CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206307Orig1s000

SUMMARY REVIEW

Deputy Division Director Review of NDA 206307

Date	December 4, 2014
From	Wiley A. Chambers, M.D.
NDA #	206307
Applicant	Alcon Research, Ltd.
Date of Submission	April 25, 2014
Type of Application	505(b)(1)
Name	XTORO (finafloxacin otic suspension) 0.3%
Dosage forms / Strength	Topical otic suspension, 0.3%
Proposed Indication(s)	Indicated for the treatment of acute otitis externa (AOE) caused by susceptible strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus*
Recommended:	Recommended for Approval

1. Introduction

Finafloxacin is a quinolone antimicrobial, new chemical entity with activity against bacteria found in the ear and believe to cause otitis externa. Similar to other quinolones, finafloxacin's mechanism of action is inhibition of DNA gyrase and topoisomerase IV. Finafloxacin otic suspension is formulated for topical otic administration as a white to off-white, sterile, preserved, aqueous suspension in a multi-dose container.

There are many topical otic drug products approved for the treatment of otitis externa. These products include topical otic anti-bacterials and topical otic anti-bacterial/corticosteroid combination products. Formulations of ciprofloxacin and ofloxacin are currently approved quinolone antimicrobial products for the treatment of otitis externa.

2. Background

Finafloxacin otic suspension has been studied under IND 110576 beginning in September 2011 with the submission of a protocol for Phase 1 studies. A Special Protocol Assessment was submitted for the Phase 3 studies (C-10-018 and C-10-019) in December 2011. A Pediatric Written Request was issued for finafloxacin in the treatment of acute otitis externa on February 22, 2013, requesting reports of clinical studies to be submitted to the Agency by June 30, 2016.

3. CMC

Finafloxacin otic suspension, 0.3% will be packaged in 4 mL (sample size) and 8 mL (trade size) white low density polyethylene (LDPE) bottles, with [redacted] (b) (4) white [redacted] (b) (4) closures. Stability studies support storage from 2°C to 25°C" for 104 weeks in the 5 mL fill trade size and for 78 weeks in the 0.5 fill mL sample size.

DRUG SUBSTANCE

(*S*, *S*) – Finafloxacin, also known as AL-60371 contains two chiral centers. The (*S*, *S*)- Finafloxacin is reported to show more than hundred fold greater antibacterial activity under neutral and acidic pH than its enantiomer, (*R*, *R*)-finafloxacin, against fluoroquinolone-susceptible pathogens. Finafloxacin exists as a white to yellow powder or crystals. The drug substance is shown to exist in [redacted] (b) (4) is present in the commercial batches of the drug substance. It is non-hygroscopic and has a melting point of about 300°C

Finafloxacin contains [redacted] the drug substance that is used for the manufacturing of the drug product. AL-60371 has somewhat low solubility in [redacted] water. The chiral purity of finafloxacin was assessed to be [redacted]% using chiral HPLC method.

The drug substance is manufactured and tested by: [redacted]

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

Component	Amount per mL	Proposed Function	Reference
Finafloxacin	0.3[a]	Active	Non-compendial
Tyloxapol	[redacted]	[redacted]	USP
Hydroxyethyl Cellulose [redacted]			NF
Sodium Chloride			USP
Magnesium Chloride [redacted]			USP
Benzalkonium Chloride		Preservative	NF
Hydrochloric acid		pH adjusting	NF
Sodium hydroxide		pH adjusting	NF
Purified Water		[redacted]	USP

[a]Adjust for purity
[b]Added as a [redacted]% solution, based on assay.

PROPOSED REGULATORY SPECIFICATIONS:

Finafloxacin ID (HPLC)	Positive
Finafloxacin ID (TLC)	Positive
Finafloxacin Impurities[b] [redacted] Any single unspecified impurity Total Impurities	 NMT [redacted]% of active NMT [redacted]% of active NMT [redacted]% of active
Benzalkonium Chloride ID (HPLC)[a]	Positive
Benzalkonium Chloride Assay (HPLC)	80%-120% of label
Appearance, Suspension Color (Visual)	White to Off-white
Osmolality (Freezing Point Depression)	260-330 mOsm/kg
pH	5.7-6.3
Viscosity (Brookfield Viscometer) CP42 LVT, 30 rpm	2-8 cps
Redispersibility (Visual or HPLC)	NMT [redacted]
Dissolution	TBD[c]
Particle Size by [redacted]	 NLT [redacted] [redacted] NMT [redacted]
Sterility	Pass USP

[a] Release test only
[b] Report any single impurity [redacted]% of label
[c] Alcon is in the process of developing

The intended commercial packaging configuration is Alcon's [redacted] package system which contains a white low density polyethylene (LDPE) bottle, [redacted] and a white [redacted] closure. A trade size of 5 mL filled in an 8 mL bottle and a sample size of 0.5 mL filled in an 4 mL bottle are proposed. In addition, a foil laminate pouch is used with the sample size to

(b) (4)

(b) (4) and the closure is sterilized by (b) (4). The (b) (4) The bottle (b) (4) sterilized by used for the construction of the bottle, (b) (4) and closure have been approved for use with other multiple ophthalmic and otic products and have been subjected to USP testing. Each filled unit will be placed inside a carton.

FACILITIES INSPECTIONS:
An overall facilities recommendation of "Acceptable" has been made by the Office of Compliance (8/8/2014).

4. Nonclinical Pharmacology/Toxicology

From a Nonclinical Pharmacology/Toxicology perspective, approval of NDA 206307 is recommended; no safety-related approvability issues were identified.

The safety of the AOE indication is supported by two GLP 14-day toxicology studies in New Zealand rabbits following twice-daily topical otic dosing. The first study detected minimal-to-mild local toxicity with finafloxacin hydroxide in phosphate buffer at pH 7.5. The high-dose (1.0% finafloxacin, ~ 2.18 mg/animal/day) was the no observed adverse effect level (NOAEL) for systemic toxicity. The second study tested finafloxacin (free base). The NOAEL was the highest dose tested, 1.2% (~ 2.78 mg/animal/day).

Four studies were conducted to assess the toxicity of direct instillation of finafloxacin suspension into the middle ear. Local toxicity, consistent with minimal-to-mild irritation, was detected. In support of other indications, oral and intravenous (iv) safety pharmacology, pharmacokinetic, and general toxicity studies in rodents and dogs have been conducted.

Finafloxacin was demonstrated to be mutagenic and clastogenic. Nonclinical carcinogenicity studies were not conducted, and are not warranted for this indication (topical otic dosing for 7 days, systemic exposure following topical otic dosing is minimal). The results of the oral nonclinical fertility and embryofetal studies are not relevant to topical otic dosing, because these studies tested a range of doses with estimated systemic exposures more than one thousand-fold higher than the highest systemic exposure detected in patients following topical otic dosing.

Topical otic route or lower systemic dose studies to further investigate fertility and developmental toxicity are not warranted to support the AOE indication. The rat general toxicity studies identified the male reproductive system as a sensitive target of finafloxacin. Consistent with this finding, the rat oral fertility study observed complete male infertility at 500 mg/kg/day. Three oral embryofetal studies were conducted; finafloxacin was clearly teratogenic.

5. Clinical Pharmacology/Biopharmaceutics

Based on 21 CFR § 320.22 (b)(1) and CFR § 320.22 (c), Biopharmaceutics is of the opinion that for good cause, the requirement for the submission of evidence of in vivo bioavailability or bioequivalence can be waived, because the proposed drug product is an otic intended only for local therapeutic effect.

The Applicant did not provide any dissolution data in their submission. However, the Applicant agreed to develop a dissolution testing method as a Post-Marketing Commitment (Seq. 0012 dated 09/19/2014).

2828-1 Submit the dissolution method development report with the complete data.

Final Protocol Submission:	N/A
Study/Trial Completion:	N/A
Final Report Submission:	05/2015

2828-2 Submit a proposal for the dissolution acceptance criterion and the complete supportive data. The selection of the proposed acceptance criterion should be based on the dissolution profile data (i.e., 10, 15, 20, 30, 45, and 60 minutes; N=12) from a minimum of 12 commercial batches and the stability data for registration batches.

Final Protocol Submission:	N/A
Study/Trial Completion:	N/A
Proposal Submission:	08/2015
Final Report Submission:	11/2015

6. Sterility Assurance

After Finafloxacin (b) (4) The applicant has met regulatory expectations for validating the process used to demonstrate container closure integrity of the subject container and the Antimicrobial Preservative Effectiveness of topical Finafloxacin Otic Suspension. It is to be noted, active ingredient is also an anti-microbial agent.

The closures are sterilized by (b) (4) . (b) (4) (b) (4) . The bottles (b) (4) are sterilized (b) (4) . This contract sterilization facility and processes have been previously approved in numerous Alcon applications the most recent being NDA (b) (4) .

7. Clinical/Statistical - Efficacy

A total of 686 subjects were randomized and treated at 67 centers across U.S., Canada, and

Puerto Rico in Study C-10-018; 613 (89.4%) were included in the ITT culture positive subset; 283 (41.2%) were included in the ITT pathogen positive subset. In Study C-10-019, 548 subjects were randomized and treated at 46 centers across U.S., Canada, and Puerto Rico; 480 (87.6%) were included in the ITT culture positive subset; 277 (50.5%) were included in the ITT pathogen positive subset.

Efficacy Variables for Study C-10-18 and C-10-19

The primary efficacy endpoint in this study was the proportion of patients who achieved clinical cure at the Test-of-Cure (Day 11) visit. A clinical cure was attained if the sum of the numerical scores for the signs and symptoms of AOE (tenderness, erythema, and edema) was 0 at Day 11. Microbiological success required that all pre-therapy bacteria were absent from the exit otic specimen obtained at Day 11. Cessation of ear pain was considered to have occurred at the first time point for which ear pain was absent (morning or evening) and did not subsequently return. Day 1 was used as the starting point for this time to event analysis.

The primary efficacy analysis population was the pathogen positive subset of the ITT population which included all patients who received study medication and had cultures positive for *Pseudomonas aeruginosa* and/or *Staphylococcus aureus* at baseline in the study ear.

Efficacy - Day 11 (TOC) – Pathogen Positive Subset

Study C-10-18	Finafloxacin	Vehicle	Delta	95% CI [a]	p value [b]
Clinical Cure	104/145 (72%)	46/138 (33%)	38.4	(27.6, 49.1)	<0.0001
Microbial Success	97/145 (67%)	18/138 (13%)	53.9	(44.4, 63.4)	<0.0001
Median days till cessation of Ear Pain	4.0	7.0	3.0		<0.0001
Mean days till cessation of Ear Pain	4.8	7.3			

Study C-10-19	Finafloxacin	Vehicle	Delta	95% CI [a]	p value [b]
Clinical Cure	101/147 (69%)	52/130 (40%)	28.7	(17.4, 40.0)	<0.0001
Microbial Success	97/147 (66%)	15/130 (12%)	54.4	(45.0, 63.9)	<0.0001
Median days till cessation of Ear Pain	3.0	6.5			<0.0001
Mean days till cessation of Ear Pain	4.0	7.0			

a 95% confidence interval based on a non-stratified analysis; b Test = stratified CMH

Each study met its primary efficacy endpoint. Finafloxacin was superior to vehicle in the proportion of patients who achieved clinical cure in the pathogen positive subset of the ITT population at Day 11 (TOC visit). The proportion of patients who achieved microbiological success in the pathogen positive subset of the ITT population at Day 11 (TOC visit) was greater in the finafloxacin group compared to

the vehicle group. The time to cessation of ear pain was shorter by 2.5 days in the Finafloxacin group compared to the Vehicle group in the Pathogen Positive subset of the ITT population.

Clinical Microbiology

In the combined AOE studies (C-10-018 and C-10-019), there were a total of 2746 pretherapy isolates recovered from the affected ear(s) of randomized patients, 71.05% (1951) of the pre-therapy isolates were gram-positive, 26.7% (732) were gram-negative and 2.3% (63) were yeast or fungi. Of the 2379 pre-therapy isolates, 560 were considered to be the etiological AOE pathogens of which 405 (72.3%) were *Pseudomonas aeruginosa* and 155 (27.7%) were *Staphylococcus aureus* isolates.

Against *Staphylococcus aureus,* microbiological eradication was achieved 72 patients (87.8%) in the finafloxacin otic 0.3% suspension treatment group and 44 patients (60.3%) in the vehicle treatment group. The eradication rate varied based on fluoroquinolone sensitivity in finafloxacin otic suspension 0.3% treated subjects; 61 patients (91.0%) that had a fluoroquinolone sensitive *S. aureus* isolate eradicated their isolate whereas 11 patients (73.3%) that had a fluoroquinolone resistant *S. aureus* isolate achieved eradication.

Against *Pseudomonas aeruginosa*, microbiological eradication was achieved in 190 patients (90.5%) in the finafloxacin otic 0.3% suspension treatment group and 117 patients (60.0%) in the vehicle treated group. In the finafloxacin otic suspension 0.3% treated group, 173 patients (90.6%) that had a fluoroquinolone sensitive *P. aeruginosa* isolate and 17 patients (89.5%) that had a fluoroquinolone-resistant *P. aeruginosa* isolate eradicated their isolate at Day 11(TOC).

The following table includes information on the proportion of patients who achieved clinical cure for selected bacterial microorganisms that were cultured at baseline. Only bacterial microorganisms observed at baseline in at least 5 study ears when combining the studies and treatments are included.

Patients who had more than one microorganism in the study ear at baseline are included in the row for each microorganism and were counted more than once within the table. Some patients had more than one isolate recovered for a specific microorganism. In these cases, the patient is only counted one time for that microorganism.

Clinical Cures at Day 11 (TOC) by Baseline Microorganism in the Study Ear Culture Positive Subset- Studies C-10-018 and C-10-019 Pooled

Organism	Finafloxacin N=550		Vehicle N=543	
	Total N	Clinical Cures n (%)	Total N	Clinical Cures n (%)
Bacillus cereus	6	3 (50.0%)	3	2 (66.7%)
Corynebacterium amycolatum	12	6 (50.0%)	10	6 (60.0%)
Corynebacterium auris	16	13 (81.3%)	8	3 (37.5%)
Enterococcus casseliflavus	5	4 (80.0%)	0	---
Enterococcus faecalis	28	15 (53.6%)	20	10 (50.0%)
Micrococcus species	7	6 (85.7%)	2	0 (0.0%)

Organism	Finafloxacin N=550		Vehicle N=543	
	Total N	Clinical Cures n (%)	Total N	Clinical Cures n (%)
Staphylococcus aureus	**82**	**56 (98.3%)**	**71**	**29 (40.8%)**
Staphylococcus auricularis	101	78 (77.2%)	92	63 (68.5%)
Staphylococcus capitis	60	43 (71.7%)	83	45 (54.2%)
Staphylococcus caprae	27	25 (92.6%)	36	22 (61.1%)
Staphylococcus epidermidis	157	108 (68.8%)	155	75 (48.4%)
Staphylococcus haemolyticus	13	8 (61.5%)	10	5 (50.0%)
Staphylococcus hominis	8	6 (75.0%)	14	8 (57.1%)
Staphylococcus lugdunensis	7	4 (57.1%0	10	3 (30.0%)
Staphylococcus pasteuri	5	5 (100.0%)	3	2 (66.7%)
Staphylococcus simulans	5	3 (60.0%)	6	3 (50.0%)
Staphylococcus warneri	21	16 (76.2%)	9	7 (77.8%)
Streptococcus agalactiae	6	2 (33.3%)	3	2 (66.7%)
Streptococcus mitis	9	8 (88.9%)	12	4 (33.3%)
Streptococcus species	8	7 (87.5%)	7	5 (71.4%)
Turicella otitidis	119	86 (72.3%)	131	77 (58.8%)
Achromobacter xylosoxidans	5	4 (80.0%)	4	1 (25.0%)
Escherichia coli	9	6 (66.7%)	8	2 (25.0%)
Klebsiella pneumonia	7	4 (57.1%)	11	2 (18.2%)
Proteus mirabilis	11	8 (72.7%)	7	4 (57.1%)
Pseudomonas aeruginosa	**230**	**163 (70.9%)**	**219**	**76 (34.7%)**
Stenotrophomonas maltophilia	16	12 (75.0%)	4	2 (50.0%)

Subjects with multiple pathogens at baseline are included in the row for each pathogen.
N= number of patients with that organism present above threshold in the study eye at baseline

The following ITT subset includes patients who were culture positive at baseline but not for *Staphylococcus aureus* or *Pseudomonas aeruginosa*. Bacterial microorganisms from patients who had one or both of the primary pathogens isolated at baseline from the study ear were excluded from the following table. Bacterial microorganisms observed at baseline in at least 5 - 9 study ears for which finafloxacin achieved ≥ 80% clinical cure rate are included. Bacterial microorganisms observed in at least 10 study ears for which finafloxacin achieved a higher clinical cure rate are also included.

Clinical Cures at Day 11 (TOC) by Baseline Microorganism in the Study Ear
ITT Population – Modified Culture Positive Subset Studies C-10-018 and C-10-019 Pooled

Organism	Finafloxacin N=550		Vehicle N=543	
	Total N	Clinical Cures n (%)	Total N	Clinical Cures n (%)
Corynebacterium auris	9	8 (88.9%)	4	2 (50.0%)
Staphylococcus capitis	45	33 (73.3%)	63	36 (57.1%)
Staphylococcus caprae	16	14 (87.5%)	21	15 (71.4%)
Staphylococcus epidermidis	91	66 (72.5%)	92	51 (55.4%)
Staphylococcus warneri	13	10 (76.9%)	8	6 (75.0%)
Turicella otitidis	67	47 (70.1%)	80	53 (66.3%)

Sample sizes presented in the headers represent the number of evaluable subjects for this analysis set.
Patients with multiple microorganisms at baseline are included in the row for each microorganism.
N= number of patients with that organism present above threshold in the study eye at baseline

There is substantial evidence of effectiveness consisting of adequate and well controlled studies (Studies C-10-018 and C-10-019) which demonstrate that finafloxacin otic suspension is superior to its vehicle in the treatment of acute otitis externa when dosed four drops twice daily for seven days or, when using an otowick, giving an initial dose of 8 drops, followed by 4 drops twice daily for seven days.

The primary efficacy endpoint, the proportion of patients with clinical cures at the Day 11 Visit, was found to be clinically and statistically significant in both studies. Finafloxacin demonstrated superiority to vehicle in clinical cure rate, microbiological success and the median time to cessation of ear pain. The clinical and statistical reviewers have recommended the approval of Finafloxcin otic suspension 0.3% for the treatment of AOE.

8. Safety

Studies/Clinical Trials Used to Evaluate Safety

Study Identifier / Study Type	Study Design	Study Population	Dosing Regimen and Duration	Treatment (N)	Safety Assessments
Safety and Efficacy Study (Confirmatory) **C-10-018**	Prospective, multicenter, double-masked, vehicle-controlled, parallel-group, randomized	Patients 11 months to 84 years with a diagnosis of AOE with a combined numerical score of ≥ 4 in at least 1 affected ear at the Day 1 exam for tenderness, erythema, and edema	4 drops in the affected ear(s) twice daily for 7 days	• Finafloxacin 0.3% (N=344) • Vehicle (N=342)	• Extent of exposure • Adverse events
Safety and Efficacy Study (Confirmatory) **C-10-019**	Prospective, multicenter, double-masked, vehicle-controlled, parallel-group, randomized	Patients age 2 to 82 years with a diagnosis of AOE with a combined numerical score of ≥ 4 in at least 1 affected ear at the Day 1 exam for tenderness, erythema, and edema	4 drops in the affected ear(s) twice daily for 7 days	• Finafloxacin 0.3% (N=274) • Vehicle (N=274)	• Extent of exposure • Adverse events
PK Study **C-10-007**	Single-center, multiple-dose, randomized, vehicle-controlled, fixed sequence study.	Healthy male and female subjects of any race/ethnicity, age 6 to 78 years	Period 1: 4 drops in both ears BID; 7 days of BID dosing followed by 1 day of dosing in both ears in the morning only 8 days) Period 2: 1 tablet (200 mg) po per day (single dose)	Period 1: Finafloxacin 0.3% (N=14) Vehicle (N=7) Period 2: AL-60371A 200 mg tablet (N=20)	• Extent of exposure • Adverse events • Vital signs (P, BP) • External ear examination • EKG • Clinical laboratory tests
PK Study **C-10-022**	Multicenter, open-label, single-dose PK study, parallel-group randomized to without and with otowick (4 drops/ear); a non-randomized group with otowick 8 drops per ear.	Acute otitis externa patients, 6 years of age and older with and without otowick	• 4 drops or 8 drops in each ear / day (a single dose)	• Finafloxacin 0.3%, 4 drops with otowick (N=12) • Finafloxacin 0.3% 4 drops without otowick (N=12) • Finafloxacin 0.3% 8 drops with otowick (N=12)	• Extent of exposure • Adverse events

Overview of Exposure to Study Drug by Protocol

Protocol Number	Safety Population	Topical Otic Dosing			Oral Dosing
		Finafloxacin (AL-60371)		Vehicle	Al-60371A [c]
		N=688		N=623	N=20
		BID	Single Dose [b]	BID	Single Dose
Efficacy and Safety Studies					
C-10-018	686	344	---	342	---
C-10-019	548	274	---	274	---
Pharmacokinetic Studies					
C-10-007	21[a]	14	---	7	20
C-10-022	36	---	36	---	---
Total	**1291**	632	36	623	20
Source Table 2.7.4.1-1					

AL-60371 = finafloxacin, free base AL-60371A = finafloxacin, hydrochloride salt

a After the otic dose period (Period 1), 20 subjects in protocol C-10-007 were also exposed to AL-60371A 200 mg tablet during the oral dose period (Period 2). One subject with exposure to Vehicle discontinued from the study prior to the oral dose period.

b Single dose = 3 groups combined (4 drops per ear with otowick group, 4 drops per ear without otowick group and 8 drops per ear with otowick group). Finafloxacin otic suspension, 0.3%; Finafloxacin otic suspension vehicle.

c AL-60371A = AL-60371A 200 mg tablet

C-10-18 Subject Disposition All Randomized Subjects

Subject Disposition	Study C-10-18		Study C-10-19	
	Finafloxacin (N=347)	Vehicle (N=346)	Finafloxacin (N=274)	Vehicle (N=275)
Safety Population	344	342	274	274
ITT Population	344	342	274	274
Culture positive subset (MITT)	311	302	239	241
Pathogen positive subset (PMITT)	145	138	147	130
Per-Protocol Population	314	324	250	244
Culture positive subset (MPP)	281	287	217	217
Pathogen positive subset (PMPP)	126	127	134	118
Completed Study	297 (85.6%)	250 (72.3%)	237 (86.5%)	179 (65.1%)
Discontinued Study	50 (14.4%)	96 (27.7%)	37 (13.5%)	95 (34.5%)
Reasons for Discontinuation				
Adverse Event	6 (1.7%)	15 (4.3%)	12 (4.4%)	7 (2.5%)
Lost to Follow-up	3 (0.9%)	4 (1.2%)	1 (0.4%)	3 (1.1%)
Subject Decision Unrelated to an AE	4 (1.2%)	3 (0.9%)	3 (1.1%)	1 (0.4%)
Treatment Failure	33 (9.5%)	66 (19.1%)	21 (7.7%)	83 (30.2%)
BL Culture + for Group A Strep	0	1 (0.3%)	0	0
BL Culture + for Yeast / Fungi	0	1 (0.3%)	0	0
Other	2 (0.6%)	2 (0.6%)	0	1 (0.4%)
Randomized in Error	2 (0.6%)	4 (1.2%)	0	1 (0.4%)
Source: Adapted from Table 10.1-1 and Table 10.1-2.				

Overall Frequency and Incidence of Adverse Events Occurring at Rates ≥ 1.0%
Studies C-10-018 and C-10-019: Pooled Safety Populations

Coded Adverse Event [a]	Finafloxacin (N=618)	Vehicle (N=616)
Ear discomfort	2 (0.3%)	9 (1.5%)
Ear pain	3 (0.5%)	9 (1.5%)
Ear pruritus	8 (1.3%)	6 (1.0%)
Headache	11 (1.8%)	18 (2.9%)
Otitis media	8 (1.3%)	14 (2.3%)
Otitis externa	11 (1.8%)	9 (1.5%)
Nausea	7 (1.1%)	1 (0.2%)

Source: Table 2.7.4.2-1
a MedDRA version 15.0

Adverse events reported by greater than or equal to 1% of patients and more frequently in the finafloxacin group were 'ear pruritus, 'otitis externa', and 'nausea.' A single adverse event was reported in Study C-10-022 in the 8 Drops with Otowick treatment group. The adverse event was coded ear hemorrhage. This adverse event resolved without treatment within 2 hours.

The application supports the safety of XTORO (finafloxacin otic suspension) 0.3% for the treatment of acute otitis externa. The safety profile of finafloxacin is similar to currently approved quinolone antimicrobial otic products.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Pediatrics

The safety and efficacy of XTORO in treating acute otitis externa in pediatric patients one year or older have been demonstrated in adequate and well controlled clinical trials (Studies C-10-018 and C-10-019). A Pediatric Written Request was issued for finafloxacin in the treatment of acute otitis externa on 2/22/13. The written request specified that pediatric patients aged 1 to 13 years be enrolled.

This application was presented at the Pediatric Exclusivity Board on 8/26/14; the application was found to be in compliance with the written request, and exclusivity was granted. This application was presented at the Pediatric Review Committee (PeRC) on 11/5/14. PeRC concurred with granting a partial waiver from studies for the pediatric age group birth to 1 year. Necessary studies would be impossible or highly impracticable because there are too few children with disease/condition to study.

11. Other Relevant Regulatory Issues

OSI

A Office of Scientific Investigations (OSI) audit was requested. Drs. Calcagno's and Schwartz's clinical sites were selected for inspection because they were among the highest enrolling sites from studies C-10-018 and -019. Neither Dr. Calcagno nor Dr. Schwartz was issued a Form FDA 483, and the final classification of these inspections was No Action Indicated (NAI). The data generated by these clinical sites appear adequate in support of the respective indication.

FINANCIAL DISCLOSURE
Alcon has determined there were no financial interests or arrangements to disclose from investigators in clinical studies C-10-018, C-10-019 and C-10-022. There are financial interests or arrangements to disclose from the investigator, Dr. (b) (6), who participated in clinical trial (b) (6). Dr. (b) (6) received approximately $32,000 in consulting fees. Alcon took the following steps to minimize potential bias of clinical study results by any of the investigators:

- The study was randomized, controlled and double-masked in Period 1.
- The biostatistical and clinical pharmacology staffs were masked to treatment assignments.
- The Principal Investigator and all sub-Investigators were prohibited from administering study drugs to patients.
- The safety variables were assessed by masked observers.
- The treatment code was not broken by the investigators or the Applicant.

DMEPA
The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review dated 11/5/14 finding the proprietary name, XTORO, to be conditionally acceptable. This review constituted a re-assessment of the proposed proprietary name, Xtoro, written in response to the resubmission of this proprietary name by the applicant. DMEPA also provided recommendations on the packaging configuration and the package insert labeling in a review finalized 9/15/14.

OPDP
The Office of Prescription Drug Promotion (OPDP) reviewed the substantially complete draft product labeling for XTORO (finafloxacin otic suspension) 0.3% and offered comments in their review finalized 10/10/14:

12. Labeling

NDA 206307, XTORO (finafloxacin otic suspension) 0.3% is recommended for approval for the treatment of acute otitis externa (AOE) caused by susceptible strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus* with the labeling found in the Appendix of the Cross Discipline Team Leader's Review.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
NDA 206307, XTORO (finafloxacin otic suspension) 0.3% is recommended for approval for the treatment of acute otitis externa (AOE) caused by susceptible strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

There is substantial evidence of effectiveness consisting of adequate and well controlled studies (Studies C-10-018 and C-10-019) which demonstrate that finafloxacin otic suspension is superior to its vehicle in the treatment of acute otitis externa when dosed four drops twice daily for seven days or, when using an otowick, giving an initial dose of 8 drops, followed by 4 drops twice daily for seven days.

The primary efficacy endpoint, the proportion of patients with clinical cures at the Day 11 Visit, was found to be clinically and statistically significant in both studies. Finafloxacin demonstrated superiority to vehicle in clinical cure rate, microbiological success and the median time to cessation of ear pain. The drug product was generally safe and well tolerated. Reactions most frequently reported with finafloxacin otic suspension were ear pruritus and nausea. The safety profile of finafloxacin is similar to currently approved quinolone antimicrobial otic products.

Pharmacology/Toxicology, Biostatistics, Product Quality, Clinical, Clinical Pharmacology, Biopharmacology, and Clinical Microbiology have recommended approval for this application.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:
There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

At the request of the Biopharmaceutics Review Team, the applicant has submitted the following post-marketing commitments:

2828-1 Submit the dissolution method development report with the complete data. Final Report to be submitted by 05/2015

2828-2 Submit a proposal for the dissolution acceptance criterion and the complete supportive data. The selection of the proposed acceptance criterion should be based on the dissolution profile data (i.e., 10, 15, 20, 30, 45, and 60 minutes; N=12) from a minimum of 12 commercial batches and the stability data for registration batches. Proposal Submission: 08/2015, Final Report Submission: 11/2015.

Wiley A. Chambers, MD
Deputy Division Director
Division of Transplant and Ophthalmology Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILEY A CHAMBERS
12/04/2014