

### Clinical Microbiology – Bacterial Eradication

Bacteriologic response is summarized in the table provided below. In the Microbiological Per Protocol population (MPP), at both the End-of-Treatment (EOT) visit and the Test-of-Cure visit, which occurred about one week after EOT, the bacteriologic response was Eradication or Presumed Eradication for the great majority of patients in both treatment groups. At the EOT visit, 96% of patients in the ciprofloxacin group and 93% in the PNH group had Eradication or Presumed Eradication.

#### Bacteriologic Response

Visit		Microbiological per Protocol Population		Microbiological Intent to Treat Population	
		Cipro (N=174)	PNH (N=174)	Cipro (N=232)	PNH (N=217)
End of Treatment	Eradication	39 (22.4%)	48 (28.4%)	53 (22.8%)	58 (26.7%)
	Presumed Eradication	128 (73.8%)	115 (66.1%)	157 (67.7%)	138 (64.1%)
	Eradication or Presumed Eradication	167 (96%)	161 (92.9%)	210 (90.5%)	196 (89.9%)
	Persistence	1 (0.6%)	5 (2.9%)	3 (1.3%)	7 (3.2%)
	Presumed Persistence	5 (2.9%)	8 (4.6%)	8 (3.5%)	11 (5.1%)
	Superinfection	1 (0.6%)	0	1 (0.4%)	0
	Indeterminate	--	--	10 (4.3%)	4 (1.8%)
Test of Cure	Eradication	16 (9.2%)	22 (12.6%)	21 (9.1%)	27 (12.4%)
	Presumed Eradication	141 (81%)	139 (74.7%)	178 (75.9%)	156 (71.4%)
	Eradication or Presumed Eradication	157 (90.2%)	152 (87.4%)	197 (84.9%)	182 (83.9%)
	Persistence	1 (0.6%)	1 (0.6%)	1 (0.4%)	2 (0.9%)
	Presumed Persistence	16 (9.2%)	21 (12.1%)	24 (10.3%)	28 (13.4%)
	Superinfection	0	0	0	0
	Indeterminate	--	--	10 (4.3%)	4 (1.8%)

Source: Table 7.1, section 8.3.3.4.12, p23; Statistical Tables 21.1.1 and 21.1.2 (Original submission)

## 8. Safety

For detailed safety information on Clinical Trial CIPROT III/ 03 IA 02, see the Medical Officer Review dated April 7, 2006. The most frequently reported adverse events were otitis externa (fungal), nasopharyngitis, ear pruritis, ear pain, and headache. These events were reported in approximately 3% or less of patients treated with Cetraxal.

## 9. Advisory Committee Meeting

No Advisory Committee was convened for Cetraxal (ciprofloxacin otic solution) 0.2%.

## 10. Pediatrics

The safety and effectiveness of Cetraxal in infants below one year of age have not been established. The efficacy of Cetraxal in treating otitis externa in pediatric patients one year or older has been demonstrated in a controlled clinical trial.

There is no evidence that the otic administration of quinolones has any effect on weight bearing joints, even though systemic administration of some quinolones has been shown to cause arthropathy in immature animals.

## 11. Other Relevant Regulatory Issues

### DSI

A Division of Scientific Investigations (DSI) audit was requested.  
Per the DSI review dated February 1, 2006:

The Review Division requested a routine data audit inspection of two study sites that conducted study Protocol #CIPROT III IA 02 and from which data was submitted in support of NDA#21-918.

Name	City, State	Country	Protocol	Insp. Date	Classification
Gary Goldstein	Palm Harbor, FL	USA	CIPROT III	12/5 to 8/2005	NAI
John Champlin	Carmichael, CA	USA	CIPROT III	11/15 to 18/2005	VAI

*NAI = No deviation from regulations. Data acceptable.*

*VAI=No Response Requested= Deviations(s) from regulations. Data acceptable.*

### FINANCIAL DISCLOSURE

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.

There is no evidence to suggest that the results of the study were impacted by any financial payments.

### DMEPA/DDMAC

The proposed name, Cetraxal was previously reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) in 2005 and re-reviewed this cycle in order to rule out any objections to the proposed proprietary name since the signature date of the previous DMEPA review. The Proprietary Name Risk Assessment findings indicate that the proposed name, Cetraxal, is not vulnerable to name confusion that could lead to medication errors. Thus, DMEPA) has no objection to the proprietary name, Cetraxal, for this product at this time. Additionally, DDMAC does not object to the proposed name, Cetraxal, from a promotional perspective.

Per the DMEPA review dated March 31, 2009:

The Division of Medication Error Prevention and Analysis (DMEPA) evaluated the container label, carton labeling, outer wrap foil pouch and insert labeling to identify vulnerabilities that could lead to medication errors. Our findings indicate that the design and the presentation of information on the proposed labels, labeling and outer wrap foil pouch appear to be vulnerable to confusion that could lead to medication errors. We specifically note that the principal display panel is cluttered because of too much information and the directions for use in the insert labeling are incomplete and may lead to inappropriate use of this product. Furthermore, we remain concerned about the packaging of Cetraxal in LDPE vials and the potential that this configuration may cause confusion and increase the risk of wrong route of administration errors associated with this product. To address these concerns, the Applicant has embossed the word — on one side of the vial along with the established name and strength. Although we remain unsure of the effectiveness of this strategy since embossed information is difficult to read on LDPE material, DMEPA aligns with the Division to allow the marketing of this product as it is currently proposed.

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Representatives from DDMAC and DMEPA were in attendance at the April 15, 2009, internal labeling meeting. Their suggestions have been incorporated into the revised, final labeling where appropriate.

## 12. Labeling

The labeling submitted on April 27, 2009, and included in the Cross Discipline Team Leader's Review was found to be acceptable.

### 13. Regulatory Action

#### RECOMMENDED REGULATORY ACTION:

NDA 21-918 is acceptable for approval for the treatment of acute otitis externa due to susceptible isolates of *Pseudomonas aeruginosa* or *Staphylococcus aureus*.

#### RISK BENEFIT ASSESSMENT:

The application supports the safety and efficacy of Cetraxal (ciprofloxacin otic solution) 0.2% for the treatment of acute otitis externa due to susceptible isolates of *Pseudomonas aeruginosa* or *Staphylococcus aureus*.

In the per protocol population of Study CIPROT III/ 03 IA 02, clinical cure was achieved at the end of a 7-day treatment in 70% (173/247) for the CETRAXAL™ treated group versus 60% (147/243) for the control treated group. The most commonly reported adverse reactions in Clinical Trial CIPROT III/ 03 IA 02 in ciprofloxacin treated subjects were fungal otitis externa (otomycosis) and headache, both at 3%. Other common adverse reactions seen in 2% of ciprofloxacin treated subjects were nasopharyngitis, ear pruritis, and ear pain.

CMC, Pharmacology/Toxicology, Clinical Pharmacology, Biostatistics and Product Quality Microbiology, Clinical Microbiology, Medical Officer and Cross Discipline Team Leader reviews support the approval for this application.

#### RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:

There are no additional proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

Wiley A. Chambers, MD  
Acting Director  
Division of Anti-Infective and Ophthalmology Products

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