1.3.3 Safety

Extent of Exposure

The mean duration of exposure was slightly longer than the 7 days specified in the protocol: 7.3 days for ciprofloxacin and 7.6 days for PNH. In the ciprofloxacin group, the majority (58%) of patients used study medication for 7 days as specified in the protocol, but a substantial minority (37%) used it for 8 days. In the PNH group, the majority of patients (64%) used study medication for 8 days. This may be related to the three-times-daily dosing for PNH, especially because it is likely than many patients started treatment late in the day. Very few patients used study medication for less than 7 days.

Discontinuations

Of patients who withdrew before completing the study, the largest proportion was lost to follow-up. Three patients in each treatment group were withdrawn because of adverse events. Consent was withdrawn by 1 patient in the ciprofloxacin group and 5 patients in the PNH group. Three patients in the ciprofloxacin group and 1 in the PNH group were withdrawn because of treatment failure.

Brief Summary of Adverse Events

Adverse events were reported for 92 (29%) patients in the ciprofloxacin group and 96 (31%) in the PNH group. Most of these AEs were not treatment-related and were not considered severe. Serious adverse events were reported for 2 (0.6%) patients in the ciprofloxacin group and no patients in the PNH group. There were no deaths. Very few patients (5 [1.6%] in the ciprofloxacin group and 4 [1.3%] in the PNH group) had AEs that caused discontinuation of study medication.

Treatment-related adverse events (TEAE) were events assessed as definitely, probably, or possibly related to study medication or with assessment missing. In both treatment groups, the most frequent TEAEs were Infections and Infestations, Ear and Labyrinth Disorders, Nervous System Disorders, and General Disorders and Administration Site Conditions.

The adverse events most often assessed as treatment-related were otitis externa fungal and ear pruritus. Treatment-related otitis externa fungal occurred in 7 patients in the ciprofloxacin group, and treatment-related otitis externa candida occurred in 1 patient in the ciprofloxacin group; both of these TEAEs are types of otomycosis. Treatment-related otomycosis did not occur in the PNH group. Treatment-related ear pruritus occurred in 3 patients in the ciprofloxacin group and 1 patient in the PNH group.

1.3.4 Dosing Regimen and Administration

In an international, multi-center, evaluator-blinded study, Ciprofloxacin Otic Solution 0.2% twice-daily for 7 days was studied in patients with acute, diffuse otitis externa. The contents of 1 single dispensing unit (deliverable volume: 0.25 mL) should be instilled into the affected ear twice daily for seven days. This should be the recommended dose regimen in the package insert.

1.3.5 Drug-Drug Interactions

Specific drug interaction studies have not been conducted with Ciprofloxacin Otic Solution 0.2%. Because the product is administered as otic drops, and is minimally systemically absorbed, the risk of clinically significant drug-drug interactions is extremely low. Based on the biopharmaceutical data submitted to the NDA, the 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.

1.3.6 Special Populations

The proposed label under the PEDIATRIC USE section is as follows:

b(4)

Medical Officer's Comments:

There are no data available on patients less than 2 years of age, but there are no known safety concerns in the disease process in this population that would preclude the use of this product in patients 1 year and older. There are other otic products approved by FDA such as Cipro HC that is labeled for children 1 year and older. We are not aware of any differences in efficacy and safety between children more than 2 years of age and children one year and older.

The labeling for pregnant women and nursing mothers is based on labeling for other ciprofloxacin otic products.

PREGNANCY

Teratogenic Effects. Pregnancy Category C:
Reproduction studies have been performed in rats and mice using oral doses of up to 100 mg/kg and IV doses up to 30 mg/kg and have revealed no evidence of harm to the fetus as a result of ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but no

teratogenicity was observed at either dose. After intravenous administration of doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed.

Animal reproduction studies have not been conducted with Ciprofloxacin Otic Solution 0.2%. No adequate and well-controlled studies have been performed in pregnant women. Caution should be exercised when Ciprofloxacin Otic Solution 0.2% is used by a pregnant woman.

NURSING MOTHERS

Ciprofloxacin is excreted in human milk with systemic use. It is not known whether ciprofloxacin is excreted in human milk following otic use. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Ciprofloxacin Otic Solution 0.2% is a sterile, aqueous-based drug product containing ciprofloxacin, a quinolone antibiotic. The otic solution is contained within [redacted] single-dose vials for twice-daily administration of 0.25 mL (0.50 mg ciprofloxacin). Excipients include Povidone, Glycerin, and Water for Injection; Sodium Hydroxide and/or lactic acid may be added to adjust pH. b(4)

2.2 Currently Available Treatment for Indications

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. The sponsor is relying, in part on the agency finding of safety and effectiveness for the ciprofloxacin HC 0.2% otic solution product. Another approved treatment is the combination of neomycin sulfate and polymyxin B sulfate and hydrocortisone (PNH) in an otic solution.

2.3 Availability of Proposed Active Ingredient in the United States

Ciprofloxacin is a fluoroquinolone antibiotic with broad-spectrum antibacterial activity. 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 quinolone antibiotics have been widely used in the treatment of systemic infections (e.g., pneumonia, urinary tract infections, and skin infections) and localized infections (e.g., OE and conjunctivitis). Topical fluoroquinolone preparations (in combination with steroids) are becoming a preferred 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.

2.4 Important Issues With Pharmacologically Related Products

The current package insert for ciprofloxacin addresses all the issues with ciprofloxacin and related quinolones. Since Cipro Otic 0.2% is a topical product, there is minimal absorption of the active ingredient, and previous studies of these topical otic products have provided evidence of safety of the otic use of ciprofloxacin.

2.5 Presubmission Regulatory Activity

The Sponsor filed an Investigational New Drug (IND) application for Ciprofloxacin Otic Solution 0.2% in April 2004. Representatives of the Sponsor and the contract research organization (CRO) met with representatives of the US Food and Drug Administration (FDA) on 29 September 2003 and again via teleconference on 14 January 2004 to discuss this IND. This study was planned based on the discussions at those meetings and on FDA guidance documents for antimicrobial drugs and for choice of control group and related issues in clinical trials.

2.6 Other Relevant Background Information

None

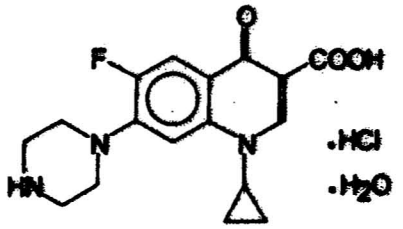
3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

According to the sponsor, the active ingredient of ciprofloxacin otic solution contains 0.233% ciprofloxacin HCl USP, equivalent to 0.2% base. The excipients are povidone, glycerin, and water for injection, with lactic acid and/or sodium hydroxide added to adjust pH. The product will be supplied in single-use polyethylene vials containing 0.25 mL drug.

Chemical Name: 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid, monohydrochloride, monohydrate

Chemical Structure:



Molecular Formula and Weight: $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$; 385.82

The Medical Officer has summarized the following relevant information from the review by Dr. Milton Sloan.:

The applicant has demonstrated via CMC data submitted in the application that this new formulation is stable throughout the proposed two year shelf life of the drug product. The manufacturing sites have all been found acceptable with the Office of Compliance. The proposed specifications have been found adequate and suitable for a quality drug product. However, concern over the newly proposed container/closure system exists. The Office of Drug Safety's Division of Medication Errors and Technical Support (DMETS) recommended against the use of the proposed LDPE [redacted] -seal container. Their concern was that this container would be mistaken for those used for oral inhalation or eye drops. DMETS noted that a number of such errors have already occurred with other products. The review team met to discuss this and a consensus was reached that this is a serious safety concern. The safety concern was communicated to the Sponsor via teleconference on March 7th 2006. Subsequently, PAREXEL International (PAREXEL) on behalf of Laboratorios SALVAT, S.A. has notified the FDA of their intent to alter the container/closure system of their pending NDA. The sponsor acknowledges that the current proposed drug product packaging does not distinguish itself from similar [redacted] sealed vials used for alternate routes of administration i.e. nebulizer/inhalation dispensers. SALVAT [redacted] Given the safety concerns noted, which could result in serious medication errors, an approvable action is recommended. b(4) b(4)

For detailed review of CMC, please refer to the review by Dr. Milton Sloan.

3.2 Animal Pharmacology/Toxicology

Refer to Dr. Amy Ellis's review dated February 10, 2006. A summary of her review is as follows:
The sponsor 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). The label for the current product would be consistent with those for the 2 approved products.
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.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This NDA (21-918) contains clinical data and information of chemistry, manufacturing, and controls supporting the use of ciprofloxacin otic solution 0.2%. Laboratorios Salvat, S.A. has conducted one Phase 3 study to evaluate ciprofloxacin otic solution for treatment of children, adolescents, and adults with acute, diffuse otitis externa. The sponsor is also relying, in part, on the Agency's previous findings of safety and effectiveness for Cipro® HC otic suspension. The Agency's previous findings of safety and effectiveness for Cipro® HC otic suspension provides supportive information that allowed for a single trial of ciprofloxacin otic solution 0.2% as the basis for approval.

4.2 Clinical Studies

Key Biopharmaceutical Studies:

The sponsor based their assessment of systemic absorption of ciprofloxacin following administration of ciprofloxacin otic solution 0.2% to patients on six published studies.

Key Clinical Study

Study CIPROT III/03 IA 02 was a randomized, parallel-group, evaluator-blinded, active-controlled, multicenter study. Six hundred twenty-eight patients (adults and children 2 years and older) were studied with acute diffuse otitis externa.

The NDA submission also contained several publications of studies conducted with different strengths, dosage and duration of ciprofloxacin otic solutions. Several published reports of studies with combination products of ciprofloxacin and hydrocortisone otic drops have been submitted too. Since none of these publications actually support efficacy and safety of ciprofloxacin otic solution 0.2% for 7 days, they were reviewed but provided little supportive data for this NDA.

4.3 Review Strategy

The review of data for the one clinical study began with detailed review of case report forms (CRF) for a 10% sample of randomly-selected patients. After blinded review of the CRF, the assessments of the reviewer were compared with those of the sponsor.

Safety review included assessment of all adverse events and analyses of AEs by various subgroups. Case-report forms of all patients that were discontinued due to an adverse event were also reviewed in detail for the one study.

4.4 Data Quality and Integrity

Based on the blinded review of the random sample, the outcome designation by the applicant of evaluable patients, cure/failure designation and reason for discontinuation in both arms of the study was similar to the outcome designation by the reviewer. It was determined that the data analyses by the applicant for the one otitis externa study were acceptable.

The Division of Scientific Investigations inspected two clinical sites that conducted study Protocol #CIPROT III IA 02 and from which data were submitted in support of NDA#21-918.

At the first site in Palm Harbor, FL (Dr. Gary Goldstein – Investigator), the FDA field investigator reviewed the case histories of 20 of the 28 subjects that were screened for the study. Source document review included informed consent forms, medical charts, progress notes, laboratory test results, and physical examination records. No significant violation was observed.

At the second site in Carmichael, CA (Dr. John Champlin – Investigator), the FDA field investigator reviewed the case histories of 16 of the 32 subjects that were screened for the study. A total of 6 patients were sited for violations. There were minor protocol violations in 5 patients. In addition to that, in 3 patients (two of those also had the protocol violations), ADRs were not reported. Patient 110-022 in the PNH arm was a clinical failure because Keflex was prescribed during the study period for worsening otitis externa. Patient 110-030 in the ciprofloxacin arm was also a clinical failure for worsening of otitis externa. The third patient 110-024 in the ciprofloxacin arm experienced increased pain and discharge but was continued in the study and was a cure at test of cure visit.

Medical Officer's Comments:

Out of 6 patients only 2 had major violations. These two patients were correctly assessed as clinical failures by the sponsor. The rest of the violations are minor, assessed correctly by the sponsor with documentation of outcomes; thus, the applicant's data is acceptable.

4.5 Compliance with Good Clinical Practices

The clinical study in this NDA involving human subjects was conducted in compliance with institutional review board regulations in 21 C.F.R. Part 56 and the informed consent regulations in 21 C.F.R. Part 50, or in accordance with the Declaration of Helsinki as referenced in 21 C.F.R. Part 312.

4.6 Financial Disclosures

There is one study for this NDA. The covered study was not funded via variable compensation and none of the investigators in this study hold any form of propriety interest in Ciprofloxacin Otic Solution 0.2%.

The applicant has examined its financial data regarding significant payments of other sorts made to all investigators in the studies and equity information as provided by the investigators, as defined in 21 CFR 54.2. None of the listed investigators had financial information to disclose.

5 CLINICAL PHARMACOLOGY

Refer to Dr. Charles Bonapace's review for this section. A part of the summary of his review is as follows:

The sponsor based their assessment of systemic absorption of ciprofloxacin following administration of ciprofloxacin otic solution 0.2% to patients on six published studies. In each of the 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. 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.

5.1 Pharmacokinetics

Refer to section 5 above and for detailed review, refer to Dr. Charles Bonapace' review. This is a topical product with minimal systemic absorption of the active ingredient, ciprofloxacin.

5.2 Pharmacodynamics

Pharmacodynamic assessments are not applicable to a locally active agent with minimal systemic absorption.

5.3 Exposure-Response Relationships

Refer to Dr. Charles Bonapace' review.