SYNOPSIS

Name of Sponsor/Company: Ortho-McNeil Pharmaceutical Inc.	Individual Trial Table Referring to Part of the Dossier:	(*For National Authority Use only):*
Name of Finished Product: Levaquin®	Volume:	
Name of Active Ingredient: levofloxacin	Page:	

Protocol No: CR005476

Title of Study: A multicenter, active-controlled, randomized study to evaluate the safety and efficacy of levofloxacin versus ciprofloxacin HCl in the treatment of mild-to-moderate skin and skin structure infections in adults

Investigators: 14 principal investigators; 1 investigator did not enroll subjects

Study Centres: 13 centers

Publications (Reference): None

Studied Period: 11 March 1991 - 22 February 1993 | **Phase of development:** 2/3

Objectives: The primary objective of this study was to compare the safety and efficacy of levofloxacin administered orally with that of ciprofloxacin HCl administered orally in the treatment of mild to moderate skin and skin structure infections in adult outpatients.

Methodology: This was a randomized, open-label, active-control, multicenter study conducted in the United States and Costa Rica. Subjects were assigned to one of two treatment groups (levofloxacin or comparator) in a 1:1 ratio according to a computer-generated randomization schedule. Efficacy evaluations included assessments during therapy (Days 3-5) and posttherapy (2-7 days after completion of study drug) and were based on microbiologic response rates by pathogen and by subject in those subjects with a response of cured or improved posttherapy. The primary efficacy variables for this study were the clinical response to treatment (defined as cured, improved, or failed) and microbiologic response to treatment. Safety evaluations included incidence of treatment-emergent adverse events, and changes from admission to posttherapy in clinical laboratory test results and physical examination.

Number of Subjects (planned and analyzed): Planned enrollment: 440 subjects. Enrolled: 469 subjects evaluable for efficacy and safety: 231 subjects received levofloxacin and 238 subjects received ciprofloxacin HCl.

Diagnosis and Main Criteria for Inclusion: Men and women aged 18 years of age or older with a diagnosis of skin and/or skin structure infection based upon evidence of localized pain, erythema, swelling, drainage, or other clinical signs; culture from infected area was available; Subjects who had multiple sites of infection may have been enrolled. Enrollment of subjects with infections due to diabetes, peripheral vascular disease, or decubitus ulcers were limited to 20% of the total enrollment. Subjects with impaired renal function and dialysis subjects may have been enrolled with provisions for adjusted dosing. Subjects with a condition requiring parenteral antimicrobial therapy; osteomyelitis; severe infection; an infection due to organisms known to be resistant to the study drug prior to study entry; signs and symptoms of septic shock; conditions requiring debridement at the site of infection; previous allergic or serious adverse reaction to any members of the quinolone class of antimicrobials; serum creatinine >2.5 mg/dL; grossly underweight (≤40 kg/88 lb); effective systemic antimicrobial therapy within 48 hours prior to study entry; requirement for a second systemic antimicrobial regiment or use of a topical antimicrobial at the infection site; presence of seizure disorder; condition requiring administration of major tranquilizers were excluded from study entry.

Test Product, Dose and Mode of Administration:
Levofloxacin 500 mg PO q24h

Duration of Treatment: 7 to 10 days

Reference Therapy, Dose and Mode of Administration:
Ciprofloxacin 500 mg PO q12h for 7 to 10 days

Criteria for Evaluation:
Efficacy:

- Clinical response assessed 2 to 7 days posttherapy. Posttherapy clinical response categorized as cured, improved, failed, or unable to evaluate.

Microbiologic outcomes:

- Microbiologic response assessed posttherapy by pathogen and subject.

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Safety:

- Occurrence of treatment-emergent adverse events during the study; changes from admission to posttherapy in clinical laboratory test results and in physical examination of the skin and physical examination.

Statistical Methods:

The primary efficacy variable was clinical response to treatment measured by reduction of pre-treatment signs and symptoms (defined as cured, improved, or failed) and the microbiologic response to treatment (defined as the eradication rate). The clinical response rates of levofloxacin and ciprofloxacin were compared using the generalized Cochran-Mantel-Haenszel procedure with marginal mid-rank scores for the ordinal response categories. The microbiologic eradication rates of the levofloxacin and ciprofloxacin regimens were compared using Fisher's exact two-sided test. The microbiologic response rates for the infections were also compared using the generalized Cochran-Mantel-Haenszel procedure with marginal mid-rank scores for the ordinal response categories.

The safety variables included incidence, severity, and type of adverse events during the study and changes in physical findings and laboratory measurements from pre- to posttherapy. The proportion of subjects in each treatment group reporting at least one adverse event was compared using Fisher's exact two-sided test. Similar tests were performed for adverse events occurring within body systems of interest. Fisher's exact two-sided test was also used to compare the proportion of subjects reporting drug-related adverse events. Two-sided t-tests for paired data were used to identify statistically significant changes in clinical laboratory results from pre- to posttherapy for each treatment group. Two-sided t-tests for two independent samples were also used to compare the mean changes between the treatment groups.

All statistical inferences were based on a Type I error rate of 0.05.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Clinical Response: Among clinically evaluable subjects in the levofloxacin treatment group, 83.0% were cured and 14.8% improved, compared with 80.3% and 14.0% for ciprofloxacin, respectively. Four (2.2%) subjects in the levofloxacin treatment group and 11 (5.7%) subjects in the ciprofloxacin treatment group failed treatment.

For clinically evaluable subjects, when the clinical response categories “cured” and “improved” were combined into a single category of “clinical success,” levofloxacin treatment resulted in 97.8% clinical success while ciprofloxacin treatment resulted in 94.3% clinical success, with a 95% confidence interval of [-7.7, 0.7] for the difference (ciprofloxacin minus levofloxacin) in clinical success rates. Using a confidence interval upper bound of 10%, this result supports a claim of therapeutic equivalence of the two treatments. Confidence intervals were computed for each study center with 10 or more clinically evaluable subjects in each treatment group and for all other centers pooled. Clinical results were generally comparable across study centers. All but one of the individual study center confidence intervals were centered at or below zero, indicating equivalent or higher success rates for levofloxacin than for ciprofloxacin.

In the modified intent-to-treat group, the clinical success rates for treatment with levofloxacin and ciprofloxacin were 88.7% and 87.4%, respectively. The individual confidence intervals for all analysis groups are consistent with therapeutic equivalence of the two treatment groups in terms of clinical success.

Clinical responses in the two treatment groups were comparable for the most common diagnosis (cellulitis), for all diagnoses combined, and by complexity and severity. Comparability was demonstrated between treatment groups for subjects with mild-to-moderate infections, which represented the majority of subjects enrolled in the study.

Microbiologic Results: The overall microbiologic eradication rates in the levofloxacin and ciprofloxacin treatment groups by subject were 97.5% and 88.8%, respectively, with a confidence interval of [-14.5, -2.7] for the difference between treatments (ciprofloxacin minus levofloxacin) assuming independence of multiple pathogens and multiple strains within a subject. The overall microbiologic eradication rates by pathogen in the levofloxacin and ciprofloxacin treatment groups were 98.3% and 90.2%, respectively, with a 95% confidence interval of [-12.6, -3.7]. Both confidence intervals favor levofloxacin over ciprofloxacin. Microbiologic results were generally comparable across analysis groups and centers. The microbiologic eradication rates for gram-positive and gram-negative aerobes in the levofloxacin group were comparable-to-higher (97.0% to 98.6%) than in the ciprofloxacin group (89.3% to 94.2%). The two most common pathogens (*S. aureus* and *S. pyogenes*) had 100% eradication in the levofloxacin group and 87.4% and 90.0% eradication, respectively, in the ciprofloxacin group with the 95% confidence interval around the difference between treatments for *S. aureus* eradication in favor of levofloxacin. The microbiologic responses for the remainder of the diagnoses and pathogens were generally comparable between the two treatment groups, as were the results by complexity and severity.

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The clinical and microbiologic response rates were comparable between treatment and among analysis groups. In both treatment groups, there is concordance between the clinical and microbiologic responses based on a cross-tabulation of clinical response versus microbiologic response, confirming the consistency and reliability of these response measures.

SAFETY RESULTS:

Four hundred sixty-two of 469 subjects were evaluated for safety. Fifty-nine (25.7%) of the 230 safety-evaluable subjects in the levofloxacin treatment group and 45 (19.4%) of the 232 safety-evaluable subjects in the ciprofloxacin treatment group reported at least one treatment-emergent adverse event during the study, including events considered by the investigator to be related or unrelated to the study drug.

The most frequently reported adverse events in both treatment groups occurred in the gastrointestinal and nervous systems and consisted primarily of nausea, diarrhea, and headache. The nature and frequency of adverse events were generally comparable across the two treatment groups. One body system, body as a whole, had a statistically significant confidence interval of [-6.4, -0.6], with a higher incidence rate in the levofloxacin group (4.3%) than in the ciprofloxacin group (0.9%). However, no single adverse event in this body system was reported by more than 1.3% (fever and malaise) of subjects who received levofloxacin. The one drug-related adverse event reported by ≥1.0% of levofloxacin-treated subjects was diarrhea (1.3%). Drug-related adverse events reported by ≥1.0% of ciprofloxacin-treated subjects were diarrhea (2.2%), nausea (1.3%), and headache (1.3%).

Most adverse events were assessed as mild in severity. Two subjects in the levofloxacin treatment group reported adverse events of marked severity; one had marked hyperkinesia, aggressive reaction, and nervousness, considered by the investigator to be probably related to study therapy, and the other had marked purpura classified as unrelated to study drug. Four subjects in the ciprofloxacin treatment group reported one or more marked adverse events: headache (two subjects), nausea (two subjects), vomiting (one subject), and diarrhea (one subjects). One case each of diarrhea and headache was considered by the investigator to be probably related to the study drug. The remaining four adverse events were assessed as having a possible relationship to the study drug.

Nine (1.9%) subjects discontinued study drug due to adverse events, four (1.7%) in the levofloxacin treatment group and five (2.2%) in the ciprofloxacin treatment group. The treatment-limiting events in the levofloxacin treatment group consisted primarily of nervous system events (e.g., dizziness and hyperkinesia) and gastrointestinal complaints (nausea, vomiting, and diarrhea). In the ciprofloxacin treatment group, the treatment-limiting adverse events consisted primarily of headache and gastrointestinal complaints (nausea, vomiting, diarrhea, and abdominal pain). No subjects died or had serious adverse events.

There were no clinically significant treatment-emergent mean changes from admission to posttherapy for laboratory analytes in either treatment group, with comparable results in both groups. The incidence of markedly abnormal test results for individual analytes for subjects with both admission and posttherapy data available was generally low and comparable between treatment groups (≤2.7%) for all analytes. Eighteen subjects (11 in the levofloxacin group and seven in the ciprofloxacin group) had markedly abnormal test results after therapy start. Overall, 10 subjects had abnormal glucose levels: five (2.7%) levofloxacin-treated subjects and one (0.5%) ciprofloxacin-treated subject had hypoglycemia; one (0.5%) levofloxacin-treated subject and three (1.5%) ciprofloxacin-treated subjects had hyperglycemia. Five subjects in the levofloxacin group and two in the ciprofloxacin group had markedly abnormal liver function tests (elevations in SGOT, SGPT, or bilirubin).

There were no clinically significant changes in vital signs from admission to posttherapy in levofloxacin-treated or ciprofloxacin-treated subjects with comparable results in the two groups. There were no clinically significant treatment-emergent physical examination abnormalities.

CONCLUSIONS:

Levofloxacin was safe, well-tolerated, and effective in the treatment of subjects with uncomplicated skin and skin structure infections. The clinical success rate in the levofloxacin treatment group was therapeutically equivalent to that observed in the ciprofloxacin group. Moreover, the microbiologic eradication rates were equivalent to those of ciprofloxacin with some suggestion of higher eradication rates for *S. aureus*. Data from this trial support the effectiveness of levofloxacin for uncomplicated skin and skin structure infections due to *S. aureus* or *S. pyogenes*.

Date of Report: 08 December 1995

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