Medical Officer's Comments:

All other sections of the proposed label are reviewed in detail in section 10.2.

9.5 Comments to Applicant

The following recommendations made by the clinical reviewer should be sent to the sponsor in a letter:

Ciprofloxacin Otic Solution 0.2% is indicated for the treatment of acute otitis externa in adult and pediatric patients, one year and older, due to susceptible strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

10 APPENDICES

Protocol CIPROT III/ 03 IA 02

Title: "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"

Principal Investigator: Margaret Drehobl, M.D., Scripps Clinic, San Diego, CA

Location of Study: Up to 50 U.S. sites and 4 to 6 sites in Spain

Objectives of Study

Primary Objective

To determine whether the proportion of patients with clinical cure after 7 days of twice-daily treatment with ciprofloxacin otic solution 0.2% is non-inferior to the proportion with clinical cure after 7 days of three-times-daily treatment with PNH otic solution in children, adolescents, and adults with acute diffuse otitis externa.

Secondary Objectives

To determine whether the proportion of patients achieving each of the following endpoints after 7 days of twice-daily treatment with ciprofloxacin otic solution 0.2% is noninferior to the proportion after 7 days of three-times-daily treatment with PNH otic solution in children, adolescents, and adults with acute diffuse otitis externa:

- Clinical cure at Visit 3;
- Clinical improvement at Visit 3 and at Visit 4;
- Resolution of otalgia at Visit 3 and at Visit 4;
- Improvement in otalgia at Visit 3 and at Visit 4;
- Clinical + microbiological cure at Visit 3 and at Visit 4;
- Clinical + microbiological improvement at Visit 3 and at Visit 4;

and to assess safety, patient/caregiver and physician satisfaction, and patient compliance with ciprofloxacin and PNH therapy

Study Design: Randomized, parallel group, evaluator-blinded, active-controlled, multicenter study.

Study Summary

Patients who are diagnosed with AOE will be randomized to receive either ciprofloxacin otic solution 0.2%, 1 vial (0.25 mL) bid for 7 days, or PNH otic solution, 3 to 4 drops tid for 7 days. Investigators will perform baseline clinical and microbiologic evaluations and follow-up clinical evaluations on days 3 to 4, at the end of therapy, and at a test of cure visit. They will perform repeat cultures in patients who have ear drainage at any follow-up visit. The primary efficacy endpoint is the proportion of patients with clinical cure at the test of cure visit.

Patient Population

Pediatric and adult patients with AOE are eligible for this study. The sponsor plans to enroll 630 patients, with approximately 50% ages 2 to 12 years and approximately 50% over age 12 years.

Inclusion Criteria

Patients must be at least 2 years old and have had AOE for less than 3 weeks, with a total symptom score of at least 5 in at least 1 ear. The symptom score is the sum of ratings for otalgia, edema, and otorrhea. The minimum symptom score must be achieved as follows:

- Otalgia: at least 2 (moderate or severe);
- Edema: at least 2 (moderate or severe);
- Otorrhea: at least 1 (mild, moderate, or severe), with sufficient quantity to culture.

For patients with bilateral AOE, the ear with the higher symptom score will be the evaluable ear. If the ears have the same score, the evaluable ear will be chosen randomly. The ears will receive the same treatment.

Exclusion Criteria

Noteworthy exclusion criteria are:

1. Use of any drug, including topical drying agents, for treatment of AOE or acute otitis media within the past 36 hours;
2. Use of any quinolone within the past 30 days;
3. Use of any topical or systemic antibiotics within the past 7 days (except for long-term use of topical antibiotics for acne);
4. Chronic otitis externa or otorrhea (duration ≥3 weeks);
5. Seborrheic dermatitis of pinna or external ear canal;
6. Known perforation of tympanic membrane or perforation within the past 6 months;
7. Tympanostomy tubes in place or removed within the past 3 months;
8. Known otomycosis;
9. Mastoid disease or mastoid surgery within the past 6 months;
10. Known uncontrolled diabetes mellitus;
11. Known immunodeficiency, including AIDS, or use of immunosuppressive or cancer chemotherapeutic drugs.

Endpoints

The primary efficacy endpoint will be the proportion of clinical per protocol patients with clinical cure at Visit 4.

The secondary efficacy endpoints will be the proportions of patients with:

- Clinical cure at Visit 3;
- Clinical improvement at Visit 3 and at Visit 4;
- Resolution of otalgia at Visit 3 and at Visit 4;
- Improvement in otalgia at Visit 3 and at Visit 4;
- Clinical + microbiological cure at Visit 3 and at Visit 4;
- Clinical + microbiological improvement at Visit 3 and at Visit 4.

Clinical Endpoint Definitions

Clinical outcome categories include:

1. Clinical Cure: Pain, edema, and otorrhea resolved (symptom score of 0).

2. Clinical Improvement: Pain, edema, and otorrhea improved [symptom score of 1 if previous score was 2 or 3], and no antimicrobial therapy other than study medication is required.

3. Clinical Failure: Pain, edema, or otorrhea do not meet the definitions of Clinical Improvement; or appearance of new signs or symptoms after a minimum of 3 days of study treatment with a compliance rate of 80% or better; or treatment with antimicrobial therapy other than study medication is required.

4. Indeterminate: Discontinued (for reasons other than Clinical Failure) or lost to follow-up.

Microbiologic Endpoint Definitions

Bacterial abundance will be assessed on a scale of 1+ to 4+, per standard laboratory grading (score = 0 if the culture is sterile). To be considered a pathogen, the cultured organism must be present at a level of 2+ or higher, or may be present a level of 1+ or higher at Visit 3 or Visit 4 if bacteriologic response is Persistence as defined below.

The following species are most likely to be pathogens: *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus* (primarily beta-hemolytic strains), and Gram-negative enteric bacilli (e.g., *Enterobacter*, *Proteus*, and *Klebsiella* species).

The following bacteria are generally colonizers and will not be categorized as pathogens: alpha-hemolytic streptococci, *Bacillus* species, *Corynebacterium* species, *Lactobacillus* species, and *Propionibacterium* species. Fungi and yeasts will not be considered as pathogens.

Bacteriologic response at Visits 3 and 4 will be classified as:

- Eradication if the culture does not show growth of any pathogen;
- Presumed Eradication if there is no material to culture and the Overall Clinical Outcome is Clinical Improvement or Clinical Cure;
- Persistence if any pathogen cultured at Visit 1 is still present;
- Superinfection if a pathogen not present at Visit 1 is now present (presence of a nonpathogenic organism will not be considered Superinfection); or
- Indeterminate if none of the above definitions are met and the bacteriologic response cannot be determined.

If Overall Clinical Outcome at Visit 3 is Clinical Failure (whether or not the patient discontinues prematurely) and no bacterial culture is performed at Visit 3, the bacteriologic response at Visit 3 will be Persistence. If Overall Clinical Outcome at Visit 4 is Clinical Failure and no bacterial culture is performed at Visit 4, the bacteriologic response at Visit 4 will be Indeterminate.

Study Drug Administration

Study Drug and Dosage

Ciprofloxacin otic solution 0.2%, 1 vial (0.25 mL; 0.5 mg) instilled into the affected ear bid for 7 days

Comparator and Dosage

PNH otic solution (neomycin 3.5 mg base/mL, polymyxin B 10,000 units/mL, hydrocortisone 1%), 3 drops (for patients ≤12 years) or 4 drops (for patients >12 years) instilled into the affected ear tid for 7 days

Randomization and Blinding

At Visit 1, patients will be randomly assigned in a 1:1 ratio to treatment groups through use of an interactive voice response system. Patients will be stratified evenly into 2 age groups (≤12 years and >12 years) to ensure a sufficient number of patients in each group. A blinded evaluator will perform clinical assessments. The sponsor states that differences in appearance and use of the study drugs preclude patient or caregiver blinding.

Concomitant Medications

The use of nonstudy investigational or antimicrobial drugs or otic treatments is prohibited during the study. The protocol recommends acetaminophen or ibuprofen for analgesia; codeine is also permitted.

Study Evaluations

Visit 1 (Screening/Study Entry; Day 1)

- History
- Physical examination
- Otologic assessment
  - Ear pain (4-point scale: 0 = absent, 3 = severe)
  - Edema (4-point scale: 0 = absent, 3 = severe)
  - Otorrhea (4-point scale: 0 = absent, 3 = severe)
- Collection of culture specimen
- Dispensation of study drug and administration of first dose
- Distribution of diary card

Visit 2 (Phone Visit; Day 3-4)

- Telephone contact, with clinic follow-up if no improvement

Visit 3 (End of Treatment; Day 8-10 or within 2 days of early discontinuation)

- Otologic assessment
  - Ear pain
  - Edema
  - Otorrhea
  - Overall clinical outcome
- Collection of culture specimen if ear discharge present
- Collection of diary cards and medication containers

Visit 4 (Post-Treatment; Day 15-17)

- Otologic assessment
  - Ear pain
  - Edema
  - Otorrhea
  - Overall clinical outcome
- Collection of culture specimen if ear discharge present

Safety Considerations

Planned Laboratory Tests or Procedures

A urine pregnancy test will be obtained for female patients of childbearing potential.

Adverse Events

Adverse event information will be collected at each visit. Procedures for defining, recording, reporting and following up adverse events, including serious adverse events, are included in the protocol.

b(4)

Statistical Analyses Proposed

The sponsor based the sample size calculation on the following assumptions: two-sided tests with $\alpha = 0.05$, power of 0.80, noninferiority margin of 0.10, proportion cured 0.80, and proportion completing the study 0.80. Planned enrollment is 630 patients, which is expected to provide approximately 252 clinically evaluable per protocol patients in each treatment group.

Safety analyses will include all patients who received any study drug.

10.1 Review of Individual Study Reports

The review of efficacy and safety data can be found in sections 6 and 7. Since there was only one clinical trial performed by the sponsor, the data in sections 6 and 7 present the review of the individual study.

10.2 Line-by-Line Labeling Review

A line-by line labeling review was not performed by the clinical reviewer. Changes proposed by all reviewers were incorporated into approved labeling for the product. The following labeling was negotiated with the applicant on April 6, 2006. The only section that will need revision is the **HOW SUPPLIED** section on submission of the supplemental NDA for revised packaging for this product.

7 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Nasim Moledina
4/6/2006 02:09:45 PM
MEDICAL OFFICER
I have given a copy of the review to Janice
Final MOR for cipro otic solution 0.2%

John Alexander
4/7/2006 11:43:31 AM
MEDICAL OFFICER

Team Leader Memorandum
NDA 21-918 – Cetraxal® (ciprofloxacin otic solution) 0.2%

Cetraxal® (ciprofloxacin otic solution) 0.2% is a new product intended for the treatment of acute otitis externa in adults and pediatric patients. 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. As described in the literature and the product labels for Cipro® HC and Ciprodex®, ciprofloxacin is minimally absorbed when applied in otic drops and has few adverse effects. Because the steroid components of Cipro® HC and Ciprodex® are not known to have antimicrobial properties, the anti-microbial effect of these products is related to the ciprofloxacin component alone. However, the proposed product contains a lower concentration of ciprofloxacin delivered in a higher volume of solution than the approved products. Therefore, the applicant performed a single clinical trial to provide evidence of the safety and effectiveness of Cetraxal® in the treatment of acute otitis externa.

The study was a randomized, parallel-group, evaluator-blinded, active-controlled, multi-center study comparing ciprofloxacin otic solution 0.2% (COS) with an otic solution containing polymixin B sulfate, neomycin sulfate, and hydrocortisone (PNH). Male and female patients with acute otitis externa were entered in the trial. Baseline cultures were performed to document the presence of bacterial pathogens, and patients with current evidence or recent history of tympanic membrane perforation or tympanostomy tubes were excluded. The trial included adults and pediatric patients as young as 2 years of age. COS was administered twice daily for seven days, while PNH was given three times daily for seven days. The evaluation of treatment was performed at a test-of cure visit (about 9 days after the end of study drug treatment). Clinical cure was based on resolution of baseline signs and symptoms of infection (ear pain, edema, and otorrhea) without need for additional antimicrobial treatment.

Efficacy: The primary outcome analyses for the study, clinical cure rates at the test of cure visit in the clinical per protocol (CPP) and clinical intent-to-treat (CITT) populations, are shown in the following table.

Primary Efficacy Analysis: Clinical Cure Rates at the Test-of-Cure Visit

	COS n/N (%)	PNH n/N (%)	Treatment Difference	95% CI for Diff. (COS-PNH)
CPP Population	214/247 (86.6%)	197/243 (81.1%)	5.6%	(-0.9%, 12.1%)
CITT Population	259/318 (81.4%)	237/309 (76.7%)	4.7%	(-1.6%, 11.1%)

The results demonstrate the equivalence of ciprofloxacin otic solution, 2% with the approved comparator. The clinical outcomes for patients with the main pathogens

associated with otitis externa are shown in the next table. The microbiological per protocol (MPP) and microbiological intent-to-treat (MITT) populations are the CPP and CITT patients identified with bacteria on the baseline culture. The results show similar clinical cure rates by pathogen across the two treatment groups. The cure rates are somewhat higher for patients with *Pseudomonas aeruginosa* in the MPP population. The difference is smaller in the MITT population.

Clinical Cure Rates by Pathogen at the Test-of-Cure Visit

	COS n/N (%)	PNH n/N (%)
MPP Population		
Pseudomonas aeruginosa	133/152 (87.5%)	121/154 (78.6%)
Staphylococcus aureus	16/22 (72.7%)	22/29 (75.9%)
MITT Population		
Pseudomonas aeruginosa	160/197 (81.2%)	147/193 (76.2%)
Staphylococcus aureus	21/33 (63.6%)	23/35 (65.7%)

In post-hoc analyses of clinical cure rates in sub-populations, differences were noted in response to treatment by age. Clinical cure rates for adults and pediatric patients at the test-of cure visit are shown in the following table. The results show that cure rates in the COS group are much higher for pediatric patients than for adults. Similar results were seen when an age cut off of 12 years was used.

Clinical Cure Rates by Age Group at the Test-of-Cure Visit

	COS n/N (%)	PNH n/N (%)
CPP Population		
<18 years of age	138/147 (93.9%)	100/127 (78.7%)
≥18 years of age	76/100 (76.0%)	97/116 (83.6%)
CITT Population		
<18 years of age	157/175 (89.7%)	121/161 (75.2%)
≥18 years of age	102/143 (71.3%)	116/148 (78.4%)

The comparison across treatment groups show a wide difference (15.2%) favoring COS in pediatric patients, and a smaller difference (7.6%) favoring PNH in adults. The reasons for these differences in this trial are unclear. Results in trials of ciprofloxacin[1] and ofloxacin[2] in the literature have not shown similar results comparing quinolone treatment with PNH. Both articles showed somewhat lower cure rates in adults compared with pediatric patients across treatment groups. There is the suggestion that compliance may be greater in children, or cerumen/hair or larger canal volume in adult ears may

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[1] B Pistorius, K Westberry, M Drehobl, D Williams, T Beck, F Lucente, M Shea, R Perronesi, A Heyd, and the Otitis Externa Study Group "Prospective, Randomized, Comparative Trial of Ciprofloxacin Otic Drops, with or without Hydrocortisone, vs. Polymixin B-Neomycin-Hydrocortisone Otic Suspension in the Treatment of Acute Diffuse Otitis Externa" *Infectious Diseases in Clinical Practice*, 1999; 8:387-395

[2] R Jones, J Milazzo, M Seidlin "Ofloxacin Otic Solution for Treatment of Otitis Externa in Children and Adults" *Arch Otolaryngol Head Neck Surg*, Nov. 1997; 123(11): 1193-1200

result in poorer outcomes in adults. These factors would not explain the extreme difference by age in the COS group, while outcomes for PNH changed little. However, as a post-hoc analysis, results should be interpreted with caution.

Safety: As expected for a topical otic product with minimal systemic absorption, there were few treatment-related adverse effects (TEAE) reported in the trial. These TEAE were ear pruritus, headache, application site pain, and dizziness, as noted in the Adverse Reactions section of the proposed label. Also noted were several reports of patients with fungal otitis externa following treatment with COS. Since topical treatment with an antibacterial product may lead to overgrowth of fungi at the site, the Precautions section includes information about the potential for fungal otitis externa following COS treatment.

Since the sponsor is relying on the FDA's previous findings of safety and effectiveness for Cipro® HC and Ciprodex®, labeling for Cetraxal® should identify the adverse effects potentially related to ciprofloxacin component of these products. Based on the information in the product labeling for Cipro® HC and Ciprodex®; ear debris, ear congestion, ear tingling, decreased hearing, cough, rash, and urticaria were identified as treatment related adverse effects not already identified as adverse reactions for Cetraxal®. The product label notes these adverse reactions as other adverse reaction reported for ciprofloxacin otic products with a steroid combination.

A separate safety issue, related to the product packaging was identified during the review process. The drug product packaging for Cetraxal proposed in the initial NDA was single-dose low-density polyethylene (LDPE) vials. As noted in a consult from the Division of Medication Errors and Technical Support (DMETS), there is the potential for medication confusion because these LDPE vials are the same used for inhalation products. The sponsor agreed to change the package configuration for Cetraxal in correspondence dated March 20, 2006, based on these safety concerns. However, the applicant would not be able to provide necessary CMC information for the new vial configuration within the timeframe of the review cycle, and the sponsor stated they would not move forward with marketing the product in an interim package configuration. Therefore, the product is considered approvable until additional CMC information on the new vial configuration can be provided with final product labeling.

Conclusions: The applicant has provided substantial evidence of the safety and efficacy of Cetraxal® (ciprofloxacin otic solution) 0.2% from a single clinical trial, with supportive evidence from the FDA's previous findings of safety and efficacy for other ciprofloxacin otic preparations containing steroids. However, the sponsor has proposed changes to the drug product packaging for the product. These changes were proposed by the sponsor to address concerns about the potential for medication confusion with inhalational products. Additional CMC information is needed to support marketing approval for a new vial configuration. Therefore, the product should be considered approvable, pending additional CMC information and final labeling for the carton/container and How Supplied section of the package insert.

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/s/

John Alexander
4/7/2006 04:58:08 PM
MEDICAL OFFICER