CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-918

CROSS DISCIPLINE TEAM LEADER REVIEW

Medical Officer/Cross-Discipline Team Leader Review
NDA 21-918

Date	April 27, 2009
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	21-918 AZ
Applicant	Parexel International (U.S. Agent for Laboratorios SALVAT, S.A.)
Date of Submission	October 31, 2008
PDUFA Goal Date	May 3, 2009
Proprietary Name / Established (USAN) names	Cetraxal (ciprofloxacin otic solution) 0.2%
Dosage forms / Strength	otic solution
Proposed Indication(s)	treatment of acute otitis externa in pediatric (age 1 year and older) and adult patients due to susceptible isolates of *Pseudomonas aeruginosa* or *Staphylococcus aureus*
Recommended:	Approval

1. Introduction

Cetraxal (ciprofloxacin otic solution) 0.2% is a sterile, aqueous-based drug product containing ciprofloxacin, a quinolone antimicrobial. Each molded single use container delivers 0.25 mL of solution equivalent to 0.50 mg of ciprofloxacin; current proposed packaging provides 14 single-use containers per foil pouch per carton.

Ciprofloxacin has in vitro activity against a variety of Gram-positive and Gram-negative bacteria. The clinical significance of this in vitro activity is not known for this specific indication except for the organisms noted in the Indications and Usage section of the final package insert, *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

The bactericidal action of ciprofloxacin results from interference with the enzyme DNA gyrase, which is needed for the synthesis of bacterial DNA.

Bacterial resistance to quinolones can develop through chromosomally- or plasmid-mediated mechanisms.

The mechanism of action of fluoroquinolones, including ciprofloxacin, is different from that of aminoglycoside, macrolide, and β-lactam antibiotics. Therefore, ciprofloxacin may be active against pathogens that are resistant to these antibiotics and these antibiotics may be active against pathogens that are resistant to besifloxacin. *In vitro* studies demonstrated cross-resistance between ciprofloxacin and some fluoroquinolones.

Acute Otitis Externa is an inflammation of the skin of the cartilaginous portion of the ear canal, the etiology of which is usually bacterial in origin. The two most characteristic presenting symptoms of otitis externa are otalgia (ear discomfort) and otorrhea (discharge in or coming from the external auditory canal).

No otic formulation containing only ciprofloxacin as an active ingredient has been approved or marketed in the USA. Formulations of ciprofloxacin 0.2% in combination with the corticosteroid hydrocortisone and ciprofloxacin 0.3% in combination with the corticosteroid dexamethasone are approved and marketed.

NDA 21-918 was submitted by Parexel International for evaluation under section 505 (b)(2) of the FD&C Act. As a 505 (b)(2) application, the applicant is relying on the FDA's previous findings of safety and effectiveness for Cipro® HC Otic (ciprofloxacin hydrochloride and hydrocortisone otic suspension) and Ciprodex® (ciprofloxacin 0.3% and dexamethasone 0.1%) Sterile Otic Suspension to provide supportive information for the proposed product. Topical preparations containing fluoroquinolones are a frequent treatment for otitis externa because they: are generally effective against both *P. aeruginosa* and *S. aureus*; are rarely associated with contact hypersensitivity; and are unlikely to have ototoxic effects.

2. Background

An Investigational New Drug (IND) application for Ciprofloxacin Otic Solution 0.2% was received in April 2004. Sponsor's representatives met with representatives of the US Food and Drug Administration (FDA) on September 29, 2003, and again via teleconference on January 14, 2004, to discuss the trial design for Protocol CIPROT III/ 03 IA 02: "A Randomized, Evaluator-Blinded Comparison of the Efficacy and Safety of Ciprofloxacin Otic Solution 0.2% with Neomycin and Polymyxin B Sulfates and Hydrocortisone [PNH] Otic Solution in the Treatment of Acute Diffuse Otitis Externa in Children, Adolescents, and Adults."

NDA 21-918 was submitted by Parexel International for evaluation under section 505 (b)(2) of the FD&C Act on June 9, 2005. Parexel International received an approvable letter dated April6, 2006, which stated that before the application could be approved, Parexel must submit a new vial configuration, stability information for the new vial, and any applicable carton and labeling changes. Based on the initial proposed drug product packaging of { —— } sealed vials, there was concern that the drug product did not distinguish itself from similar products used for alternate routes of administration i.e. nebulizer/inhalation dispensers. b(4)

3. CMC

From the CMC Reviews dated April 6, 2006, March 26, 2009, and April 28, 2009:

DRUG SUBSTANCE:

Ciprofloxacin is a synthetic fluoroquinolone antimicrobial with broad-spectrum antibacterial activity. It is a well-characterized compound that is used intravenously, orally, and topically to treat a variety of infections. The primary mode of action of the fluoroquinolones is inhibition of the bacterial gyrase enzyme. Thus, ciprofloxacin inhibits the synthesis of bacterial nucleic acids. The proposed drug product, Ciprofloxacin Otic Solution 0.2% is a sterile, preservative-free solution for otic use. Each single-dose vial of Ciprofloxacin Otic Solution 0.2% delivers 0.25 mL ciprofloxacin hydrochloride equivalent to 0.50 mg of ciprofloxacin in a sterile, preservative-free solution. The inactive ingredients are povidone, glycerin, and water for injection. Sodium hydroxide and/or lactic acid may be added to adjust pH. Ciprofloxacin is available as the monohydrochloride, monohydrate salt of l-cyclopropyl- 6-fluoro-l ,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is: $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$, molecular weight is 385.82.

The drug substance, Ciprofloxacin Hydrochloride USP, is manufactured by [redacted] S.A.. The manufacturer's complete address is listed below: b(4)

[redacted]

The synthesis, purification and controls for ciprofloxacin hydrochloride are described in [redacted] DMF [redacted] The general synthetic scheme for ciprofloxacin hydrochloride is not significantly different from other manufacturers of approved ciprofloxacin drug products. The sponsor references the DMF for a complete description of the active drug substance, including physical and chemical characteristics and stability. Ciprofloxacin hydrochloride drug substance is tested according to its USP Monograph with additional tests for Residual Solvents. A letter of authorization to access [redacted] DMF [redacted] for Ciprofloxacin Hydrochloride USP is included in the submission. b(4)

DRUG PRODUCT:

Cetraxal (ciprofloxacin otic solution) 0.2% is a sterile, aqueous-based solution manufactured and packaged vi[redacted] seal manufacturing technology. The drug product is packaged in a semi-permeable, low-density polyethylene (LDPE) single-dose vial with a deliverable volume of 0.25 mL. Ciprofloxacin is light-sensitive, and an aluminum foil overwrap pouch for protection is placed over 14 single dispensing containers ([redacted] 14 vials for a complete dosage regimen) then placed into a carton for distribution. Each vial delivers one dose of 0.25 mL or approximately 0.50 mg of ciprofloxacin. All excipients used to manufacture Cetraxal (ciprofloxacin otic solution) 0.2% are in accord with USP monographs. The drug product is not compendial; however, some of the same drug substance test methods are utilized for the drug product. b(4)

Table 1: Composition of the Drug Product

Ingredient	Amount (%) per unit dose	Functional category
Ciprofloxacin hydrochloride, USP	0.233[1]	Active
Povidone K90F USP		
Glycerin USP		
Lactic Acid USP	As needed to 4.6-4.9	
Sodium hydroxide, NF	As needed to 4.6-4.9	pH adjustment
Water for Injection, USP	qs to 0.25 mL	Vehicle for main batch

b(4)

Table 2: Specifications for CETRAXAL® (ciprofloxacin otic solution) 0.2%

Test Parameter	Acceptance Criteria	Test Method
Assay		HPLC
Related Compounds Ciprofloxacin		HPLC
Clarity	Clear	Visual
Identification (release only)	HPLC-UV spectra between nm	USP
Content Uniformity (release only)		USP<905>
Osmolarity		USP
pH	4.5-5.0	pH meter
Color		USP
Density		
Sterility		USP
Weight Loss		
Water Loss[1]		
Extractables/Leachables[2]		

b(4)

[1] In a March 2, 2009, response to the Agency, the applicant agreed to add Water Loss to the drug product specifications but proposed that the acceptance criteria for weight loss should be for all stability points.

b(4)

[2] From the CMC list of deficiencies to be transmitted to the applicant: Continue extractable/leachables monitoring on the finished drug product to the end of expiry at the long-term stability condition for the new package and labeled printing configuration.

All facilities were found acceptable for NDA 21-918 by Compliance in EES as attached at the end of the CMC reviews dated April 6, 2006, March 26, 2009, and April 28, 2009:

4. Nonclinical Pharmacology/Toxicology

From the Pharmacology/Toxicology Review dated February 13, 2006:

The applicant has requested that the Division rely on its findings of safety for previously approved otic ciprofloxacin products to support the current NDA, as described in Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. There are 2 approved otic products containing ciprofloxacin that are marketed in the U.S. They are Cipro HC Otic Suspension (0.2% ciprofloxacin and 1% hydrocortisone, approved for acute otitis externa) and Ciprodex Otic Suspension (0.3% ciprofloxacin and 0.1% dexamethasone, approved for acute otitis externa and acute otitis media with tympanostomy tubes).

SALVAT has also submitted an annotated summary of ciprofloxacin toxicity and pharmacokinetic data from the literature and reports from studies of similar, but not identical, otic products that the sponsor markets in Europe.

In short, ciprofloxacin is not ototoxic following topical otic or intratympanic exposure, and none of the topical ciprofloxacin products is a primary irritant. Additionally, ciprofloxacin products are not considered potent sensitizers.

There is no objection to the approval of this NDA based on the nonclinical information submitted in this application and the Division's findings of safety for other ciprofloxacin products.

5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review dated April 5, 2006:

The applicant did not conduct any clinical pharmacology studies to determine the systemic absorption of ciprofloxacin following administration of ciprofloxacin otic solution 0.2%. As an alternative, the sponsor based their assessment of the systemic absorption of ciprofloxacin following administration of ciprofloxacin otic solution to patients on six published studies. In these six studies, ciprofloxacin was administered as ciprofloxacin otic solution 0.2%, ciprofloxacin otic solution 0.3%, ciprofloxacin otic solution 0.5%, or ciprofloxacin 0.3%/ dexamethasone 0.1% otic suspension to one or both infected ears. The dose administered and dosing frequency varied between studies. Although not all studies stated the time when the blood sample was obtained, it was generally obtained 1-2 hrs post-dose when reported in the study. Among five studies in which the lower limit of quantitation was either 5 or 10 ng/mL,

not a single subject had detectable plasma concentrations of ciprofloxacin following multiple-dose administration.

In the sixth study, the maximum serum concentration of ciprofloxacin following single-dose administration of 4-5 drops of ciprofloxacin 0.3%/dexamethasone 0.1% otic suspension in each ear was 1.55 ng/mL (lower limit of quantitation not reported). The maximum plasma concentration reported in this study is below the lower limit of quantitation in the other studies and is consistent with their findings. The results from this study are consistent with the findings in the CIPRODEX® (ciprofloxacin 0.3%/dexamethasone 0.1%) otic suspension approved label in which the mean (SD) peak plasma concentration of ciprofloxacin following administration of 4 drops of CIPRODEX® in each ear (total dose = 0.28 mL, 0.84 mg ciprofloxacin) was 1.39 (0.880) ng/mL and ranged from 0.543 to 3.45 ng/mL. Peak serum concentrations were observed within 15 min to 2 hrs post application. Thus, the systemic absorption of ciprofloxacin following administration of ciprofloxacin otic solution is limited and plasma concentrations are anticipated to be approximately 1/1000th of those following oral administration of clinical doses (250 to 500 mg).

6. Sterility Assurance

The application is recommended for approval by the Product Quality Microbiology Reviewer in a review dated April 15, 2009.

The application as submitted does not contain a specification for endotoxin. The drug product is intended to be applied to the external ear canal and not to a mucous membrane.

7. Clinical/Statistical - Efficacy

For a detailed review of Clinical Study CIPROT III 03 IA 02, see the Medical Officer Review dated April 7, 2006.

NDA 21-918 was submitted by Parexel International for evaluation under section 505 (b)(2) of the FD&C Act. As a 505 (b)(2) application, the applicant is relying on the FDA's previous findings of safety and effectiveness for Cipro® HC Otic (ciprofloxacin hydrochloride and hydrocortisone otic suspension) and Ciprodex® (ciprofloxacin 0.3% and dexamethasone 0.1%) Sterile Otic Suspension to provide supportive information for the proposed product.

The proposed product contains a lower concentration of ciprofloxacin delivered in a higher volume of solution than the approved products Cipro® HC Otic (ciprofloxacin hydrochloride and hydrocortisone otic suspension) and Ciprodex® (ciprofloxacin 0.3% and dexamethasone 0.1%) Sterile Otic Suspension. The applicant performed a single clinical trial to provide evidence of the safety and effectiveness of Cetraxal® in the treatment of acute otitis externa.

Clinical Study CIPROT III 03 IA 02 was a randomized, evaluator-blinded comparative study designed to confirm the hypothesis that ciprofloxacin otic solution 0.2% was at least as clinically effective as the active comparator. The comparator, Neomycin Sulfate and Polymyxin B Sulfate and Hydrocortisone Otic Solution (PNH) had demonstrated efficacy against treatment of acute diffuse otitis externa in children, adolescents, and adults.

A total of 630 patients were randomized, 318 to the ciprofloxacin group and 312 to the PNH group. Safety population included 319 patients in the ciprofloxacin group and 309 in the PNH group, while the clinical intent to treat (CITT) population included 318 patients in the ciprofloxacin group and 309 in the PNH group. Approximately 22% of patients in each treatment group were excluded from the clinical intent to treat (CPP) and microbiological per protocol (MPP) populations. Only patients for whom adequate microbiological data were available were included in the MITT and MPP populations.

Analysis of Primary Endpoint(s) – Clinical Cure

Clinical Cure was defined as absence of all three clinical signs: pain, edema, and otorrhea resolved (symptom score of 0) at Visit 4 (Day 15-17).

Results for the primary efficacy endpoint are shown in the tables below for the CPP population and the CITT population. In the CPP population, 214 (86.6%) patients in the ciprofloxacin group and 197 (81.1%) in the PNH group had Clinical Cure at Visit 4. The difference between treatment groups in proportion of patients with Clinical Cure (i.e., the proportion for PNH minus the proportion for ciprofloxacin) was -5.6% (95% CI -12.1%, 0.9%). The upper limit of the 95% CI, 0.9%, was smaller than the predefined limit of 10%; thus, ciprofloxacin was non-inferior to PNH in the CPP population.

Clinical Cure at Visit 4: CPP Population

	Number (%) of Patients		Treatment difference
	Ciprofloxacin (N=247)	PNH (N=243)	(PNH-ciprofloxacin) with 95% CI
Number of patients	247	243	
Clinical Cure	214 (86.6)	197 (81.1)	-5.6 (-12.1,0.9)*
Sustained Clinical Cure	170 (68.8)	140 (57.6)	
Subsequent Clinical Cure	44 (17.8)	57 (23.5)	
Clinical Failure	33 (13.4)	46 (18.9)	

*Meets the protocol criteria for non-inferiority.

Clinical Cure at Visit 4: CITT Population

	Number (%) of Patients		Treatment difference
	Ciprofloxacin (N=318)	PNH (N=309)	(PNH-ciprofloxacin) with 95% CI
Number of patients	318	309	
Clinical Cure	259 (81.4)	237 (76.7)	-4.7 (-11.1, 1.6)*
Sustained Clinical Cure	208 (65.4)	171 (55.3)	
Subsequent Clinical Cure	51 (16.0)	66 (21.4)	
Clinical Failure	59 (18.6)	72 (23.3)	
Indeterminate	14 (4.4)	11 (3.6)	

* Meets the protocol criteria for non-inferiority.

Although Clinical Cure was defined as absence of all three clinical signs (pain, edema, and otorrhea resolved (symptom score of 0) at Visit 4), Visit 4 takes place approximately 9 days after a 7 day course of therapy. The length of time after diagnosis (16 days) raises questions about whether it is possible to distinguish an inferior drug product at this point in time.

A more useful evaluation is the secondary endpoint of Clinical Cure at Visit 3 (End of Treatment; Day 8-10 or within 2 days of early discontinuation). There was a substantial difference between treatment groups in proportions of patients with Clinical Cure at Visit 3. In the CPP population, the proportions were 70% for the ciprofloxacin group and 61% for the PNH group; in the CITT population, the proportions were 67% and 59%.

Clinical Cure at Visit 3: CPP Population

	Number (%) of Patients		Treatment difference (%)
	Ciprofloxacin (N=247)	PNH (N=243)	(PNH-ciprofloxacin) with 95% CI
Number of patients	247	243	
Clinical Cure	173 (70.0)	147 (60.5)	-9.5 (-17.9, -1.2)
Clinical Failure	74 (30.0)	96 (39.5)	
Clinical Improvement	56 (22.7)	68 (28.0)	