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.