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21-918

MEDICAL REVIEW(S)

CLINICAL REVIEW

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Established Name Ciprofloxacin Otic Solution 0.2%
(Proposed) Trade Name Cetraxal[®]
Therapeutic Class Fluoroquinolone
Applicant Parexel International (US Agent
for Laboratorios SALVAT, S.A.)

Priority Designation S

Formulation Otic Drops
Dosing Regimen 0.25 mL twice daily for 7 days
Indication Acute Otitis Externa
Intended Population Adult and Pediatric patients

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Based on the initial proposed drug product packaging of _____ sealed vials, the sponsor acknowledges that the current proposed drug product packaging does not distinguish itself from similar products used for alternate routes of administration i.e. nebulizer/inhalation dispensers; therefore, given the safety concerns which could result in serious medication errors, an approvable action is recommended by the chemistry and manufacturing reviewer. SALVAT

b(4)

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 recommended for approval for the following indication based on the results of one clinical study, and FDA's findings of safety and efficacy for other referenced ciprofloxacin otic products, Cipro HC[®] and Ciprodex[®]:

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*.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

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

1.2.2 Required Phase 4 Commitments

No clinical Phase 4 commitments are recommended.

1.2.3 Other Phase 4 Requests

None requested.

1.3 Summary of Clinical Findings

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1.3.1 Brief Overview of Clinical Program

Indication and Study Design

The applicant presented data supporting the efficacy of ciprofloxacin otic solution 0.2% in the treatment of acute diffuse otitis externa. A Phase 3 study supporting this indication was a randomized, evaluator-blinded comparative study designed to confirm the hypothesis that ciprofloxacin otic solution 0.2% was at least as clinically effective as the active comparator. The comparator, Neomycin Sulfate and Polymyxin B Sulfate and Hydrocortisone Otic Solution (PNH) had demonstrated efficacy against treatment of acute diffuse otitis externa in children, adolescents, and adults, and had relevant regulatory approval in the U.S.A.

Endpoints and Analysis

Five populations were defined for this study: Clinical Per-Protocol (CPP), Clinical Intent-to-Treat (CITT), Microbiological Intent-to-Treat (MITT), Microbiological Per-Protocol (MPP), and Safety. The CPP and CITT populations were the primary populations for efficacy analysis and were also used for analysis of the secondary clinical efficacy endpoints. Analysis of the secondary clinical and microbiological endpoints was performed using the MPP and MITT populations. All safety analyses were performed using the Safety population.

Efficacy: Frequency tables summarizing clinical, microbiological, and clinical + microbiological outcomes were produced. Two-tailed 95% confidence intervals (CIS) for the difference between treatment groups in the proportion of patients experiencing an outcome were used to test the hypothesis that ciprofloxacin was non-inferior to PNH. Non-inferiority was claimed if the clinically meaningful difference of 0.10 (i.e., 10%) was greater than the upper limit of the 95% CI. Frequency tables for pathogens isolated at Visit 1, Visit 3, and Visit 4 were produced.

Safety: Summaries were produced for numbers and percentages of patients reporting treatment-emergent AEs, treatment-emergent serious adverse events (SAEs), deaths, and AEs leading to discontinuation. Shift tables comparing Visit 1 with Visit 4 were used to summarize changes in physical examination findings. For vital sign parameters at each visit and changes from Visit 1 to Visit 4, descriptive statistics (n, mean, and standard deviation, median, minimum, and maximum) were presented.

1.3.2 Efficacy

Indication: Acute Diffuse Otitis Externa

Efficacy and safety data were obtained from a single randomized, evaluator-blinded comparison of ciprofloxacin otic solution 0.2% with neomycin and polymyxin B sulfates and hydrocortisone otic solution in the treatment of acute diffuse otitis externa in children, adolescents, and adults.

Efficacy Findings

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Disposition of Patients

Disposition of patients is summarized in Table 1. Six hundred sixty-six patients were screened, of whom 630 entered the study and were randomized. Of the patients who did not enter the study, most were excluded because their otitis did not meet the protocol requirements for acute diffuse otitis externa. Study medication was distributed to 54 study centers, 48 in the US and 6 in Spain. Patients were randomized at 47 study centers, 42 in the US and 5 in Spain. The large majority of patients, 95% of patients in both treatment groups, completed the study. 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.

Table 1: Enrollment and Disposition of Patients

Category	Number (%) of Patients		
	Ciprofloxacin	PNH	Total
Patients randomized*	318 (100.0)	312 (100.0)	630 (100.0)
Patients who completed the study*	302 (95.0)	296 (94.9)	598 (94.9)
Patients who withdrew before completion*	16 (5.0)	16 (5.1)	32 (5.1)
Reasons for withdrawal: [†]			
Lost to follow-up	9 (56.3)	6 (37.5)	15 (46.9)
Adverse event	3 (18.8)	3 (18.8)	6 (18.8)
Withdrawal of consent	1 (6.3)	5 (31.3)	6 (18.8)
Treatment failure	3 (18.8)	1 (6.3)	4 (12.5)
Death	0	0	0
Risk to the patient	0	0	0
Other	0	1 (6.3)	1 (3.1)

* Percentages based on the numbers of patients randomized.

† Percentages based on the numbers of patients who withdrew.

Data Sets Analyzed

Data sets analyzed in this study are shown in Table 2. A total of 630 patients were randomized, 318 to the ciprofloxacin group and 312 to the PNH group. Safety population included 319 patients in the ciprofloxacin group and 309 in the PNH group, while the CITT population included 318 patients in the ciprofloxacin group and 309 in the PNH group. Approximately 22% of patients in each treatment group were excluded from the CPP and MPP populations. Only patients for whom adequate microbiological data were available were included in the MITT and MPP populations.

Table 2: Summary of Analysis Populations: All Randomized Patients

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

^a 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.

^b 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.

^c CITT patients whose Visit 1 microbiological culture yielded 1 or more pathogens.

^d CPP patients who's Visit 1 microbiological culture yielded 1 or more pathogens and who had microbiological results from Visit 3 and for Visit 4.

Analysis of Efficacy

Primary Efficacy Endpoint: Clinical Cure at Visit 4 (TOC)

In the CPP population, 214 (86.6%) patients in the ciprofloxacin group and 197 (81.1 %) in the PNH group had Clinical Cure at Visit 4. The difference between treatment groups in proportion of patients with Clinical Cure (i.e., the proportion for PNH minus the proportion for ciprofloxacin) was -5.6% (95% CI -12.1%, 0.9%). The upper limit of the 95% CI, 0.9%, was smaller than the predefined limit of 10%; thus, ciprofloxacin was non-inferior to PNH in the CPP population. Similar results were seen in the CITT population; 259 (81.4%) patients in the ciprofloxacin group and 237 (76.7%) in the PNH group had Clinical Cure at Visit 4. The difference between treatment groups in proportion of patients with Clinical Cure was 4.7 % (95% CI -11.1%, 1.6%).

Microbiological Results

In the MPP population, 174 patients in each treatment group had at least 1 pathogen at Visit 1. *Pseudomonas aeruginosa* was isolated from a majority of these patients (87% in the ciprofloxacin group and 89% in the PNH group). *Staphylococcus aureus* was isolated from 13% of patients in the ciprofloxacin group and 17% in the PNH group. Eradication or presumed eradication was reported for 157 (90.2%) ciprofloxacin patients and 152 (87.4%) PNH patients in the MPP population at visit 4. Similar results were seen in the MITT population; eradication or presumed eradication was reported for 197 (84.9%) ciprofloxacin patients and 182 (83.9%) PNH patients in the MITT population at visit 4.