SYNOPSIS

NAME OF COMPANY: Ortho-McNeil Pharmaceutical 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.: Protocol CR005551 **Title of Study:** A Multicenter, Double-Blind Study to Compare the Safety and Efficacy of Levofloxacin to That of Ciprofloxacin in the Treatment of Chronic Prostatitis (RWJ-25213-097)		
Investigators: Sixty-six (66) principal investigators; one investigator (Levin) enrolled one subject who did not receive study drug; 48 other investigators did not enroll subjects		
Study Centre(s): 65 study centers		
Publication (Reference): None		
Studied Period (years): 04 May 2000 - 13 November 2001		**Phase of Development:** 3B
Objectives: The objective of this study was to evaluate the safety and efficacy of levofloxacin 500 mg p.o. q.d. compared with ciprofloxacin 500 mg p.o. b.i.d. for a four-week course in the treatment of chronic bacterial prostatitis. The six-month follow-up information will be reported separately.		
Methodology: This was a multicenter, double-blind, randomized, Phase 3B study conducted in the United States. Subjects were to be assigned to one of two treatment groups (levofloxacin or ciprofloxacin) in a 1:1 ratio according to a computer-generated randomization schedule stratified by study center and according to whether the subject enrolled in the study based on white blood cell (WBC) count in the voided bladder 3 (VB_3) specimen or microbiologic culture results from the expressed prostatic fluid (EPS) or VB_3 specimens. Efficacy evaluations included assessments of posttherapy (5 to 18 days following last dose of active study drug) microbiologic and clinical response rates, poststudy (24 to 45 days following last dose of active study drug) relapse/new infection rates, and follow-up (six months following last dose of study drug) assessment of prostatitis recurrence rates. Microbiologic eradication rate by subject's infection at the posttherapy visit (test of cure) in microbiologically evaluable subjects was the primary efficacy variable in this study. Safety evaluations included the incidence of treatment-emergent adverse events and changes from admission to posttherapy in clinical laboratory test results, vital signs, and physical examination findings.		
Number of Subjects (planned and analyzed): Planned enrollment: 400 subjects to provide approximately 70 microbiologically evaluable in each treatment group. Enrolled 383 subjects: 261 evaluable for microbiologic efficacy (levofloxacin, 136; ciprofloxacin, 125); 377 subjects evaluable for safety.		
Diagnosis and Main Criteria for Inclusion: Men 18 years of age or older with a clinical diagnosis of prostatitis including: a soft, tender prostate without noticeable nodularity and the presence of one or more additional protocol-specified clinical signs and symptoms; a history of prostatitis, defined as at least one previous symptomatic episode of four weeks' duration or two or more episodes of any duration during the 12 months prior to study enrollment; and laboratory evidence of prostatitis based on WBC count in the VB_3 specimen or microbiologic culture results from the VB_3 or EPS specimens. Over-the-counter medications for chronic prostatitis were to be continued at the same dose throughout the study or discontinued prior to study entry, as specified in the protocol. Subjects were excluded from the study if they had: a requirement for parenteral therapy for prostatitis, a second systemic antibiotic regimen for any reason, or medications that affected bladder or prostate function. Additional exclusion criteria were: a pathogen of known or suspected resistance to either study drug, allergy to quinolone antibacterials, creatinine clearance <50 mL/min, known prostatic carcinoma, or a condition that could interfere with evaluation of study drug (e.g., transurethral prostatectomy in the previous six months, presence of a permanent transurethral catheter, or history of cystostomy or nephrostomy).		
Test Product, Dose and Mode of Administration, Batch No.: Levofloxacin 500 mg p.o. q.d. and placebo p.o. q.d. Oral levofloxacin 500 mg FD 25213-097-BE-31 (Batch Numbers R10389, R10396, R10441, R8969a) Placebo FD 90000-000-EMX-31 (Batch Number R10397, R8970)		

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Duration of Treatment: 28 days for both regimens

Reference Therapy, Dose and Mode of Administration, Batch No.: Ciprofloxacin 500 mg p.o. b.i.d. Oral ciprofloxacin 500 mg FD 22060-002-C-31 (Batch Numbers R10390, R8971, R10442, R10398)

Criteria for Evaluation: The primary efficacy endpoint was microbiologic efficacy based on microbiologically evaluable subjects. The clinical response rates were based on the resolution of signs and symptoms posttherapy. This included clinical cure, clinical improvement, and clinical failure.

Efficacy: Microbiologic

- Microbiologic response assessed posttherapy by pathogen and categorized as eradicated, persisted, presumed persisted, persisted with acquisition of resistance, or unknown.
- Microbiologic response assessed posttherapy by subject's infection and categorized as eradicated, persisted, or unknown.
- Microbiologic response assessed poststudy by pathogen and categorized as eradicated, presumed eradicated, relapse, presumed relapse, persisted, presumed persisted, or unknown.
- Microbiologic response assessed poststudy by subject's infection and categorized as long-term eradication, relapse, persisted, or unknown.

Efficacy: Clinical

- Clinical response assessed posttherapy 5 to 12 days (expanded to 5 to 18 days) after the last dose of active study drug and categorized as cure, improvement, failure, or unable to evaluate.
- Clinical response assessed poststudy 28 to 35 days (expanded to 24 to 45 days) after the last dose of active study drug for subjects with a clinical outcome of cure or improvement at the posttherapy visit and categorized in three ways: cure/long-term success, clinical relapse/new infection, or unable to evaluate.

Safety: Incidence of treatment-emergent adverse events during the study; changes from admission to posttherapy in clinical laboratory test results, vital signs, and physical examination findings.

Statistical Methods: The primary efficacy variable was microbiologic response by subject's infection at the posttherapy visit (test of cure) based on microbiologically evaluable subjects. Secondary efficacy variables were: (1) posttherapy microbiologic response by pathogen; (2) one-month poststudy microbiologic relapse by subject's infection for subjects who were cured or improved at the posttherapy visit; (3) one-month poststudy microbiologic relapse by pathogen for subjects who were cured or improved at the posttherapy visit; (4) clinical cure posttherapy; (5) clinical success (cured or improved) posttherapy; (6) the resolution and improvement of clinical signs and symptoms from admission to posttherapy, as assessed by the investigator; (7) the transition in scores from the prostatitis symptoms index from admission to posttherapy; (8) one-month poststudy clinical success for subjects who were cured or improved at the posttherapy visit; and (9) six-month poststudy assessment of recurrence for subjects who were cured or improved at the posttherapy visit and who had recurrence data available at six months. Two-sided 95% confidence intervals using the normal approximation to the binomial with a continuity correction were computed around the difference (ciprofloxacin minus levofloxacin) in microbiologic eradication rates to assess microbiologic non-inferiority. Two-sided 95% confidence intervals were computed around the treatment difference in clinical cure and clinical success rates to assess clinical non-inferiority.

Safety data were summarized using descriptive statistics (frequency, mean, standard deviation) for treatment-emergent adverse events reported during the study and for pretherapy-to-posttherapy changes in clinical laboratory test results and vital signs. Two-sided 95% confidence intervals were calculated for the differences between the two treatment groups in the total number of subjects with treatment-emergent adverse event rates and in the incidence of treatment-emergent adverse events for each body system.

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SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

Microbiologic Results: The posttherapy microbiologic eradication rate by subject's infection (eradication of all admission pathogens for a subject) for microbiologically evaluable subjects was 75.0% in the levofloxacin treatment group and 76.8% in the ciprofloxacin treatment group (95% CI [–8.98, 12.58]). The upper bound of the 95% confidence interval was within 20%, and the interval contained zero, indicating that levofloxacin was as effective as ciprofloxacin. The microbiologic eradication rates by admission pathogen were similar in the two treatment groups. In microbiologically evaluable subjects, the overall eradication rate by pathogen was 80.8% (172/213) in the levofloxacin treatment group and 82.9% (160/193) in the ciprofloxacin treatment group. Microbiologic eradication rates for individual pathogens of interest ranged from 72.2% to 93.3% in levofloxacin-treated subjects and from 75.0% to 100.0% in ciprofloxacin-treated subjects.

Clinical Results: The posttherapy clinical success rate for subjects evaluable for microbiologic efficacy was 75.0% for levofloxacin-treated subjects and 72.8% for ciprofloxacin-treated subjects (95% CI [-13.27, 8.87]), indicating that levofloxacin was clinically as effective as ciprofloxacin. The results were generally comparable among all efficacy analysis populations.

SAFETY RESULTS:

Both the levofloxacin and the ciprofloxacin regimen were safe and well tolerated. The type and frequency of treatment-emergent adverse events reported in this study are consistent with the known safety profiles of these agents. Overall, 44.2% of subjects in the levofloxacin treatment group and 37.2% of subjects in the ciprofloxacin treatment group reported at least one treatment-emergent adverse event (95% CI [-17.12, 3.23]). There were no notable differences between the levofloxacin and ciprofloxacin treatment groups with regard to the incidence of adverse events in individual body systems, markedly severe adverse events (7.6% versus 3.9%), drug-related adverse events (9.6% versus 5.6%, respectively), serious adverse events (one subject in each treatment group), or adverse events that resulted in the discontinuation of therapy (5.6% versus 4.4%, respectively). One subject in the levofloxacin treatment group had a serious adverse event (brain stem hemorrhage) that resulted in death. One subject in the ciprofloxacin treatment group experienced increased anxiety and depression that were considered serious. All serious adverse events were assessed by the investigator as not related to study drug.

CONCLUSION:

Levofloxacin 500 mg administered orally once daily was shown to be as well tolerated and as effective as ciprofloxacin 500 mg administered orally b.i.d. for a four-week course in the treatment of chronic bacterial prostatitis. The results of this study support the efficacy of levofloxacin in the treatment of chronic bacterial prostatitis associated with the following pathogens: *Escherichia coli*, *Enterococcus faecalis*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Streptococcus agalactiae*, and *Streptococcus mitis*.

Date of the report: 19 June 2002

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