CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-918

SUMMARY REVIEW

Division Director Summary Memorandum

Date	April 27, 2009
From	Wiley A. Chambers, M.D.
NDA#	NDA 21-918
Applicant	Parexel International (U.S. Agent for Laboratorios SALVAT, S.A.)
Date of Submission	October 31, 2008
PDUFA Goal Date	May 3, 2009
Name	Cetraxal (ciprofloxacin otic solution) 0.2%
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*
Action:	Approval

1. Introduction

Cetraxal (ciprofloxacin otic solution) 0.2% is a sterile, aqueous-based drug product containing ciprofloxacin, a quinolone anti-infective. 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 *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.

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).

Currently, 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 literature and 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. As a topical product, the link for bioavailability is based on direct application.

2. Background

An Investigational New Drug (IND) application for Ciprofloxacin Otic Solution 0.2% was received in April 2004. 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' ——— vials, there was concern by the review team that the drug product did not distinguish itself from similar products used for alternate routes of administration i.e. nebulizer/inhalation dispensers.

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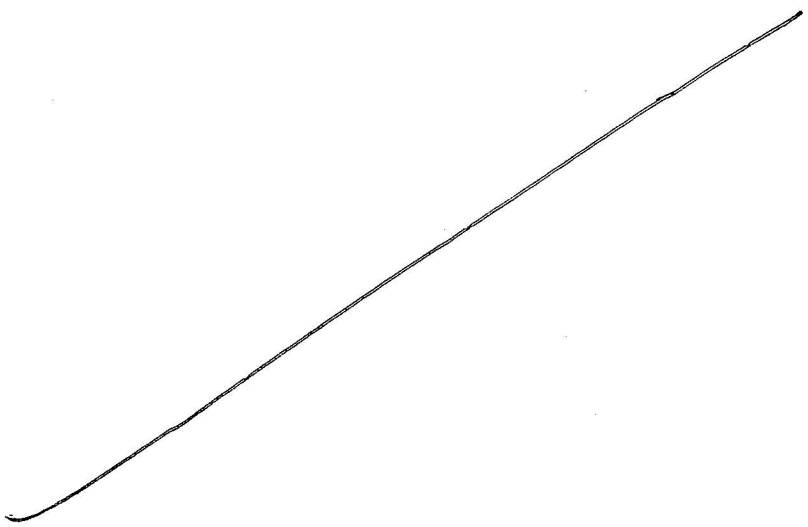
Rosenfeld et al performed a systematic review of topical antimicrobial therapy for AOE as part of a multidisciplinary, evidence-based, clinical practice guideline created by the American Academy of Otolaryngology--Head and Neck Surgery Foundation (AAO-HNSF). Their goal was to identify relevant randomized controlled trials (RCTs) and derive summary estimates of effect size by statistically pooling data from similar studies. Descriptive characteristics of 20 randomized trials included in the final data set are summarized in the following table. Year of publication ranged from 1967 to 2005, with 50% of studies published after 1994 and 25% in 2002 or later.



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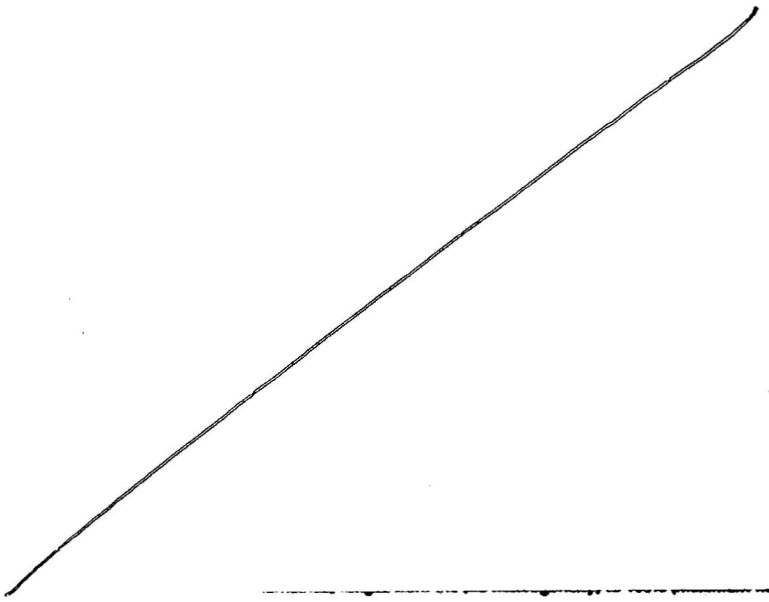

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Table 5, Rosenfeld, et al

In the preceding table, topical quinolone antibiotic and topical non-quinolone antibiotic achieved comparable clinical cure rates for AOE at 3 to 4 days, 7 to 10 days, and 14 to 28 days. Quinolones used in the meta-analyses were ofloxacin (1 study), ciprofloxacin alone (3), or ciprofloxacin combined with dexamethasone (2) or hydrocortisone (1).

In the preceding table, topical antimicrobial/steroid and topical antimicrobial alone achieved comparable clinical and bacteriologic cure rates for AOE at 7 days. Most studies were single blind, of low quality, and performed aural toilet. Antimicrobial/steroid combinations used in the meta-analyses were ciprofloxacin/hydrocortisone, ciprofloxacin/ dexamethasone, and acetic acid/triamcinolone.

Comparable clinical outcomes occur with antiseptic vs antibiotic, quinolone vs nonquinolone antibiotic, and antimicrobial vs antimicrobial plus steroid; steroid alone had better outcomes than steroid plus antibiotic. The incidence of bacteriologic cure tends to exceed the clinical response, with about 80% to 95% bacteriologic efficacy at the test of cure visit. Quinolones have slightly better bacteriologic efficacy than nonquinolone antibiotics.

3. CMC

From the CMC Reviews dated April6, 2006, March 26, 2009, and April 28, 2009

Ciprofloxacin is a well-characterized, synthetic fluoroquinolone anti-infective. 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. 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] b(4)
The manufacturer's complete address is listed below:

[redacted]

The synthesis, purification and controls for ciprofloxacin hydrochloride are described in [redacted] b(4)
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.

The drug product is packaged in a [redacted] low-density polyethylene b(4)
(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 (2 X 7 per pouch = 14 vials for a complete dosage regimen) then placed into a carton for distribution. The drug product is not [redacted] however, some of the same drug substance test methods are utilized for the drug product.

Table 1: Composition of the Drug Product

Ingredient	Amount (%) per unit dose	Functional category
Ciprofloxacin hydrochloride, USP	0.233[1]	Active
Povidone K90F USP	[redacted]	
Glycerin USP	[redacted]	
Lactic Acid USP	[redacted]	
Sodium hydroxide, NF	[redacted]	pH adjustment
Water for Injection, USP	[redacted]	

b(4)

[1]Corresponds to 0.2% ciprofloxacin base. Lactic Acid, Sodium hydroxide and Purified Water are premixed in a pH adjustment solution that is added to the main batch.

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)	NMT (of label claim) with an RSD of NMT and no unit is outside of [If outside refer to current USP]	USP<905>
Osmolarity	mOsm/Kg	USP
pH	4.5	pH meter
Color	Matching solution prepared using Fluid	USP
Density	About /mL	-
Sterility	No growth after days	USP
Weight Loss	NMT	
Water Loss	NMT	
Extractables/Leachables	report results to ppm (LOD) and ppm (LOQ)	

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All facilities were found acceptable for NDA 21-918 by Compliance.

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 1/1000* 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.

7. Clinical/Statistical - Efficacy

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

Clinical Study CIPROT IIV 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 Neomycin Sulfate and Polymyxin B Sulfate and Hydrocortisone Otic Solution (PNH). 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. 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 per protocol (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. Although the protocol defined Clinical Cure 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. Otis externa is a potentially self limited condition. Evaluation 16 days after diagnosis and 9 days after treatment may not provide the ability to distinguish between treatments and may therefore not have a justifiable non-inferiority margin. A more relevant evaluation was the secondary endpoint of Clinical Cure at Visit 3 (End of Treatment; Day 8-10 or within 2 days of early discontinuation).

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%)	147 (60%)	-9.5 (-18,-1)
Subsequent Clinical Cure	44 (17.8)	57 (23.5)	

Clinical Cure at Visit 3: 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	214 (67%)	183 (59%)	-8.1 (-16,-1)
Subsequent Clinical Cure	51 (16.0)	66 (21.4)	

As noted above, Ciprofloxacin demonstrated superiority to PNH at the end of treatment. This efficacy is not lost at subsequent evaluations.

Since previous trials in the literature and previous approvals of ciprofloxacin for a variety of indications support ciprofloxacin otic preparations for acute otitis externa, a single additional clinical trial has been considered adequate to support this application.

Clinical Microbiology – Identification of Pathogens/Microbiological Efficacy

In Clinical Study CIPROT IIV 03 IA 02, the Microbiological Per-Protocol (MPP) population[1], 174 patients in each treatment group (70% and 72% of the Clinical Per-Protocol [CPP] populations for ciprofloxacin and polymyxin B/neomycin/ hydrocortisone [PNH] groups respectively) had at least one pathogen at pre-therapy. *Pseudomonas aeruginosa* was isolated from a majority of these patients (87% in the ciprofloxacin group and 89% in the PNH group). *Staphylococcus aureus* was isolated from 13% of patients in the ciprofloxacin group and 17% in the PNH group.

The percentages of patients infected with *P. aeruginosa* and *S. aureus* in the MITT population were similar to those in the MPP population.

A central laboratory tested the sensitivity of each isolate of *S. aureus* and *P. aeruginosa* to a standard panel of antibiotics based upon Clinical and Laboratory Standards Institute (CLSI) breakpoint standards using an automated Vitek TM antibiotic microtiter panel. In addition, the central laboratory tested the sensitivity of each isolate to ciprofloxacin using a _____ created specifically for this study (the ciprofloxacin-custom" series) to determine the MIC of ciprofloxacin for each isolate. These data were then used to determine the MIC50 and MIC90 of ciprofloxacin for *S. aureus* and *P. aeruginosa*. b(4)

The MIC_{50} and MIC_{90} of ciprofloxacin are shown in the table found below. There were no differences in MIC between isolates from patients in the ciprofloxacin group and isolates from patients in the PNH group. For *P. aeruginosa*, the MIC_{50} of ciprofloxacin was 0.12 µg/mL and the MIC_{90} was 0.50 µg/mL. For *S. aureus*, the MIC_{50} was 0.25 µg/mL and the MIC_{90} was 1 µg/mL.

Ciprofloxacin MIC_{50} and MIC_{90} (µg/mL) for *P. aeruginosa* and *S. aureus* -MITT Population

		Ciprofloxacin	PNH	Total
P.aeruginosa	n	163	159	322
	MIC_{50}	0.12	0.12	0.12
	MIC_{90}	0.50	0.50	0.50
S. aureus	n	33	36	69
	MIC_{50}	0.25	0.25	0.25
	MIC_{90}	1.0	1.0	1.0

Source: Table 5, section 5.3.5.4.11, p36; Statistical Tables 4.1.1.1 and 4.1.2.1

[1] The MPP population includes all CPP patients whose Visit 1 microbiological culture yields one or more pathogens and who have microbiological results (Eradication, Presumed Eradication, Persistence, or Superinfection) from Visit 3 and/or Visit 4.