# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-918**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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|---|---|
| NDA# | 21-918 (N-000) |
| PRODUCT | Ciprofloxacin hydrochloride |
| FORMULATION | Otic Solution 0.2% |
| SUBMISSION DATE | June 9, 2005, August 3, 2005, August 5, 2005, August 8, 2005 |
| SUBMISSION TYPE | Original 505(b)(2) New Drug Application |
| SPONSOR | Laboratorios SALVAT, S.A., Barcelona Spain |
| OCP DIVISION | Division of Clinical Pharmacology 4 |
| MEDICAL DIVISION | Division of Anti-Infective & Ophthalmology Products |
| REVIEWER | Charles R. Bonapace, Pharm.D. |
| TEAM LEADER | Venkat R. Jarugula, Ph.D. |

# CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

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## 1. EXECUTIVE SUMMARY

Parexel International, the US Agent for Laboratorios SALVAT, S.A., submitted a New Drug Application (NDA) for ciprofloxacin otic solution 0.2% 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. In support of the NDA submission, the sponsor used published ciprofloxacin data, reference to the determination of safety and efficacy of ciprofloxacin, and performed a pivotal Phase 3 clinical trial to support the safety and efficacy of ciprofloxacin otic solution 0.2% compared to neomycin sulfate, polymixin B sulfate, and hydrocortisone (PNH) otic solution in children, adolescents, and adults with acute diffuse otitis externa.

### 1.1 RECOMMENDATIONS:

The Office of Clinical Pharmacology /Division of Clinical Pharmacology 4 has reviewed NDA 21-918 and it is acceptable from a Clinical Pharmacology perspective.

The labeling comments outlined in the annotated label should be conveyed to the sponsor.

### 1.2 PHASE IV COMMITMENTS:

No Phase IV commitments are recommended.

### 1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The sponsor 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$^{th}$ of those following oral administration of clinical doses (250 to 500 mg).

Charles R. Bonapace, Pharm.D.
Office of Clinical Pharmacology
Division of Clinical Pharmacology 4

RD/FT Initialed by Venkat R. Jarugula, Ph.D.,_____
Team Leader

cc:
Division File: NDA 21-918
HFD-520 (CSO/Samanta)
HFD-520 (MO/Alexander, Moledina)
HFD-880 (Division File, Lazor, Selen, Jarugula, Bonapace)
CDR (Clin. Pharm./Biopharm.)

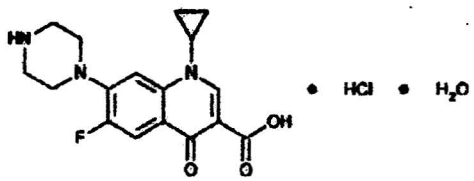
## 2. QUESTION-BASED REVIEW

Since this submission was a 505(b)(2) NDA with no clinical pharmacology studies, only the relevant questions from QBR format have been addressed below.

### 2.1 General attributes of the drug

**2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?**

Ciprofloxacin otic solution 0.2% contains the fluoroquinolone antibiotic, ciprofloxacin. The molecular formula of ciprofloxacin HCl is $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$ and the molecular weight is 385.82. The structural formula is shown below.




Ciprofloxacin otic solution 0.2% is a sterile, aqueous-based solution manufactured and packaged via ——— seal manufacturing technology. The drug product is packaged in a low-density polyethylene single-dose dispensing unit with a deliverable volume of 0.25 mL. The quantitative composition of ciprofloxacin otic solution 0.2% is shown in Table 1.

b(4)

**Table 1. Composition of ciprofloxacin otic solution 0.2% drug product per 0.25 mL**

| Ingredient | Function | Amount (%) per unit dose |
|---|---|---|
| Ciprofloxacin hydrochloride, USP | Active ingredient | 0.223%* |
| Povidone ——— USP | | |
| Glycerin, USP | | |
| Lactic acid, USP | | |
| Sodium hydroxide, NF | | |
| Water for injection, USP | | |

b(4)

*corresponds to 0.2% ciprofloxacin base

**2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?**

The primary mode of action of ciprofloxacin results from inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, both of which are required for bacterial DNA replication, transcription, repair, and recombination. Ciprofloxacin has antimicrobial activity against a wide range of Gram-positive and Gram-negative organisms.

The proposed therapeutic indication of ciprofloxacin otic solution 0.2% is for the treatment of acute diffuse otitis externa in adult and pediatric patients, one year and older, due to susceptible strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

**2.1.3 What are the proposed dosage(s) and route(s) of administration?**

The proposed dosage and route of administration for children (age 1 yr and older) and adults is the contents of a single-dose dispensing unit (deliverable volume 0.25 mL) instilled into the affected ear(s) twice daily for seven days. Ciprofloxacin otic solution 0.2% is supplied as single-use dispensing units. Each dispensing unit delivers 0.25 mL.

**2.2 General Clinical Pharmacology**

**2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?**

The sponsor relied on published studies to support the minimal absorption of ciprofloxacin following administration of ciprofloxacin otic solution to patients with otorrhea, chronic suppurtive otitis media, diffuse otitis externa, or prior to placement of tympanostomy tubes. In addition, the sponsor performed a single Phase 3 clinical trial (Study CIPROT III/03 IA 02) to assess the safety and efficacy of ciprofloxacin otic solution 0.2% compared to neomycin sulfate, polymixin B sulfate, and hydrocortisone (PNH) otic solution in children, adolescents, and adults with acute diffuse otitis externa. Patients in the ciprofloxacin arm of the study administered the contents of one dispensing unit (0.25 mL) twice daily to the affected ear(s) for seven days. Patients in the PNH arm of the study administered 4 drops three times daily (>12 yrs of age) or 3 drops daily (≤12 yrs of age) to the affected ear(s) for seven days.

**2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?**

The primary endpoint in study CIPROT III/03 IA 02 was the overall clinical outcome at the test of cure visit (study days 15-17). The clinical outcome was categorized as clinical cure (otalgia, edema, and otorrhea resolved), clinical improvement (otalgia, edema, and otorrhea improved and no antimicrobial therapy other than study medication was required), clinical failure (otalgia, edema, or otorrhea scores did not meet the definition of clinical improvement, or appearance of new signs or symptoms after a minimum of 3 days of study treatment), or indeterminate (discontinued or loss to follow-up).

**2.2.5.3 What are the characteristics of drug absorption?**

The extent of ciprofloxacin absorption was assessed in six published studies following the administration of 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 ears. The individual study reports can be found in Section 4.2 Published Study Reports. Although the dose administered and dosing frequency varied between studies, no subjects in five of the six studies had detectable plasma concentrations of ciprofloxacin (lower limit of quantitation ranged from 5 to 10 ng/mL) following multiple-dose administration. In the sixth study (n=11), the maximum serum concentration of ciprofloxacin following a 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. In addition, the results from the sixth 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.

Based on the approved label for CIPRO® (ciprofloxacin hydrochloride) tablets, the mean serum concentration of ciprofloxacin is 1.2 µg/mL and 2.4 µg/mL following single-dose administration of ciprofloxacin 250 mg and 500 mg tablets to healthy volunteers, respectively. Thus, the maximum plasma concentration of ciprofloxacin following administration of ciprofloxacin otic solution 0.2% is anticipated to be less than 0.1% of a single-dose administration of ciprofloxacin 500 mg oral tablets. Clinically relevant adverse effects associated with the systemic exposure of ciprofloxacin are not anticipated following administration of ciprofloxacin otic solution 0.2%. Please refer to the Pharmacology/Toxicity review for local toxicities.

**2.3 Intrinsic Factors**

Not applicable.

**2.4. Extrinsic factors**

Not applicable.

**2.5 General Biopharmaceutics**

Not applicable.

**2.6 Analytical Section**

**2.6.4 What bioanalytical methods are used to assess concentrations?**

The concentration of ciprofloxacin in plasma or serum was determined in the published studies using a validated HPLC assay. The lower limit of quantitation was either 5 or 10 ng/mL in five studies. The lower limit of quantitation was not reported in the sixth study but results less than 5 ng/mL were reported. It is assumed that the lower limit of quantitation in this study is less than 5 ng/mL.

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## 3. DETAILED LABELING RECOMMENDATIONS

**See Appendix 4.1. Proposed Package Insert**

# 8 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

*Withheld Track Number: Clin Pharm/Bio-* 1

**4.2 Published Study Reviews**

**4.2.1 Determination of plasma ciprofloxacin levels in children treated with topical ciprofloxacin 0.2% for tympanic perforation**

Clarós P, Sabater F. Clarós A Jr., Clarós A. Determination of plasma ciprofloxacin levels in children treated with topical ciprofloxacin 0.2% for tympanic perforation. Acta. Otorrinolaringol. Esp. 2000;51(2):142-144.

**METHODS:**
This study evaluated the safety and efficacy of topical ciprofloxacin in 30 patients aged 0 to 12 yrs with otorrhoea after transtympanic drainage or otorrhoea secondary to an infection of the middle ear secondary to a tympanic perforation, a simple chronic otitis, or a superinfected antroatticotomy cavity. Treatment with topical ciprofloxacin 0.2% was administered at the frequency of one application every twelve hrs for 7-10 days. Ten days after the start of treatment, a second visit took place and 5 mL of blood was obtained to determine plasma concentrations of ciprofloxacin. Plasma concentrations of ciprofloxacin were quantitated using a high-performance liquid chromatography (LLOQ is 5 ng/mL).

**RESULTS:**
Of the 30 children included in the study, a cure (absence of otorrhoea at the control visit) was observed in 25 cased (83.3%). Of the 5 cases considered as therapeutic failures, marked signs of otorrhoea persisted in three cases (10%) and phlogotic signs of the ear in two cases (6.7%). None of the 30 subjects had detectable concentrations of ciprofloxacin in plasma 10 days after the start of treatment.

**AUTHOR'S CONCLUSION:**
Ciprofloxacin was not absorbed through the mucosa of the middle ear and it can be used in the pediatric population without the risk of producing systemic adverse events.

**COMMENTS:**
1. The number of ciprofloxacin drops administered in each ear and the number of ears treated are not stated in the published study. Thus, the reviewer is not able to compare the results from this study to other studies since the administered dose of topical ciprofloxacin 0.2% is unknown.

2. It appears that patients received 7-10 days of topical ciprofloxacin 0.2% therapy, whereas a blood sample was obtained 10 days after the start of treatment. Since the time the blood sample was obtained in relation to the dosing (or last dose) of ciprofloxacin is not stated, it is possible that several days may have passed before a blood sample was collected. Although the amount of ciprofloxacin absorbed may be minimal, this study does not support the statement that topical ciprofloxacin 0.2% is not absorbed since the concentration of ciprofloxacin may be less than the lower limit of quantitation.

**4.2.2 Controlled multicenter study on chronic suppurative otitis media treated with topical applications of ciprofloxacin 0.2% solution in single-dose containers or combination of polymixin B, neomycin, and hydrocortisone suspension**

Miró N and the Spanish ENT Study Group. Controlled multicenter study on chronic suppurative otitis media treated with topical applications of ciprofloxacin 0.2% solution in single-dose containers or combination of polymixin B, neomycin, and hydrocortisone suspension. Otolaryngol. Head Neck Surg. 2000;123(5):617-623.

**METHODS:**
This study was a prospective, randomized, open-label, comparative, multicenter clinical trial of patients aged 14 to 71 yrs with chronic suppurative otitis media (CSOM). Patients were randomly allocated to receive ciprofloxacin sterile and preservative-free 0.2% solution (CIP) 0.5 mL twice daily for 10 days or polymixin B sulfate, neomycin, and hydrocortisone suspension (PNH) 0.15 mL four times daily for 10 days.

To evaluate the potential systemic absorption of topically applied ciprofloxacin, researchers in one center drew a 10-ml blood sample from patients 1-2 hrs after the first dose. Plasma concentrations of ciprofloxacin were analyzed using a validated high-performance liquid chromatography method. The lower limit of quantitation was 10 ng/mL.

**RESULTS:**
Three hundred and twenty-eight patients were enrolled and 322 patients were randomly allocated to study treatments. In the per protocol population, 108 of 119 (91%) patients in the CIP group and 98 of 113 (87%) patients in the PNH group were cured at visit 2. The rate of eradication (including presumed eradication) was 79% in the CIP group and 76% in the PNH group. The bacteriologic outcome was classified as indeterminate in 38 patients (20 in the CIP group and 18 in the PNH group). The concentrations of ciprofloxacin in plasma were below the limit of quantitation among the 14 subjects (9 CIP, 5 PNH) from whom blood was drawn 1-2 hrs after the first dose.

**COMMENTS:**
1. Previous studies have demonstrated that peak concentrations of ciprofloxacin following ototopical administration typically occur within 15 min and 2 hrs following administration. Thus, the timing of the blood samples are adequate to assess the absorption of ciprofloxacin. The absorption of ciprofloxacin following topical administration of 0.5 mL ciprofloxacin 0.2% twice daily is minimal since plasma concentrations were less than the lower limit of quantitation (10 ng/mL).

**4.2.3 Study to determine plasma levels of ciprofloxacin after the administration of ciprofloxacin 0.3% ear drops in children with diffuse otitis externa**

García-Monge E, Sabater F. Study to determine plasma levels of ciprofloxacin after the administration of ciprofloxacin 0.3% ear drops in children with diffuse otitis externa. Pediatria Rural Y Extrahospitalaria. 1997;27(249):3-8.

**METHODS:**
This was a prospective, open-label study of 12 male and female children (6 male, 6 female) aged 3 to 11 yrs with diffuse otitis externa to determine the plasma concentrations of ciprofloxacin after the administration of topical ciprofloxacin 0.3% ear drops. Each subject received five drops of ciprofloxacin 0.3% every 8 hrs for 8 days in the infected external ear canal (not specified whether administered to one or both ears). At the end of treatment visit on day 8, a blood sample (6 mL) was obtained from each subject to determine the plasma concentration of ciprofloxacin. Plasma concentrations were determined using liquid chromatography with fluorescence detection. The lower limit of quantitation was 5 ng/mL.

**RESULTS:**
In the 12 children studied, the diffuse otitis externa was clinically cured in all cases (100% cure rate). All plasma concentrations were below the limit of quantitation (5 ng/mL).

**AUTHOR'S CONCLUSION:**
The efficacy of topical ciprofloxacin in the treatment of diffuse otitis external in children together with the practical absence of adverse reactions and the non-absorption of the drug make it the drug of choice in the topical treatment of otitis external in children.

**COMMENTS:**
The amount of ciprofloxacin absorbed in this study appears to be minimal. Since the time in which blood samples were obtained in relation to the administration of ciprofloxacin was not stated, ciprofloxacin concentrations may have been greater if obtained within 2 hrs after drug administration.

**4.2.4 Topical ciprofloxacin for otorrhea after tympanostomy tube placement**

Force RW, Hart MC, Plummer SA, Powell DA, Nahata MC. Topical ciprofloxacin for otorrhea after tympanostomy tube placement. Arch. Otolaryngol. Head Neck Surg. 1995;121(8):880-884.

**METHODS:**
This was a non-randomized, open-label study of 10 children (11 infected ears) aged 3 to 8 yrs with chronic suppurative otitis media to evaluate the safety, efficacy, and systemic absorption of ciprofloxacin following the administration of ototopical ciprofloxacin 0.3%. Each subject received three drops (approximately 0.060 mL) of ciprofloxacin 0.3% three times daily for 14 days. On day 7, a blood sample (~1 mL) was obtained from each subject just before and 1 hr after the dose was administered. Plasma concentrations were determined using high-performance liquid chromatography with fluorescence detection. The lower limit of quantitation was 5 ng/mL.

**RESULTS:**
Of the 11 infected ears (in 10 patients), 10 (in nine patients) were cured or improved at 7 days. Ten of 11 ears were completely cured at 2 weeks. Blood samples to determine the trough ciprofloxacin concentrations were available for eight of the 10 patients. Peak ciprofloxacin concentrations were available for seven of the 10 patients. The concentration of ciprofloxacin was below the lower limit of quantitation for all of these samples.

**AUTHOR'S CONCLUSION:**
Ciprofloxacin drops were effective in nine of the 10 children (10 of 11 infected ears). None of the children developed adverse events attributed to topical ciprofloxacin and the plasma concentration of ciprofloxacin were below the lower limit of quantitation in the plasma samples.

**COMMENTS:**
Based on the results from previous studies, the peak concentration of ciprofloxacin is likely to occur at approximately 1 hr following ototopical administration of ciprofloxacin. Thus, the timing of the blood samples is adequate to assess the absorption of ciprofloxacin. The absorption of ciprofloxacin following ototopical administration of ciprofloxacin 0.3% three times daily is minimal since plasma concentrations were less than the lower limit of quantitation (5 ng/mL).

**4.2.5 Prospective randomized double-blind study of the effectiveness and tolerance of topical ciprofloxacin versus topical gentamicin in the treatment of simple chronic suppurative otitis media and diffuse otitis externa**

Sabater F, Maristany M, Mensa J, Villar E, Traserra J. Prospective randomized double-blind study of the effectiveness and tolerance of topical ciprofloxacin versus topical gentamicin in the treatment of simple chronic suppurative otitis media and diffuse otitis externa. Acta. Otorrinolaringol. Esp. 1996;47(3):217-220.

**METHODS:**
This was a prospective, double-blind, randomized study conducted with topical ciprofloxacin at a concentration of 5 mg/mL (0.5%), at a dose of five drops three times a day (Group A) and topical gentamicin at a concentration of 3 mg/mL (0.3%) at a dose of three times a day (Group B). Each treatment was administered for 8 days.

One subgroup included 47 patients with chronic suppurative otitis media. Twenty patients were treated with ciprofloxacin and 27 with gentamicin. Another subgroup included 54 patients with diffuse otitis externa and otoscopic signs of otitis externa. Of the 54 patients, 30 were assigned to the group treated with ciprofloxacin and 24 with gentamicin. In the subgroup of patients affected by chronic otitis media, blood samples from five patients treated with ciprofloxacin were analyzed to determine the plasma concentrations of the drug. The concentration of ciprofloxacin was determined using high performance liquid chromatography. (LLOQ not stated).

**RESULTS:**
Both treatments were effective for the treatment of chronic otitis media. The percentage of clinical cures (complete disappearance of otorrhoea) was 80% with ciprofloxacin and 74% with gentamicin. The final overall assessment of the efficacy of the treatment was 95% success with ciprofloxacin and 96.3% with gentamicin. In the group of patients affected with diffuse otitis externa, the overall percentage of success was 87% with ciprofloxacin and 79% with gentamicin. In five patients from the group with chronic otitis media treated with ciprofloxacin, the concentration of ciprofloxacin in blood samples was below the lower limit of quantitation.

**AUTHOR'S CONCLUSION:**
Following topical administration of ciprofloxacin otic ear drops, there appears to be no absorption through the ear mucosa which means that the drug can be used in children less than 18 yrs of age.

**COMMENTS:**
1. The time blood samples were obtained from the chronic otitis media group treated with ciprofloxacin was not stated. In addition, the lower limit of quantitation for the assay was not stated, making it difficult to compare the results from this study to other published studies which have shown that ciprofloxacin concentrations are below the lower limit of quantitation (5 or 10 ng/mL) following ototopical administration.

**4.2.6 New quinolone/steroid combination for topical treatment of acute otitis: Early- and late-phase study results**

Conroy PJ. New quinolone/steroid combination for topical treatment of acute otitis: Early- and late-phase study results. Ear Nose Throat J. 2003;82(8 Suppl 2):2-4.

**METHODS:**
In a randomized, controlled, double-blind, Phase 1/2 study, ciprofloxacin 0.3%/dexamethasone 0.1% otic suspension was administered to 11 patients aged 1 to 12 yrs who were undergoing surgical incision for the placement of tympanostomy tubes. Patients received a single dose of 4 or 5 drops in each ear immediately following tube insertion. Serum concentrations of ciprofloxacin and dexamethasone were measured six times over a 6-hr period (times not specified).

**RESULTS:**
Maximum serum concentrations of ciprofloxacin and dexamethasone were 1.55 ng/mL and 0.86 ng/mL, respectively. The respective half-life of each drug was 2.9 and 2.8 hrs.

**COMMENTS:**
The limit of quantitation of the ciprofloxacin analytical methods was not stated in the study. However, the results from this study are consistent with those reported in the Ciprodex (ciprofloxacin 0.3%/dexamethasone 0.1%) otic suspension approved label.

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