SYNOPSIS

NAME OF SPONSOR/COMPANY: PriCara, Unit of Ortho-McNeil, Inc. NAME OF FINISHED PRODUCT: LEVAQUIN® NAME OF ACTIVE INGREDIENT(S): Levofloxacin	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: CAPSS-290 (CR004678)

Title of Study: An Open-Label, Multi-Center, Non-Comparative Sinus Puncture Study of 750 mg, Short-Course Levofloxacin in The Treatment of Acute Maxillary Sinusitis

Principal Investigator: Multicenter (U.S.); three investigators enrolled subjects, 1 additional investigator did not enroll subjects

Publication (Reference): None at time of report issue.

Study Initiation/Completion Dates: 6 February 2004 / 6 June 2005	**Phase of development:** 4

Objectives: The primary objective was to establish the rate and extent of bacteriological eradication, defined as eradication of pathogens from the maxillary sinus utilizing levofloxacin 750 mg orally once daily for 5 days for the treatment of acute bacterial sinusitis in adults. Secondary objectives included 1) to document the clinical efficacy of levofloxacin 750 mg orally once daily for 5 days in the treatment of acute maxillary sinusitis in adults; 2) to evaluate the safety profile of levofloxacin in subjects receiving levofloxacin 750 mg orally once daily for 5 days; 3) to determine levofloxacin plasma and sinus aspirate concentration-time profiles in adult subjects with acute maxillary sinusitis during steady state; and 4) to determine changes in levels of inflammatory mediators found in the sinus aspirate material and serum as subjects are treated for acute maxillary sinusitis with levofloxacin.

Methodology: This was an open-label, multi-center, non-comparative sinus puncture clinical study involving outpatients 18 years or older presenting with protocol-defined acute maxillary bacterial sinusitis suitable for treatment with oral antibiotics. Subjects received levofloxacin 750 mg orally once daily for 5 days. Subjects were assessed clinically at 7 visits: a Preliminary Visit, at 4 On-Therapy Visits (Study Day 1-baseline and first dose of therapy, and Days 2, 3, 4), at End-of-Therapy (Study Day 5- last day of therapy), and at Posttherapy (in the interval of Study Days 12 through 19). Efficacy evaluations included clinical and microbiologic responses to treatment. Pharmacokinetic sampling of plasma and sinus aspirate fluids to assay for levofloxacin concentrations at steady state, and serum and sinus aspirate fluids to assay for inflammatory mediators, was performed during the study. Safety evaluations included incidence of treatment-emergent adverse events (AEs) and changes from admission to posttherapy in clinical laboratory test results and vital signs. Data were pooled across investigational sites for analysis.

Number of Subjects (planned and analyzed): 20 microbiologically evaluable subjects were planned; 18 subjects were enrolled, 17 subjects were evaluable for efficacy (ITT population) of which 15 were clinically evaluable and 4 were microbiologically evaluable. 17 subjects comprised the Safety population.

Diagnosis and Main Criteria for Inclusion: Adult (18 years of age or older) male and female outpatients were eligible for enrollment if they had a clinical diagnosis of acute bacterial sinusitis, defined by the presence of clinical signs and symptoms lasting for >5 days but less than 28 days, the presence of visible nasal purulence, computed tomography (CT) or standard sinus x-rays showing total sinus opacification or an air fluid level, and two or fewer episodes of bacterial sinusitis within the preceding 12 months, no episode of bacterial sinusitis in the last month. Subjects must have agreed to undergo maxillary sinus puncture and catheter placement at Visit 1 for collection of a sinus specimen and agreed to use only Tylenol® as an analgesic and/or pseudoephedrine HCl as a decongestant. Subjects were excluded from study entry if they had a diagnosis of chronic sinusitis; had need for hospitalization or intravenous (i.v.) antimicrobial therapy; had infection caused by a pathogen resistant to levofloxacin; past or current head, neck, and nasal cancer or surgery; required systemic, inhalational, or intranasal corticosteroids, aspirin, NSAIDs, or leukotriene antagonists within 7 days prior to study entry or during the study; had cystic fibrosis; had neutropenia; had calculated creatinine clearance <50 mL/min; had documented infection with HIV with CD4 counts <200 cells/mm^3; were pregnant or nursing; had seizure disorder or a psychiatric condition requiring use of major tranquilizers; or life expectancy <72 hours.

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Test Product, Dose and Mode of Administration, Batch No.: R12208

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable

Duration of Treatment: 5 days

Criteria for Evaluation:

Pharmacokinetics:

•Levofloxacin plasma and sinus aspirate concentration-time profiles at steady state

• Changes in levels of inflammatory mediators/markers (IL-8, TNF-α, IL-6, IL-12, IFN-γ, IL-10, LTB_4, MPO) found in the sinus aspirate material and serum as subjects are treated for acute maxillary sinusitis with levofloxacin

Efficacy:

Clinical Outcomes:

• Clinical response rates at the End-of-Therapy and Posttherapy Visits based on resolution of signs and symptoms observed on admission. Clinical response was categorized as cure, improvement, failure, or unable to evaluate.

• Proportions of subjects with resolution of sinusitis signs and symptoms at the End-of-Therapy and Posttherapy Visits

Microbiologic Outcomes:

• Time to eradication of original bacterial pathogen from the maxillary sinus. Responses were assessed by subject's infection (categorized as eradicated/presumed eradicated, persisted/presumed persisted, or unknown) and by pathogen (categorized as eradicated, presumed eradicated, persisted, presumed persisted, persisted with acquisition of resistance, or unknown)

Inflammatory Mediators:

• Concentrations of inflammatory markers (IL-6, IL-8, IL-10, TNF-α, and IFN-γ, IL-12, LTB_4, NE, and MPO) in serum and sinus aspirate lavage samples

Safety:

Incidence of treatment-emergent adverse events during the study, and by changes in physical findings including vital signs and clinical laboratory tests from baseline through the Posttherapy Visit.

Pharmacokinetic/Pharmacodynamic Relationships:

The measure of levofloxacin penetration based on the AUC ratio (AUC_{sinus}/AUC_{plasma}) at steady state.

Statistical Methods: This study was primarily descriptive in nature to obtain preliminary information, with no *a priori* hypothesis stated. Descriptive statistics were generated for all data captured including safety, AEs, plasma and sinus fluid levofloxacin concentrations, and levels of inflammatory mediators. Pharmacokinetic/pharmacodynamic parameters and relationships were not analyzed for this report. Time to bacterial eradication of the original pathogen(s) could not be performed due to an insufficient number of microbiologically-evaluable subjects; however a listing of times to eradication for each pathogen was generated. Proportions of subjects with resolution of signs and symptoms of sinusitis were summarized.

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SUMMARY - CONCLUSIONS

PHARMACOKINETICS: will be provided in vendor report separately from this clinical study report as soon as datasets are analyzed.

EFFICACY RESULTS: In all 4 subjects who had a pathogen considered to be causative for acute bacterial sinusitis in their sinus aspirate admission culture, the pathogen(s) were confirmed eradicated at end of therapy. At posttherapy (Study Days 12-19) the pathogen(s) were considered presumed eradicated based on clinical symptoms. Clinical responses of the 17 ITT subjects were cured/improved (in 100% of subjects at end of therapy) and >93% of subjects at posttherapy (1 subject was unevaluable). There were no clinical failures. Most subjects experienced resolution of their signs/symptoms of sinusitis at end of therapy, and by posttherapy, experienced greater resolution (both in proportions of subjects and in number of symptoms resolved) compared with the end of therapy resolution results. Importantly for this pilot study, inflammatory mediator/marker levels were detectable in serum and sinus aspirate fluid samples. Assessment of statistical and biological significance was limited by the small sample size.

SAFETY RESULTS: The type and rate of treatment-emergent AEs (in 9/17 safety evaluable subjects) were consistent with the known safety profile of levofloxacin. There were no deaths or other SAEs in this study; 1/17 subjects discontinued due to an AE; 3/17 subjects were reported with a drug-related AE. No clinically significant changes from admission to posttherapy were observed in clinical laboratory results or vital signs. Importantly, there were no treatment-emergent safety concerns arising from the presence of a sinus-indwelling catheter over the 5-day course of levofloxacin therapy.

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS: These results will be provided in a vendor report separately from this clinical study report as soon as datasets are analyzed.

CONCLUSION: In this pilot, sinus puncture study, levofloxacin 750 mg was administered p.o. once daily for five days in the treatment of subjects with acute maxillary sinusitis. In all 4 subjects who had a pathogen considered to be causative for acute bacterial sinusitis in their sinus aspirate admission culture, the pathogen(s) were confirmed eradicated at end of therapy and at posttherapy were considered presumed eradicated based on clinical symptoms. Clinical responses were cured/improved (in 100% of subjects at end of therapy) and >93% of subjects at posttherapy (1 subject was unevaluable). There were no clinical failures. Inflammatory mediator/marker levels were detectable in serum and sinus aspirate fluid samples, although considerable subject-to-subject and specimen-to-specimen variability in mediator levels was noted in sinus lavage samples. The rates of treatment-emergent AEs were consistent with the known safety profile of levofloxacin. No treatment-emergent safety concerns arose from the presence of a sinus-indwelling catheter. Overall, levofloxacin 750 mg p.o. q.d. for five days was efficacious and well-tolerated.

Date of report: 15 December 2005

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