CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206307Orig1s000

OFFICE DIRECTOR MEMO

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	John Farley, M.D.,M.P.H.
Subject	Deputy Office Director Decisional Memo
NDA #	206307
Applicant Name	Alcon Research Ltd.
Date of Submission	April 25, 2014
PDUFA Goal Date	December 25, 2014
Proprietary Name / Established (USAN) Name	Xtoro/ Finafloxacin otic suspension, 0.3%
Dosage Forms / Strength	Topical otic suspension
Proposed Indication	Treatment of acute otitis externa caused by susceptible strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus*
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of Discipline Reviewers**
Medical Officer Review	Rhea Lloyd, M.D.
Statistical Review	Yunfan Deng, Ph.D.
Pharmacology Toxicology Review	Andrew McDougal, Ph.D.
CMC/Biopharmaceutics/Product Quality Microbiology Reviews	Mariappan Chelliah, Ph.D., Chunchun Zhang, Ph.D., Banu Zolnik, Ph.D., Vinayak Pawar, Ph.D.
Clinical Microbiology Review	Simone Shurland, Ph.D.
Clinical Pharmacology Review	Yongheng Zhang, Ph.D.
OPDP	Christine Corser, Pharm.D.
OSI	Roy Blay, Ph.D.
DMEPA	Rachna Kapoor, Pharm.D.
DRISK	Joyce Weaver, Pharm.D.
CDTL Review	William Boyd, M.D.
Deputy Division Director Review	Wiley Chambers, M.D.

OND=Office of New Drugs
CMC= Chemistry, Manufacturing and Controls
OPDP= Office of Prescription Drug Products
OSI= Office of Scientific Investigations
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

1. Introduction

Finafloxacin is a quinolone antibacterial drug. Its mechanism of action is similar to other quinolones, inhibition of bacterial type II topoisomerases, DNA gyrase and topoisomerase IV which are essential for bacterial DNA replication, transcription, recombination and repair.

The proposed indication is treatment of acute otitis externa (AOE) caused by susceptible strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus.* The dosage form is a topical otic suspension. The proposed dosing regimen is instillation of 4 drops in the affected ear(s) twice daily for 7 days. An initial dose of 8 drops may be used if patients require an otowick.

The efficacy review for this NDA relies upon the results of two adequate and well-controlled trials, Trials C-10-018 and C-10-019. The review team has reviewed issues pertinent to their respective disciplines with regard to the safety and efficacy of finafloxacin otic suspension, 0.3% for the indication proposed. For a detailed discussion of NDA 206307, the reader is referred to individual discipline specific reviews, the Cross-Discipline Team Leader (CDTL) review, and the Deputy Division Director review.

2. Background/Regulatory

Finafloxacin is a new molecular entity. Finafloxacin otic suspension was studied under IND 110576.

In December 2011, a Special Protocol Assessment was submitted for the Phase 3 trials (Trials C-10-018 and C-10-019). A Special Protocol Agreement Letter was issued in January 2012.

A Pediatric Written Request was issued for finafloxacin otic suspension for the treatment of AOE on February 22, 2013 (see Section 10). As NDA 206307 included data which the applicant stated fulfilled the Pediatric Written Request, the NDA received a Priority Review.

3. Chemistry Manufacturing and Controls / Biopharmaceutics/ Product Quality Microbiology

The CMC reviewers, Biopharmaceutics reviewer, and Product Quality Microbiology reviewer all recommended NDA approval. I concur that there are no outstanding CMC issues precluding approval.

The reviewers concluded that the applicant has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specification to assure consistent product quality of the drug substance and drug product. The NDA was assessed as providing sufficient stability information on the drug product to support the expiration dating period of 104 weeks for the 5 mL fill trade size and 78

weeks for the 0.5 mL fill sample size. The Biopharmaceutics reviewer indicated that the NDA is recommended for approval from the Biopharmaceutics perspective with agreement by the applicant to develop a dissolution testing method as a PMC. The Product Quality Microbiology reviewer concluded that methods and controls were adequate for sterility assurance and recommended approval of this NDA. All manufacturing facilities have acceptable site recommendations.

In the course of the review, it was noted that one of the starting materials, (b) (4) The manufacturing process is being validated and details/specification will be submitted as a post-approval CBE-30 supplement in July 2015. This was acceptable to the CMC review team.

The applicant did not provide any dissolution data in their submission. Since the drug product is a suspension, the dissolution test should be added to the specifications of the drug product. The applicant agreed to a PMC to develop a dissolution testing method for the product and provide validation data. This was agreeable to the Biopharmaceutics review team.

4. Non-Clinical Pharmacology Toxicology

The Pharmacology Toxicology reviewer concluded that finafloxacin otic suspension was shown to be safe for the proposed indication. I concur that there are no outstanding pharmacology toxicology issues that preclude approval.

The applicant conducted two 14-day toxicology studies in rabbits with twice daily otic dosing. Minimal to mild local toxicity was observed and there were no notable clinical pathology findings. Four studies were conducted to assess the toxicity of direct installation of finafloxacin suspension into the middle ear. These nonclinical toxicity data associate direct instillation of finafloxacin and its vehicle into the middle ear with mild hearing loss and local toxicity. In support of other indications, oral and intravenous safety pharmacology and general toxicity studies in rodents and dogs have been conducted. Finafloxacin was found to be mutagenic and clastogenic, but this is not considered relevant to otic dosing due to minimal systemic exposure. Carcinogenicity studies were not conducted and are not warranted due to short period of otic dosing and minimal systemic exposure. Male infertility and sperm toxicity was observed in oral fertility studies. Results of oral fertility and embryofetal studies are not considered relevant to topical otic dosing due to minimal systemic exposure. Pregnancy Category C is recommended as there are no adequate and well-controlled studies in pregnant women, but finafloxacin was shown to be teratogenic in rabbits and rats following oral administration. Neural tube defects and skeletal anomalies in both species and limb anomalies in rabbits were observed at exposures estimated to be 1300 to 60,000 times the maximum human systemic exposure following topical otic administration.

5. Clinical Pharmacology

The Clinical Pharmacology reviewer recommended approval.

The applicant submitted two Phase 1 pharmacokinetic studies: C-10-007 a randomized, multidose, fixed sequence PK study (otic and oral) in healthy subjects, and C-10-022 an open-label, single-dose PK study in AOE patients. There was limited systemic exposure following ototopical doses. No PK parameters could be determined. Clinically significant drug-drug interactions are not expected.

6. Clinical Microbiology

The Clinical Microbiology reviewer concluded that the information provided by the applicant supports efficacy for the indication proposed and recommended that labeling reflect the pre-specified primary analysis population (see Section 7). I concur that there are no Clinical Microbiology issues precluding approval.

In-vitro studies were conducted that evaluated the activity of finafloxacin against Gram-positive and Gram-negative isolates by determining the minimum inhibitory concentration (MIC) under conditions of varying pH concentrations. In these in-vitro studies, finafloxacin antibacterial activity was enhanced at lower pH compared with neutral pH. Against several bacterial species, including *P. aeruginosa,* the finafloxacin MICs determined over pH ranges of 4.5 to 7.5 with increments of approximately 0.25 pH units, showed a pH dependent increase in activity (decrease in MIC) against all tested strains at pH values below 7.4. This was not observed with other quinolone antibacterial drugs tested. Time kill studies and minimum bactericidal concentration (MBC) determinations of finafloxacin showed bactericidal activity against *S. aureus* and *P. aeruginosa* strains.

In vitro studies suggested the potential for the development of resistance to finafloxacin was variable depending on testing conditions, with lower spontaneous frequencies of resistant organism under acidic testing conditions (pH 6). The predominant mechanisms of resistance to fluoroquinolones are the alteration of chromosomal target genes gyrA/B and parC/E encoding DNA gyrase and topoisomerase IV, respectively. In vitro testing showed that single step mutants showed a 2 – 32 fold increase in MIC in finafloxacin against Gram-negative and Gram-positive organisms. There was little or no effect on the activity of finafloxacin against known Gram-positive efflux pumps (e.g., reserpine and NorA). However, efflux pumps played a role in the reduced susceptibility to some Gram negative organisms (e.g., due to inactivation of the repressor MarR), *P. aeruginosa* (e.g., MDE efflux pumps such as mexCD and mexAB) as well as *Acinetobacter* spp. (e.g., AdeB).

In a guinea pig experimental model of acute otitis externa, finafloxacin demonstrated a dose-dependent response at concentrations tested from 0.03% to 0.3% suspension formulations. A 0.15% suspension concentration of finafloxacin or higher resulted in reduction of *P. aeruginosa* colony forming unit (CFU) counts to below the limit of

detection. The reviewer agreed with the methods for assessing microbiologic response in the primary analysis populations in the Phase 3 trials. No susceptibility testing interpretive criteria for this topical product are recommended.

7. Clinical/Statistical Efficacy

The Clinical reviewer, Statistical reviewer, CDTL, and Deputy Division Director concluded that efficacy had been demonstrated and recommended approval. I agree that trials C-10-018 and C-10-019 are adequate and well-controlled and the trial results provide substantial evidence of efficacy.

Trials C-10-018 and C-10-019 were identical Phase 3 trials conducted in parallel. The objective was to demonstrate the superiority of finafloxacin otic suspension, 0.3% relative to vehicle based on clinical cure at test-of-cure (TOC) for the treatment of AOE. The trials were prospective, multicenter, randomized, double-masked, vehicle-controlled, and parallel-group in design. Enrolled patients were randomized in a 1:1 ratio to receive finafloxacin otic suspension or vehicle administered as 4 drops in the affected ear(s) twice daily for 7 days. Patients were evaluated for safety and efficacy during the four post-baseline visits: an on-therapy visit (Day 3), an end-of-therapy visit (Day 8), and a TOC visit (Day 11). Patients completed a telephone diary twice daily in which they recorded assessments of ear pain, pain medication use, and impact of ear pain on their sleep and other daily activities. In addition, patients completed an AOE treatment satisfaction questionnaire (AOE-TSQ) at the end-of-therapy visit (Day 8).

For both trials, patients aged 6 months and older, with a clinical diagnosis of AOE in at least one ear of presumed bacterial origin were enrolled. In addition, eligible patients had to have a combined numerical score of 4 or greater in at least 1 affected ear at enrollment for tenderness, erythema, and edema. Each of these 3 signs was scored as follows: none=0, mild=1, moderate=2, severe=3. The analytic plan specified adjustment for baseline otowick use.

If *Pseudomonas aeruginosa* and/or *Staphylococcus aureus* was isolated from a specimen from the enrolled ear(s) at enrollment, the patient was included in the Pathogen Positive ITT population, which was the pre-specified primary analysis population.

The primary efficacy endpoint was clinical cure at the Day 11 (TOC) Visit. A clinical cure was defined as the sum of the numerical scores of the 3 signs and symptoms of AOE (tenderness, erythema, and edema) of 0 at Day 11 (TOC). A secondary efficacy endpoint was microbiological successes at the Day 11 (TOC) visit. Microbiological success was attained if all pre-therapy bacteria were absent from the otic culture specimen at TOC. Another secondary endpoint was the median time (in days) to cessation of ear pain as reported by the patient or parent/legal guardian via the telephone diary.

A total of 686 subjects were randomized and treated at 67 centers across U.S., Canada, and Puerto Rico in Study C-10-018; 283 (41.2%) were included in the Pathogen Positive ITT population. In Study C-10-019, 548 subjects were randomized and treated at 46

centers across U.S., Canada, and Puerto Rico; 277 (50.5%) were included in the Pathogen Positive ITT population.

For the primary analysis population, there was a statistically significant treatment difference over vehicle favoring finafloxacin otic suspension for the primary efficacy endpoint (clinical cure at TOC), as well as the two secondary efficacy endpoints (microbiologic success at TOC and median time to cessation of ear pain). For the overall ITT population, a statistically significant treatment effect favoring finafloxacin was also observed for clinical cure at TOC and median time to cessation of ear pain. (see Table 1)

Table 1: Summary of the Primary and Secondary Efficacy Endpoint Results for the Pathogen Positive ITT Population (Primary Analysis Population) and the ITT Population (Source: Tables 1, 15, 19, Statistical Review, NDA 206307)

Clinical Cure at TOC – Primary Efficacy Endpoint						
	Study C-10-018			**Study C-10-019**		
	Finafloxacin	**Vehicle**	**Finafloxacin vs. Vehicle Difference (95% CI)[a]**	**Finafloxacin**	**Vehicle**	**Finafloxacin vs. Vehicle Difference (95% CI)[a]**
Pathogen Positive ITT	104/145 (71.7%)	46/138 (33.3%)	38.4% (27.6%, 49.1%)	101/147 (68.7%)	52/130 (40.0%)	28.7% (17.4%, 40.0%)
ITT	245/344 (71.2%)	173/342 (50.6%)	20.6% (13.5%, 27.8%)	194/274 (70.8%)	134/274 (48.9%)	21.9% (13.9%, 29.9%)
Microbiological Success at TOC – Secondary Efficacy Endpoint						
	Study C-10-018			**Study C-10-019**		
	Finafloxacin	**Vehicle**	**Finafloxacin vs. Vehicle Difference (95% CI)[a]**	**Finafloxacin**	**Vehicle**	**Finafloxacin vs. Vehicle Difference (95% CI)[a]**
Pathogen Positive ITT	97/145 (66.9%)	18/138 (13.0%)	53.9% (44.4%, 63.4%)	97/147 (66.0%)	15/130 (11.5%)	54.4% (45.0%, 63.9%)
Median Time (day) to Cessation of Ear Pain – Secondary Efficacy Endpoint						
	Study C-10-018			**Study C-10-019**		
	Finafloxacin	**Vehicle**	**Finafloxacin vs. Vehicle Difference (95% CI)[b]**	**Finafloxacin**	**Vehicle**	**Finafloxacin vs. Vehicle Difference (95% CI)[b]**
Pathogen Positive ITT	4.0	7.0	-3.0 (-5.0, -0.8)	3.0	6.5	-3.6 (-5.0, -2.0)
ITT	4.0	5.0	-1.0 (-2.0, -0.5)	3.0	5.5	-2.2 (-3.0, -1.0)

[a] 95% CI calculated based on normal approximation to binomial data.
[b] Difference and 95% confidence interval estimated using bootstrap procedure with 10,000 bootstrap samples, non-stratified analysis.

The applicant included a third population in their analytic plan and study report, the Culture Positive ITT population. The Culture Positive ITT population included all ITT

subjects who were culture positive (any bacterial isolate) in the study ear at baseline. The applicant proposed including the analyses for this sub-population in labeling and the Clinical Reviewer concurred. I do not agree and find the results of analyses of this sub-population difficult to interpret. My rationale for presenting the Pathogen Positive ITT population and the overall ITT population in labeling is as follows:

- The applicant's prespecified primary analysis population was the Pathogen Positive ITT population, which included all ITT subjects who had *Pseudomonas aeruginosa* and/or *Staphylococcus aureus* isolated on culture of the study ear at baseline. This is an important population as *Pseudomonas aeruginosa* is historically the most common organism isolated in cases of AOE, and is the most common pathogen associated with the serious complication of necrotizing otitis externa. *Staphylococcus aureus* is the historically the most common Gram-positive isolate in cases of AOE, and is associated with dissemination of infection to bone.
- In practice, nearly all patients presenting with AOE will be treated based on symptoms and culture will not be obtained. The ITT population is therefore closest to the patients that will be treated with the drug in clinical practice. There was a statistically significant treatment difference favoring finafloxacin otic suspension over vehicle in the ITT population, and this was considered in the review as important evidence of efficacy.
- In trials C-10-018 and C-10-019, 73 of 686 ITT patients and 68 of 548 ITT patients respectively had a negative baseline culture and were therefore not included in the Culture Positive ITT population. This is unexpected as the culture was obtained from an ear canal exudate, and may be due to sampling technique or specimen transport problems. Therefore, the meaning of non-inclusion in the Culture Positive ITT population is unclear.
- The applicant did not specify criteria, if any, used to differentiate pathogens from colonizers or contaminants, and most patient cultures were positive for more than one bacterial species. As the Clinical Microbiology reviewer noted, AOE pathogens in the ear canal reside in a balance with normal flora, and AOE may represent a disturbance in that balance. Many of the isolates in the Culture Positive ITT population such as *Staphylococcus epidermidis* and *Corynebacterium auris* are considered normal flora in cerumen, (b) (4) as these bacteria had been isolated in the Culture Positive ITT population. The applicant has not presented sufficient data to conclude that isolated organisms such as these were in fact the pathogen causing AOE.

8. Safety

The Medical Officer, CDTL, and Deputy Division Director concluded that there were no safety issues precluding approval, and I concur with this conclusion.

In trials C-10-018, C-10-019, C-10-007, and C-10-022 combined, 668 subjects received at least one dose of finafloxacin otic suspension and 623 subjects were treated with vehicle. There were no deaths reported during the studies, and only one patient in the

vehicle group experienced two serious adverse events, anxiety and gastroenteritis. There were a large number of study discontinuations in the vehicle group, and nearly all of these were attributed to treatment failure. Clinical laboratory evaluations were obtained in the PK Study, C-10-007. There was a single healthy subject who experienced a decrease in absolute neutrophil count after receiving a single dose of finafloxacin 200 mg oral tablet as well as finafloxacin otic suspension, 0.3%. The adverse event of decrease in absolute neutrophil count resolved without treatment after 12 days.

Adverse events reported in the clinical trials by greater than or equal to 1% of patients and more frequently in the finafloxacin group were ear pruritus and nausea.

No thorough QT study was conducted. ECG readings were performed for all subjects in the PK study, C-10-007. No subjects experienced a clinically relevant change in ECG findings.

DRISK concurred with the review team that the risks can be communicated through labeling and a REMS is not recommended.

9. Advisory Committee Meeting

An Advisory Committee was not convened to discuss this NDA as there were no review issues for which Advisory Committee advice was needed.

10. Pediatrics

The PeRC PREA Subcommittee discussed the application on Nov. 5, 2014. The PeRC agreed with a partial waiver for pediatric patients aged birth to less than 1 year because studies would be impossible or highly impractical. The PeRC agreed with the assessment for pediatric patients aged 1 to 17 years and concluded that PREA requirements had been fulfilled.

A Pediatric Written Request was issued for finafloxacin for the treatment of AOE on February 22, 2013. The Pediatric Written Request specified that at least 60 patients aged 1 to 13 years be studied. In trials C-10-018 and C-10-019, a total of 274 patients in this age group were enrolled. This NDA was presented at the Pediatric Exclusivity Board on August 26, 2014. The data in the NDA was found to be in compliance with the Pediatric Written Request, and exclusivity was granted.

11. Other Relevant Regulatory Issues

Two clinical sites were inspected and the final classification of these inspections was No Action Indicated. The Office of Scientific Investigations concluded that the data generated by these clinical sites appeared adequate to support the NDA.

The applicant determined there were no financial interests or arrangements to disclose regarding investigators in clinical studies C-10-018, C-10-019 and C-10-022. One

investigator in clinical trial (b) (6) received consultancy payment from the applicant. As the trial was randomized and double-masked, the review team concluded that adequate measures to reduce investigator bias were in place, and I concur with this conclusion.

There are no other unresolved relevant regulatory issues.

12. Labeling

DMEPA found the proposed proprietary name, Xtoro, acceptable.

OPDP labeling recommendations were included as appropriate.

The rationale for presenting the Pathogen Positive ITT population and the overall ITT population in labeling is described in Section 7.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action: Approval

Risk Benefit Assessment: Substantial evidence of efficacy for finafloxacin otic suspension for the indication of AOE caused by susceptible strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus* has been provided. In clinical trials, finafloxacin otic suspension was safe and well tolerated. Adverse reactions most frequently reported with finafloxacin otic suspension were ear pruritus and nausea. The product will offer another safe and effective option for the treatment of AOE.

Recommendations for Post-marketing Risk Evaluation and Mitigation Strategies: None

Recommendation for Postmarketing Requirements: None

Recommendation for Postmarketing Commitments:

> The applicant should submit the dissolution method development report with the complete data.
>
> The applicant should 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.

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

/s/

JOHN J FARLEY
12/17/2014