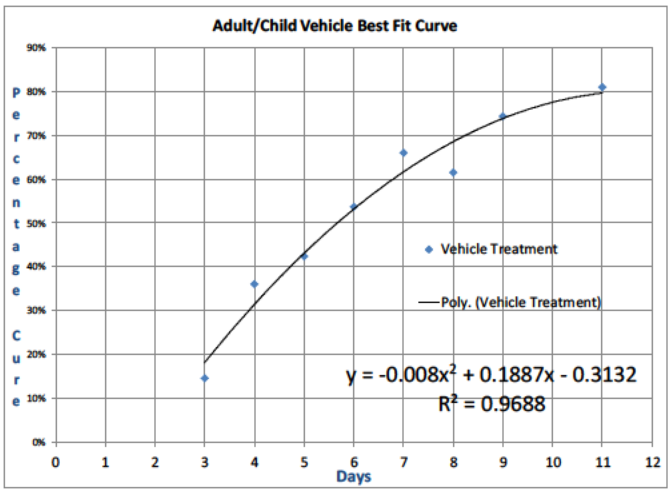
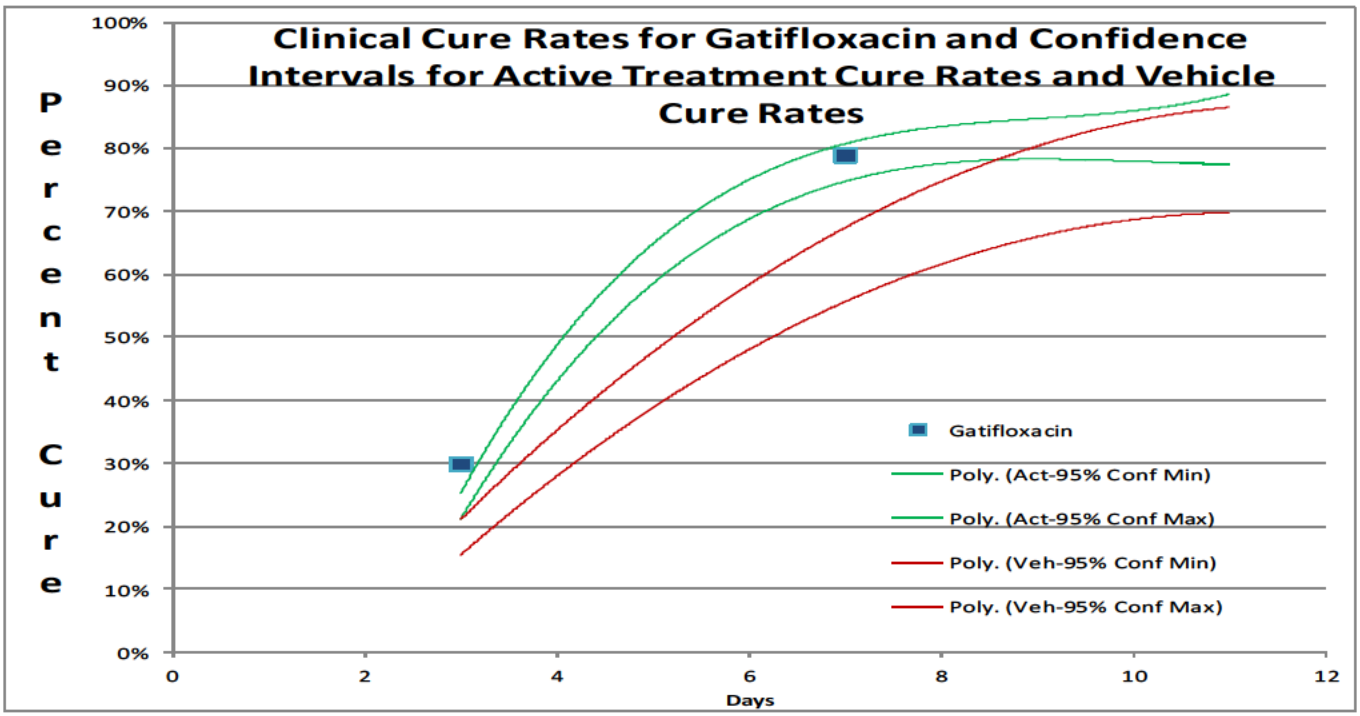
Best Fit Polynomials







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 Gatifloxacin ophthalmic solution was considered effective because the group demonstrated efficacy greater than the expected vehicle control rate at Day 7.

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)

Organism	Gatifloxacin 0.3% (N= 56)	Moxifloxacin 0.5% (N=64)
Acinetobacter calcoaceticus	1/1	2/2
Chryseobacterium indologenes	1/1	1/1
Corynebacterium accolens	1/1	1/1
Corynebacterium group G	-	1/1
Corynebacterium macginleyi	1/1	1/1
Corynebacterium pseudodiphtheriticum	1/1	2/2
Corynebacterium species	-	1/1
Enterobacter cloacae	-	2/2
Entercocccus faecium	-	0/1
Gemella haemolysana	1/1	-
Gram negative bacillus	1/1	-
Haemophilus influenzae	2/2	5/6
Haemophilus parahaemolyticus	1/1	-
Haemophilus parainfluenzae	2/2	1/1
Kocuria varians	-	1/1
Lactococcus lactis spp. lactis	1/1	-
Moraxella catarrhalis	1/1	2/2
Neisseria cinerea	-	1/1
Serratia marcescens	3/3	-
Staphylococcus aureus	3/4	5/5
Staphylococcus capitis	1/1	-
Staphylococcus epidermidis	12/17	16/22
Staphylococcus haemolyticus	-	4/4
Staphylococcus hominis	2/2	4/4
Staphylococcus simulans	-	1/1
Staphylococcus warneri	-	1/1
Streptococcus agalactiae	1/1	-
Streptococcus mitis	6/7	7/7
Streptococcus mitis group	15/15	9/10
Streptococcus oralis	8/8	11/11
Streptococcus parasanguinis	2/2	1/1
Streptococcus pneumoniae	4/4	3/3
Streptococcus salivarius	2/2	3/3
Streptococcus sanguis	-	1/1
Streptococcus thermophilus	1/1	1/1
Streptococcus vestibularis	2/2	-
Coagulase negative staph	1/1	-
Streptococcus viridans	2/2	-

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.

POSTMARKETING EXPERIENCE
Following review of all cases in the postmarketing safety data base from March 28, 2003, through March 2016, no significant safety issues were observed either in adults or in pediatric patients.

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
Safety and effectiveness in infants below the age of one year have not been established.

…

14 CLINICAL STUDIES
In a randomized, double-masked, multicenter clinical trial, where patients were dosed for 5 days, **ZYMAR®** solution was superior to its vehicle on day 5-7 in patients with conjunctivitis and positive conjunctival cultures. Clinical outcomes for the trial demonstrated clinical cure of 77% (40/52) for the gatifloxacin-treated group versus 58% (28/48) for the placebo-treated group. Microbiological outcomes for the same clinical trial demonstrated a statistically superior eradication rate for causative pathogens of 92% (48/52) for gatifloxacin vs. 72% (34/48) for placebo. Please note that microbiological 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

In a randomized, double-masked, multicenter clinical trial, where patients were dosed for 5 days, **ZYMAR®** solution was superior to its vehicle on day 5-7 in patients with conjunctivitis and positive conjunctival cultures. Clinical outcomes for the trial demonstrated clinical cure of 77% (40/52) for the gatifloxacin-treated group versus 58% (28/48) for the placebo-treated group. Microbiological outcomes for the same clinical trial demonstrated a statistically superior eradication rate for causative pathogens of 92% (48/52) for gatifloxacin vs. 72% (34/48) for placebo. Please note that microbiological eradication does not always correlate with clinical outcome in anti-infective trials."

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 ZYMAR or another anti-infective agent for 7 days. Clinical outcomes for the trial demonstrated clinical cure of 79% (44/56) for the gatifloxacin-treated group."

9. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:

NDA 21-493 SE5 S-009, Zymar (gatifloxacin ophthalmic solution) 0.3% should be approved. 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