

Clinical Review
Nasim Moledina, M.D.
NDA 21-918
Ciprofloxacin 0.2% Otic Solution

Safety Conclusions

The adverse event profile in this study was typical for the patient population. Most TEAEs were mild and not related to study medication. Several patients treated with ciprofloxacin developed otomycosis after completing their course of study treatment, and the majority of these events were considered related to study medication. Otomycosis following topical otic fluoroquinolone therapy has been reported previously and is not an unexpected finding. All SAEs, and all AEs leading to discontinuation in the ciprofloxacin group, were assessed as not related to study medication. There were no clinically relevant trends in vital signs or physical examination findings. In conclusion, results from this study did not suggest any new or unexpected safety concerns related to the use of ciprofloxacin otic solution 0.2%.

7.1.5.1 Eliciting adverse events data in the development program

Refer to Section 7.1 methods.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Refer to Section 7.1.

7.1.5.3 Incidence of common adverse events

Refer to Section 7.1.5.

7.1.5.4 Common adverse event tables

Refer to Section 7.1.5.

7.1.5.5 Identifying common and drug-related adverse events

Refer to Section 7.1.5.

7.1.5.6 Additional analyses and explorations

None

7.1.6 Less Common Adverse Events

Refer to Section 7.1.5.

7.1.7 Laboratory Findings

Clinical Laboratory Evaluation

Clinical laboratory tests were not performed as part of this study.

Clinical Review
Nasim Moledina, M.D.
NDA 21-918
Ciprofloxacin 0.2% Otic Solution

7.1.7.1 Overview of laboratory testing in the development program

N/A

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

N/A

7.1.7.3 Standard analyses and explorations of laboratory data

N/A

7.1.7.4 Special assessments

Not done

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

There were no clinically relevant differences between treatments groups. Changes from Visit 1 to Visit 4 showed no clinically relevant trends.

Physical Examination Findings

Most patients had abnormal findings at Visit 1 and normal findings at Visit 4 for the ear. In the other body systems, the large majority of patients had normal findings at both Visit 1 and Visit 4. There were no clinically relevant differences between treatment groups.

7.1.8.2 Additional analyses and explorations

None

7.1.9 Electrocardiograms (ECGs)

Not done

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

N/A

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Clinical Review
Nasim Moledina, M.D.
NDA 21-918
Ciprofloxacin 0.2% Otic Solution

N/A

7.1.9.3 Standard analyses and explorations of ECG data

N/A

7.1.9.4 Additional analyses and explorations

Not done

7.1.10 Immunogenicity

N/A

7.1.11 Human Carcinogenicity

Refer to the current label for ciprofloxacin products.

7.1.12 Special Safety Studies

There are no special safety studies for ciprofloxacin otic solution.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Ciprofloxacin does not have the potential to be a drug of abuse.

7.1.14 Human Reproduction and Pregnancy Data

7.1.15 Assessment of Effect on Growth

N/A

7.1.16 Overdose Experience

None.

7.1.17 Postmarketing Experience

Ciprofloxacin otic solution 0.2% has been approved for marketing in Spain as of the time of this submission, but no postmarketing data for this product is available. Relevant information obtained for previous postmarketing experience with other ciprofloxacin otic formulations is reflected in the labeling of those products.

Clinical Review
 Nasim Moledina, M.D.
 NDA 21-918
 Ciprofloxacin 0.2% Otic Solution

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Table 31: Summary of Analysis Populations: All Randomized Patients

Category	Number (%) of Patients		
	Ciprofloxacin (N=318)	PNH (N=312)	Total (N=630)
Safety population*	319 (100.3)	309 (99.0)	628 (99.7)
Clinical Intent-to-Treat population*	318 (100.0)	309 (99.0)	627 (99.5)
Clinical Per-Protocol population [†]	247 (77.7)	243 (77.9)	490 (77.8)
Microbiological Intent-to-Treat population [‡]	232 (73.0)	217 (69.6)	449 (71.3)
Microbiological Per-Protocol populations [§]	174 (54.7)	174 (55.8)	348 (55.2)

* Randomized patients who received at least 1 dose of study medication. Note: One patient randomized to receive PNH actually received ciprofloxacin otic suspension. This is the reason that the number of patients in the safety population for ciprofloxacin is one higher than the number of patients randomized to receive ciprofloxacin.

* Randomized patients who received 80%-120% of the doses of study medication and completed Visit 3 and Visit 4 (unless the patient's outcome was Clinical Failure at an earlier visit than Visit 4), excluding those patients who had any protocol deviations.

[†] CITT patients whose Visit 1 microbiological culture yielded 1 or more pathogens.

[§] CFP patients whose Visit 1 microbiological culture yielded 1 or more pathogens and who had microbiological results from Visit 3 and/or Visit 4.

7.2.1.2 Demographics

Demographic and Other Baseline Characteristics

Demographic characteristics of the Safety population are summarized in Table 32.

Approximately half of the patients were male; however, there were more males in the ciprofloxacin group (55%) than in the PNH group (45%). The age and ethnic compositions of the two treatment groups were very similar. Mean age was approximately 24 years; median age was 14 years in the ciprofloxacin group and 15 years in the PNH group. Slightly less than half of the patients were 12 years old or younger. Slightly more than half of the patients were under 18 years old. Almost three-quarters of the patients participated in the study in the US, and the remainder participated in Spain. The majority (approximately 87%) of patients were Caucasian; approximately 7% were Hispanic; approximately 3% were black; and the remainder were Asian or of other ethnic groups.

Disease characteristics are shown in Table 33 for the Safety population. In both treatment groups, approximately 11% of patients had bilateral OE and approximately 9% used ear wicks. The proportion of patients who underwent irrigation of the ear was small in both treatment groups, but was slightly larger in the ciprofloxacin group (8%) than in the PNH group (6%).

Table 32: Demographic Characteristics: Safety Population

		Ciprofloxacin (N=319)	PNH (N=309)	Total (N=628)
Age, years	Mean (SD)	23.5 (18.8)	23.9 (18.6)	23.7 (18.7)
	Median	14	15	15
	Min, Max	2, 83	2, 76	2, 83
Age category, n (%)	≤12 years	145 (45.5)	131 (42.4)	276 (43.9)
	>12 years	174 (54.5)	178 (57.6)	352 (56.1)
	<18 years	175 (54.9)	161 (52.1)	336 (53.5)
	≥18 years	144 (45.1)	148 (47.9)	292 (46.5)
Sex, n (%)	Male	176 (55.2)	140 (45.3)	316 (50.3)
	Female	143 (44.8)	169 (54.7)	312 (49.7)
Country, n (%)	United States	233 (73.0)	222 (71.8)	455 (72.5)
	Spain	86 (27.0)	87 (28.2)	173 (27.5)
Race, n (%)	Caucasian	281 (88.1)	266 (86.1)	547 (87.1)
	Hispanic	21 (6.6)	22 (7.1)	43 (6.8)
	Black	11 (3.4)	10 (3.2)	21 (3.3)
	Asian	2 (0.6)	4 (1.3)	6 (1.0)
	Other	4 (1.3)	7 (2.3)	11 (1.8)

Table 33: Otitis Externa Characteristics: Safety Population

		Cipro (N=319)	PNH (N=309)	Total (N=628)
Bilateral disease, n (%)	Yes	35 (11.0)	35 (11.3)	70 (11.1)
	No	284 (89.0)	274 (88.7)	558 (88.9)
Use of ear wicks, n (%)	Yes	30 (9.4)	27 (8.7)	57 (9.1)
	No	289 (90.6)	282 (91.3)	571 (90.9)
Irrigation of ear, n (%)	Yes	25 (7.8)	18 (5.8)	43 (6.8)
	No	294 (92.2)	291 (94.2)	585 (93.2)

7.2.1.3 Extent of exposure (dose/duration)

Duration of exposure to study medications is summarized in Table 34. 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 that many patients started treatment late in the day. Very few patients used study medication for less than 7 days.

Table 34: Extent of Exposure to Study Medication: Safety Population

	Ciprofloxacin (N=319)	PNH (N=309)
Duration of treatment (days)		
Number of patients	304	302
Mean	7.3	7.6
Median	7	8
Number of days	Number (%) of patients taking study medication for this number of days	
1	0	3 (1.0)
2	1 (0.3)	0
3	2 (0.7)	5 (1.7)
4	2 (0.7)	2 (0.7)
5	0	1 (0.3)
6	5 (1.6)	5 (1.7)
7	176 (57.9)	83 (27.5)
8	113 (37.2)	192 (63.6)
>8	5 (1.6)	11 (3.6)

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

N/A

Clinical Review
Nasim Moledina, M.D.
NDA 21-918
Ciprofloxacin 0.2% Otic Solution

7.2.2.2 Postmarketing experience

Ciprofloxacin Otic Solution 0.2% has been approved for marketing in Spain as of the time of this submission, but postmarketing data are not available.

7.2.2.3 Literature

The applicant has submitted copies of 39 literature articles with this submission, but all of the articles reviewed report on studies with a different strength of ciprofloxacin otic solution than the one in the proposed labeling. The relevance of efficacy data from the literature references is limited since most of the studies cited use a higher concentration of ciprofloxacin otic solution and also ciprofloxacin is used in combination with steroids; thus, the data from these articles can not be used to support the clinical efficacy for the indication of acute diffuse otitis externa. The safety data are similar to that reported from the one study in this NDA.

7.2.3 Adequacy of Overall Clinical Experience

The data from one Phase 3 study included 304 patients who received ciprofloxacin otic solution 0.2% and 302 patients who received the comparator PNH. The sponsor is also relying in part on the FDA's previous findings of safety and effectiveness for other ciprofloxacin otic preparations, and that the product has minimal systemic absorption, so few systemic side effects are expected.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

None were submitted to this NDA, and the sponsor is relying on previous experience with other ciprofloxacin otic products to address the above issues. For detailed review, please refer to the pharmacology/toxicology review by Dr. Amy Ellis.

7.2.5 Adequacy of Routine Clinical Testing

Reference is made to clinical review section 6.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

There is adequate information submitted to this NDA, and previous experience of other otic products to adequately conclude that there is minimal absorption of ciprofloxacin otic solution 0.2%. Refer to Biopharmaceutics review by Dr. Charles Bonapace for details.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The study procedures were adequate to identify potential adverse effects of the drug product. There are no recommendations to perform additional studies.

Clinical Review
Nazim Meledina, M.D.
NDA 21-918
Ciprofloxacin 0.2% Otic Solution

7.2.8 Assessment of Quality and Completeness of Data

Refer to detailed review by DSI, and summary in section 4.4. There is adequate information in the NDA submission to fully assess the results of the study.

7.2.9 Additional Submissions, Including Safety Update

No additional safety data were submitted.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Refer to section 7 for details.

8 ADDITIONAL CLINICAL ISSUES

8.1 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.

8.2 Drug-Drug Interactions

Specific drug interaction studies have not been conducted with Ciprofloxacin Otic Solution 0.2%. Because there is minimal systemic absorption of ciprofloxacin, the potential for drug interactions is extremely small.

8.3 Special Populations

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

b(4)

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

Clinical Review
Nasim Moledina, M.D.
NDA 21-918
Ciprofloxacin 0.2% Otic Solution

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.

8.4 Pediatrics

b(4)

Medical Officer's Comments:

There are no data available for children less than 2 years of age. But based on the previous experience with other otic preparations like cipro HC, there are no differences in outcomes expected between children more than 2 years of age and children between ages of 1 year and 2 years. Thus, the above section is acceptable.

8.5 Advisory Committee Meeting

There are no plans for an Advisory Committee.

8.6 Literature Review

Refer to section 7.2.2.3.

8.7 Postmarketing Risk Management Plan

None

8.8 Other Relevant Materials

Clinical Review
Nasim Moledina, M.D.
NDA 21-918
Ciprofloxacin 0.2% Otic Solution

None

9 OVERALL ASSESSMENT

9.1 Conclusions

Ciprofloxacin otic solution 0.2% administered twice daily for 7 days was found to be non-inferior to the approved comparator, neomycin sulfate and polymyxin B sulfate and hydrocortisone otic solution, for the treatment of acute diffuse otitis externa in children, adolescents, and adults.

Ciprofloxacin otic solution 0.2% was effective against the 2 primary bacterial pathogens associated with acute diffuse otitis externa, *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

Ciprofloxacin otic solution 0.2% was well tolerated when administered topically to children, adolescents, and adults with OE.

9.2 Recommendation on Regulatory Action

Based on the review of safety and efficacy data submitted in this NDA, the following recommendations are made by the Medical Officer:

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*.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Given prior experience with ciprofloxacin otic products, no special risk management activity is required.

9.3.2 Required Phase 4 Commitments

No clinical Phase 4 commitments are recommended.

9.3.3 Other Phase 4 Requests

None requested.

9.4 Labeling Review

Clinical Review
Nasim Moledina, M.D.
NDA 21-918
Ciprofloxacin 0.2% Otic Solution

In the INDICATIONS AND USAGE section, the following is proposed:

INDICATIONS AND USAGE

Ciprofloxacin Otic Solution 0.2% is indicated for the treatment of acute _____ otitis externa _____ due to susceptible strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

Medical Officer's Comments:

The above paragraph is acceptable, except delete ' _____ ' from the first sentence.

Under the WARNINGS section, the following is proposed:

WARNINGS

b(4)

Medical Officer's Comments:

The above statement should be revised as follows:

**"Ciprofloxacin Otic Solution 0.2% is for otic use only.
NOT FOR OPHTHALMIC USE. NOT FOR INHALATION. NOT FOR INJECTION."**

Under PRECAUTIONS section for GENERAL subsection, add the following add the second sentence of the first paragraph:

b(5)

Under PRECAUTIONS section for INFORMATION FOR PATIENTS subsection, the second sentence should read:

b(5)

Clinical Review
Nasim Meledina, M.D.
NDA 21-918
Ciprofloxacin 0.2% Otic Solution

Under **PEDIATRIC USE** section, _____

b(5)

Under **ADVERSE REACTIONS**, the following should be added to the table in that section:

b(5)

b(5)

In the **DOSAGE AND ADMINISTRATION** section, the following is proposed:

b(4)

Medical Officer's Comments:

b(5)

The _____ should be revised to read _____

The first sentence of the second paragraph under **DOSAGE AND ADMINISTRATION** should be revised as follows:

The solution should be warmed, by holding the _____ in the hand for at least 1 minute, to avoid the dizziness that may result from the instillation of a cold solution into the ear canal.

b(5)

The **CLINICAL STUDIES** section of the labeling should be revised as follows:

CLINICAL STUDIES

b(5)

2 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

✓ Draft Labeling (b5)

 Deliberative Process (b5)