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APPLICATION NUMBER:
21-918

MICROBIOLOGY REVIEW(S)

Division of Anti-Infective and Ophthalmology Products

NDA No.21-918
Ciprofloxacin Otic
Laboratorios Salvat

1 of 4
Clinical Microbiology Review #2
06 April 2009
Peter Coderre, PhD

NDA: 21-918

DATE COMPLETED: 08 April 2009

APPLICANT:

Laboratorios Salvat, SA
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08950 Espinades de Llobregat
Barcelona, Spain

CONTACT:

Parexel International
195 West Street
Waltham, MA 02451-1163
781-487-9900

CHEM/THER. TYPE: Antimicrobial

SUBMISSION REVIEWED: NDA 21-918

PROVIDING FOR: Treatment of acute diffuse otitis externa in adults and pediatric populations, one year and older, due to susceptible strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

PRODUCT NAMES:

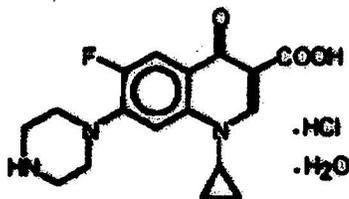
Proprietary: Cetraxal, ACROTO

Non-proprietary/USAN: Ciprofloxacin otic solution 0.2%

CAS number: [86393-32-0]

CHEMICAL NAME: 1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperaziny)-3-quinolincaroxylic acid, monohydrochloride, monohydrate

STRUCTURAL FORMULA:



MOLECULAR FORMULA AND WEIGHT: C₂₀H₂₆N₂O₇, 385.8

DOSAGE FORMULATIONS AND ROUTE OF ADMINISTRATION: A sterile, aqueous-based solution utilizing the active substance, ciprofloxacin hydrochloride. Each single-dose vial delivers one dose of 0.25 ml or approximately 0.50 mg of ciprofloxacin. The contents of one vial are instilled twice daily; therefore the total daily dose is 1 mg for a treatment regimen of seven days.

PHARMACOLOGICAL CATEGORY: Antimicrobial

DISPENSED: Rx

INITIAL SUBMISSION DATES:

Division of Anti-Infective and Ophthalmology Products

NDA No.21-918
Ciprofloxacin Otic
Laboratorios Salvat

2 of 4
Clinical Microbiology Review #2
06 April 2009
Peter Codarra, PhD

Received by CDER: 13 June 2005
Received by Reviewer: 20 June 2005
Review Completed: 31 March 2006
Label Review Completed: 08 April 2009

Related Documents: IND 67,173 SN013

Remarks:

The Applicant submitted a NDA for Ciprofloxacin Otic Solution 0.2% in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Ciprofloxacin Otic Solution 0.2% is a sterile otic solution in unit dose vials proposed for the twice daily treatment of otitis externa (OE).

The Application was approvable but required the Package Insert be formatted in the most recent format required by the Agency. What follows is a re-format of the Microbiology Section of the Package Insert.

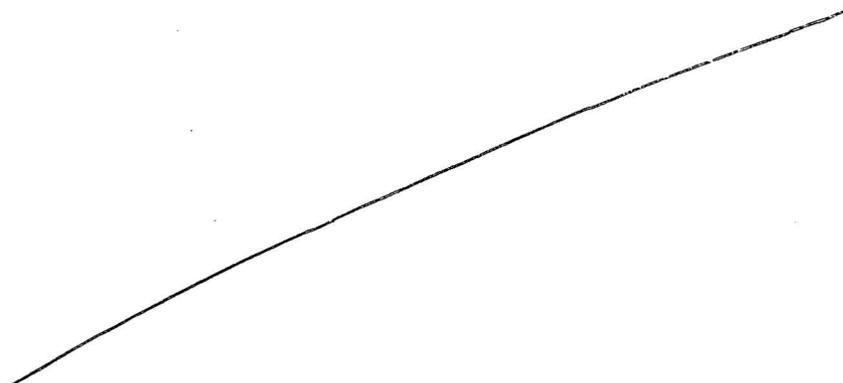
Conclusions/Recommendations:

From the Microbiology perspective, NDA 21-918 is approvable contingent upon the recommended changes to the Package Insert, as specified below.

Previously, the format of the Package Insert was as follows:

MICROBIOLOGY SECTION OF THE PACKAGE INSERT

MICROBIOLOGY



b(4)

Reviewer's comments: The above label was placed into DFS on: 31 March 2006. The following is the contents of the label placed into the most recent format. Information on resistance was taken from old labels and inserted into the proposed modified label. Changes recommended by this Reviewer are indicated as follows: additions are underlined and in blue font and ~~deletions are stricken through and in red font~~.

2 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Peter Coderre
4/29/2009 12:11:17 PM
MICROBIOLOGIST

Frederic Marsik
4/29/2009 12:14:11 PM
MICROBIOLOGIST

**Division of Anti-Infective and Ophthalmology Products
Clinical Microbiological Review # 1**

NDA: 21-918

Date Completed: March 31, 2006

Applicant:
Laboratorios Salvat, SA
Gall, 30-36
08950 Esplugues de Llobregat
Barcelona, Spain

Contact:
Parexel International
195 West Street
Waltham, MA 02451-1163
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Chem/Ther. Type: Antimicrobial

Submission Reviewed: NDA 21-918

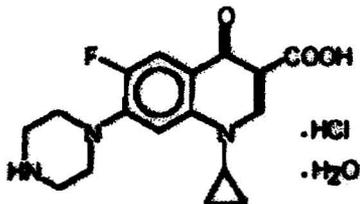
Providing for: Treatment of acute diffuse otitis externa in adults and pediatric populations, one year and older, due to susceptible strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

Product Names:

Proprietary: Cetraxal, ACEOTO
Non-proprietary/USAN: Ciprofloxacin otic solution 0.2%
CAS number: [86393-32-0]

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

Structural Formula:



Molecular Formula and Weight: C₂₂H₂₇N₃O₇, 385.8

Dosage Formulations and Route of Administration: A sterile, aqueous-based solution utilizing the active substance, ciprofloxacin hydrochloride. Each single-dose vial delivers one dose of 0.25 ml or approximately 0.50 mg of ciprofloxacin. The contents of one vial are instilled twice daily; therefore the total daily dose is 1 mg for a treatment regimen of seven days.

Pharmacological Category: Antimicrobial

Dispensed: Rx OTC

Initial Submission Dates:

Received by CDER: June 13, 2005
Received by Reviewer: June 20, 2005
Review Completed: March 31, 2006

Related Documents: IND 67,173

b(4)

Remarks:

The Applicant submits a NDA for Ciprofloxacin Otic Solution 0.2% in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Ciprofloxacin Otic Solution 0.2% is a sterile otic solution in unit dose vials proposed for the twice daily treatment of otitis externa (OE).

The Applicant discussed with the Division during several meetings, the NDA is submitted as a 505(b)2 NDA using Cipro® HC (ciprofloxacin hydrochloride and hydrocortisone otic suspension) 0.2% as the reference listed drug (RLD). In contrast to the RLD, the proposed drug product consists of a single active ingredient, ciprofloxacin hydrochloride, devoid of any corticosteroid component. Data are included from one pivotal Phase III, randomized, double-blind, multicenter (CIPROT III/03 IA 02) conducted under IND 67,173 and involving 630 adult and pediatric patients in both the US and Spain to demonstrate non-inferiority of the proposed drug product to a comparator, Polymyxin B/Neomycin/Hydrocortisone (PNH).

Ciprofloxacin is a fluoroquinolone antibiotic with broad-spectrum antibacterial activity. It is a well-characterized compound that is used intravenously, orally, and topically to treat a variety of infections. Topical formulations containing ciprofloxacin in combination with hydrocortisone and dexamethasone have been approved in the US for the treatment of OE. Otic formulations containing ciprofloxacin alone have been approved outside the US.

Conclusions/Recommendations:

From the Microbiology perspective, NDA 21-918 is approvable contingent upon the recommended changes to the Package Insert, as specified below:

MICROBIOLOGY SECTION OF THE PACKAGE INSERT

Changes recommended by this Reviewer are indicated as follows: additions are underlined and ~~deletions are stricken through~~.

MICROBIOLOGY

~~_____~~

b(4)

**NDA No.21-918
Ciprofloxacin Otic
Laboratorios Salvat**

**3 of 51
Clinical Microbiology Review**

b(4)

**APPEARS THIS WAY
ON ORIGINAL**

EXECUTIVE SUMMARY

Ciprofloxacin is a fluoroquinolone agent with broad-spectrum antibacterial activity. The bactericidal action of ciprofloxacin results from interference with the enzyme DNA gyrase, which is needed for the synthesis of bacterial DNA. Ciprofloxacin has been shown to be effective against pathogens commonly identified with otitis externa (OE), including *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

Due to their broad spectrum of antibacterial activity, fluoroquinolones are increasingly of interest in the topical treatment of common ear infections. Topical formulations containing ciprofloxacin in combination with hydrocortisone and dexamethasone (CIPRODEX®) have been approved in the US for the treatment of OE.

The Applicant submits a NDA for Ciprofloxacin Otic Solution 0.2% in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The proposed drug product consists of a single active ingredient, ciprofloxacin hydrochloride, devoid of any corticosteroid component. Ciprofloxacin Otic Solution 0.2% is a sterile otic solution in unit dose vials proposed for the twice daily treatment of OE.

The Applicant has conducted *in vitro* and clinical studies with ciprofloxacin to evaluate its antimicrobial activity. In the Core and several of the published studies, the pathogens associated with OE have been identified and, when tested, demonstrated susceptibility to ciprofloxacin. While the Applicant did not conduct *in vitro* susceptibility testing of recent clinical isolates of *S. aureus* or *P. aeruginosa*, they did submit surveillance data from SENTRY, TRUST and TSN generated within the past five years. It should be noted that recent data from the literature on susceptibility of *S. aureus* and *P. aeruginosa* to ciprofloxacin is not abundant.

A recent search of the FOCUS database by this Reviewer (16 March 2006) yielded data indicating reduced susceptibility to ciprofloxacin by both *S. aureus* and *P. aeruginosa*. These interpretations are based on the interpretive criteria established for the systemic use of ciprofloxacin. Susceptibility to ciprofloxacin in *S. aureus* decreased from 58.8% of total isolates (N=63,664) in 2005 to 57.3% of total isolates (N=5050) in 2006. Susceptibility to ciprofloxacin in *P. aeruginosa* decreased from 66.2% of total isolates (N=68,511) in 2005 to 64.1% of total isolates (N=5350) in 2006. Resistance to ciprofloxacin in *S. aureus* increased from 37.7% of total isolates (N=23,923) in 2005 to 38.3% of total isolates (N=2894) in 2006. Resistance to ciprofloxacin in *P. aeruginosa* increased from 28.1% of total isolates (N=19,281) in 2005 to 29.4% of total isolates (N=1573) in 2006. The changes in susceptibility and resistance to ciprofloxacin in both organisms were not dramatic when data from 2005 were compared to 2006.

However, when the 2005 and 2006 data are compared to the data provided in the ARM data for organisms isolated in SSTIs, ciprofloxacin resistance in *S. aureus* and *P. aeruginosa* has increased. Resistance to ciprofloxacin in *S. aureus* increased from 26.5% of total isolates in 2000 (SENTRY data) to 38.3% of total isolates (FOCUS data) in 2006. Resistance to ciprofloxacin in *P. aeruginosa* increased from 20.4% of total

isolates in 2000 (SENTRY data) to 29.4% of total isolates in 2006 (FOCUS data). The resistance data from the SSTIs may be high due to the prevalence of nosocomial infections which tend to display more antibiotic resistance than community-acquired infections. Nonetheless, the increase in ciprofloxacin resistance is disconcerting.

Cross-resistance has been observed between ciprofloxacin and other fluoroquinolones.

Evidence from the literature indicates that ciprofloxacin resistance has increased in both *P. aeruginosa* and *S. aureus*, particularly MRSA. This ciprofloxacin resistance is based upon interpretive criteria established for systemic use of ciprofloxacin. Hwang et al. report that *S. aureus* had become more common than *P. aeruginosa* in acute otitis externa in Taiwan since 1986 [29]. The incidence of MRSA had increased from 2% in 1974 to ~50% in 1997. The resistance of MRSA to ciprofloxacin has also been reported by several investigators.

Viray et al. reported that 60% of all *P. aeruginosa* isolates from three long-term care facilities were susceptible to ciprofloxacin [31]. This value is considerable less than those from isolates from previous years. Taken with the data presented from the Applicant, this would indicate that the susceptibility of *P. aeruginosa* to ciprofloxacin has decreased over time.

Results from recent investigations indicate the potential for creating fluoroquinolone resistance in *S. aureus* and *P. aeruginosa*. Gilbert et al. studied the *in vitro* development of phenotypic resistance to fluoroquinolones in single exposure and serial passage experiments with *S. aureus* and *P. aeruginosa* [30]. Based on the single passage experiments, MSSA and MRSA phenotypic resistance to ciprofloxacin develops rapidly. These investigators observed an increase in MIC₉₀ from 0.5 µg/ml at pre-serial passage for both MSSA and MRSA to post-serial passage MIC₉₀ of 64 and 128 µg/ml for MSSA and MRSA, respectively. The goal of these experiments was to study changes in the MIC over time under the influence of repeated drug exposure, as might happen clinically to the endogenous flora of the skin, nasopharynx or gastrointestinal tract.

The literature indicates an increase in resistance and decrease in susceptibility of *S. aureus* and *P. aeruginosa* to ciprofloxacin. However, the likelihood of the development of ciprofloxacin resistance during therapy is low due to the topical nature of the drug product. As ciprofloxacin is provided as a 0.2% solution, the drug would provide a ciprofloxacin concentration that is 2000 fold greater than the susceptible MIC (≤ 1 µg/ml) for either *S. aureus* or *P. aeruginosa*. Thus the likelihood of exposing these pathogens to sub-inhibitory concentrations of ciprofloxacin is extremely low and consequently, the likelihood of selecting for ciprofloxacin organisms in such an environment is extremely low.

Due to the topical nature of the drug product, the Applicant did not conduct clinical pharmacology studies due to the limited systemic exposure to the drug product. In six published studies in children and adults with ear disorders, ciprofloxacin solution at

concentrations of 0.2%, 0.3%, or 0.5%, was applied in the ear canal and blood samples were taken. Serum concentrations of ciprofloxacin were below the limit of detection.

Neither human pharmacokinetics nor animal models of efficacy studies were performed. The Applicant does not provide MIC interpretive criteria for *S. aureus* or *P. aeruginosa* susceptibility to ciprofloxacin. However, the Applicant uses the current MIC interpretive criteria used by CLSI as shown below. These criteria were applied to the clinical microbiology studies performed in the application. These interpretations are based on the interpretive criteria established for the systemic use of ciprofloxacin. These criteria are of limited use as the use of topical antibiotics is not based upon susceptibility breakpoints.

Organism	MIC ($\mu\text{g/ml}$)	Interpretation
<i>P. aeruginosa</i>	≤ 1	Susceptible (S)
and	2	Intermediate (I)
<i>S. aureus</i>	≥ 4	Resistant (R)

The Applicant provided data from one pivotal Phase III, randomized, double-blind, multicenter (CIPROT III/03 IA 02) conducted under IND 67,173 and involving 630 adult and pediatric patients in both the US and Spain to demonstrate non-inferiority of the proposed drug product to a comparator, Polymyxin B/Neomycin/Hydrocortisone (PNH).

The Applicant identified the pathogens associated with OE and their susceptibility to ciprofloxacin was tested. The most common pathogens identified were *Pseudomonas aeruginosa* followed by *Staphylococcus aureus*. This pattern was observed consistently in both the Pivotal Studies and in published studies conducted in North America, [1, 2], Europe [3-7], the Middle East [8], and Southeast Asia [9]. The exception to this was a single study in professional divers, who work in unusual environmental conditions that interfere with the skin's natural defenses against infection [10]. In that study, the primary pathogens isolated were enteric Gram-negative bacteria, which have also been associated with OE in more routine clinical settings.

Most isolates of pathogens associated with OE were susceptible to ciprofloxacin. In the Pivotal Study, 96% to 99% of isolates of *P. aeruginosa* and approximately 90% of isolates of *S. aureus* were assessed as susceptible to ciprofloxacin. In a multicenter study in the US [1], 99% of the 1089 isolates of *P. aeruginosa* and 89% of the 221 isolates of *S. aureus* were sensitive to ciprofloxacin. Results of published studies show susceptibility to ciprofloxacin in pathogens associated with OE in general [6, 9, 10] or in *P. aeruginosa* in particular [3, 7]. Since *P. aeruginosa* is the prevalent cause of infection in patients with OE, a large amount of information is available for this species. In a multicenter study in which susceptibilities to several antibiotics were compared, ciprofloxacin was found to be one of the more effective antibiotics [8]. Very few isolates of *P. aeruginosa* in any of the studies reviewed were resistant to ciprofloxacin.

MIC values were remarkably consistent between the Pivotal Study and published studies. In the Pivotal Study, MIC values for ciprofloxacin were calculated based on data from

382 isolates of *P. aeruginosa* and 68 isolates of *S. aureus*. For *P. aeruginosa*, the MIC₅₀ for ciprofloxacin was 0.12 µg/ml and the MIC₉₀ was 0.5 µg/ml. For *S. aureus*, the MIC₅₀ was 0.25 µg/ml and the MIC₉₀ was 1 µg/ml.

MIC values were also calculated in one of the published studies [1]. For *P. aeruginosa*, the MIC₅₀ of ciprofloxacin was 0.12 µg/ml and the MIC₉₀ was 0.25 µg/ml. For *S. aureus*, the MIC₅₀ was 0.5 µg/ml and the MIC₉₀ was 2 µg/ml. In a review article summarizing sensitivities of pseudomonal and staphylococcal isolates from a variety of body sites [11], the MIC₅₀ and MIC₉₀ for ciprofloxacin were reported to be 0.25 µg/ml and 0.5 µg/ml for *P. aeruginosa* and 0.5 µg/ml and 1 µg/ml for *S. aureus*.

There did not appear to be a correlation between increasing MICs and clinical failure. Only one pattern was observed that showed increasing MICs and decreasing clinical efficacy. There was a possible trend toward decreasing clinical response with increasing ciprofloxacin MIC for patients with *P. aeruginosa* treated with PNH, but no such trend was noted for patients with *S. aureus* treated with PNH. Four *S. aureus* isolates in the MITT population had MICs ≥ 4 µg/ml (ciprofloxacin resistance) but these patients were clinical successes. Three *P. aeruginosa* isolates in the MITT population had MICs ≥ 4 µg/ml (ciprofloxacin resistance) but were clinical successes. One *P. aeruginosa* isolate in the MITT population had a MIC =2 µg/ml (ciprofloxacin intermediate) but was a clinical success. Taken together, these observations suggest that MIC is not a predictor of clinical success, at least in the ciprofloxacin treatment arm.

For patients from whom a bacterial pathogen was cultured and identified before treatment and an attempt was made to perform a follow-up culture after treatment, the effects of otic treatment with ciprofloxacin solution were consistent across studies. In the Pivotal Study, the great majority of patients (between 85% and 96% of patients in the ciprofloxacin treatment group, depending on the population examined and time of assessment) had bacteriological responses of Eradication (i.e., ear canal culture did not show growth of any pathogen) or Presumed Eradication (i.e., no ear exudates to culture and the patient experienced Clinical Improvement or Clinical Cure) at Visit 3 (the end-of-treatment [EOT] visit), or at Visit 4 (the test-of-cure visit, which occurred about one week after EOT), or both. Proportions of patients with Eradication or Presumed Eradication were slightly higher for ciprofloxacin than for the comparator PNH.

In the MITT population that included both countries, *S. aureus* response to ciprofloxacin was lower than the *S. aureus* response to PNH for both the EOT and the TOC visits. Patients in the US population showed a lower response than in the Spanish population. This observation suggests PNH may be more effective than Cipro Otic against *S. aureus* particularly in the Spanish population. However, the above results suggest that ciprofloxacin is as effective as PNH against *P. aeruginosa*.

When clinical cure rates were assessed by pathogen, higher rates of clinical cure were observed in patients in the ciprofloxacin arm than in the PNH arm. Spanish patients demonstrated a higher rate of clinical cure than American patients for *S. aureus*, but not