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.: CR005554

Title of Study: Multicenter, Double-Blind, Randomized Study to Compare the Safety and Efficacy of Levofloxacin 750 mg Once Daily for Five Days Vs. Levofloxacin 500 mg Once Daily for 10 Days in the Treatment of Mild to Severe Community-Acquired Pneumonia in Adults

Principal Investigator: 70 principal investigators enrolled subjects; 58 additional investigators did not enroll subjects

Publication (Reference): None

Study Initiation/Completion Dates: 05 March 2001 - 07 June 2002 **Phase of development:** 3B

Objectives: The primary objective of this study was to show that a five-day course of levofloxacin, 750 mg once a day (q.d.), given intravenously (i.v.) or orally (p.o.), is at least as effective as a 10-day course of levofloxacin, 500 mg q.d., i.v. or p.o., in the treatment of mild to severe community-acquired pneumonia (CAP). The secondary objective was to assess further the safety of levofloxacin.

Methodology: This was a multicenter, randomized, double-blind Phase 3B study conducted in the United States. Subjects were assigned to one of two treatment groups (levofloxacin 750 mg for five days or levofloxacin 500 mg for 10 days) in a 1:1 ratio according to a computer-generated randomization schedule stratified by study center and by Fine Risk Score (≤70 versus >70 but ≤130). Subjects with Fine Risk Scores ≤70 could be treated as inpatients or outpatients, while those with Fine Risk Scores >70 but ≤130 were to be treated as inpatients. There were two posttherapy evaluations, Visit 3 (12-16 days after first dose) and Visit 4 (17-21 days after first dose) and one poststudy evaluation, Visit 5 (31-38 days after first dose). Efficacy evaluations included clinical and microbiologic responses to treatment. Safety evaluations included incidence of treatment-emergent adverse events and changes from admission to posttherapy in clinical laboratory test results and vital signs.

Number of Subjects (planned and analyzed): Planned enrollment: 400 to 500 subjects to provide 344 clinically evaluable subjects (172 per group). Enrolled 530 subjects: 528 in the intent-to-treat population (256 in the 750 mg group and 272 in the 500 mg group); 521 evaluable for safety (256 in the 750 mg group and 265 in the 500 mg group); 390 evaluable for clinical efficacy (198 in the 750 mg group and 192 in the 500 mg group); 195 evaluable for microbiologic efficacy (103 in the 750 mg group and 92 in the 500 mg group).

Diagnosis and Main Criteria for Inclusion: Men and women 18 years of age or older with a diagnoses of CAP based on the following evidence: clinical signs and symptoms of a lower respiratory tract infection, and radiographic evidence of pneumonia (chest x-ray with acute infiltrate consistent with pneumonia as determined by a radiologist) within 24 hours of study drug administration. The presence of fever, hypothermia, leukocytosis, or bands >10% was also required. Subjects must have had a Fine Risk Score of 130 or less. Subjects were excluded from study entry if they had infections due to organisms known to be resistant to levofloxacin; pneumonia acquired in a hospital; diagnosis of cystic fibrosis, bronchiectasis, or lung abscess; chronic use of >20 mg/day of prednisone or equivalent dose of other corticosteroids; neutropenia; calculated creatinine clearance <50 mL/min; documented infection with HIV with CD4 counts ≤200 cells/mm^3; pregnancy; nursing; or meningitis.

Test Product, Dose and Mode of Administration, Batch No.: Levofloxacin 750 mg i.v. or p.o. q.d. Subjects started on i.v. levofloxacin could be switched to oral levofloxacin at the investigator's discretion.

The 750 mg levofloxacin capsules (GFI-25213-097-B-008) were supplied as overencapsulated 750 mg LEVAQUIN® commercial tablets. Parenteral levofloxacin solution was supplied in 20 mL single-dose commercial vials (500 mg/vial) NDC 0045-0069-51.

SYNOPSIS (Continued)

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Reference Therapy, Dose and Mode of Administration, Batch No.: Levofloxacin 500 mg i.v. or p.o. q.d. Subjects started on i.v. levofloxacin could be switched to oral levofloxacin at the investigator's discretion.

The 500 mg levofloxacin capsules (GFI-25213-097-B-006) were supplied as overencapsulated 500 mg LEVAQUIN commercial tablets. Parenteral levofloxacin solution was supplied in 20 mL single-dose commercial vials (500 mg/vial) NDC 0045-0069-51.

Placebo capsules (FD 90000-000-EMX-31) were identical to the levofloxacin capsules but contained corn starch filler. Dextrose or sodium chloride solution was used when an i.v. dose of placebo was needed. To maintain the blind, all bags used for i.v. administration of study medication were covered with opaque bags in the pharmacy by a pharmacist who remained unblinded.

Duration of Treatment: Five days of levofloxacin followed by five days of placebo for subjects assigned to receive 750 mg/day, and 10 days of levofloxacin for subjects assigned to receive 500 mg/day.

Criteria for Evaluation:

Efficacy Outcomes:

- Clinical response at Posttherapy Visits 3 and 4, based on resolution of signs and symptoms observed on admission. Posttherapy clinical response was categorized as cure, improvement, failure, or unable to evaluate.
- Clinical response at Poststudy Visit 5 in subjects who were cured or improved at the posttherapy visits. Poststudy clinical response was categorized as long-term cure, long-term improvement, relapse, or unable to evaluate.
- Changes in signs and symptoms, from admission to posttherapy.
- Changes in x-ray findings from admission to posttherapy and to poststudy.

Microbiologic Outcomes:

- Microbiologic response at Posttherapy Visits 3 and 4. Responses were assessed by subject's infection (categorized as eradicated, persisted, or unknown) and by pathogen (categorized as eradicated, presumed eradicated, persisted, presumed persisted, persisted with acquisition of resistance, or unknown).
- Microbiologic response at Poststudy Visit 5 for subjects who were cured or improved at the posttherapy visits. Responses were assessed by subject's infection (categorized as long-term eradication, microbiologic relapse, persisted, or unknown) and by pathogen (categorized as eradicated, microbiologic relapse, presumed microbiologic relapse, or unknown).

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

Statistical Methods: The primary efficacy variable was the clinical success rate (proportion cured or improved) in subjects evaluable for clinical efficacy, based on results obtained at the posttherapy visit that occurred 7 to 11 days after the last dose of active study medication (expanded to 7 to 14 days for analysis). A two-sided 95% confidence interval (CI) around the difference between treatment groups (10-day regimen minus five-day regimen) was computed. If the clinical success rate in one of the groups was 90% or higher, the upper bound of the 95% CI had to be 10% or lower to demonstrate equivalence.

Secondary efficacy variables were: 1) posttherapy microbiologic response by subject's infection; 2) posttherapy microbiologic response by admission pathogen; 3) changes in signs and symptoms from admission to posttherapy and changes in x-ray findings from admission to posttherapy and to poststudy; and 4) poststudy clinical and microbiologic responses of subjects who were cured or improved at the posttherapy visit and returned or had a telephone contact at poststudy. Two-sided 95% CIs around the treatment differences in posttherapy infection eradication rates overall and for the most prevalent pathogens were computed. A secondary analysis of clinical success rates and microbiologic eradication rates at the visit that occurred 12 to 19 days after the last active dose in the 750 mg group and 7 to 14 days after the last active dose in the 500 mg group was also performed (referred to as the analysis based on Posttherapy Visit 4).

Descriptive statistics (frequency, mean, standard deviation) were used to summarize treatment-emergent adverse events and pretherapy to posttherapy changes in laboratory test results and vital signs. Two-sided 95% CIs were calculated for the differences between the two treatment groups in the rates of treatment-emergent adverse events overall and within each body system.

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SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

Clinical Results: For clinically evaluable subjects, the clinical success rates at the posttherapy visit that occurred 7 to 14 days after the last dose of active medication were 92.4% in the 750 mg group and 91.1% in the 500 mg group; the 95% CI around the difference was (-7.0, 4.4). The upper bound of the 95% CI was within 10%, indicating that levofloxacin 750 mg for five days was at least as effective as levofloxacin 500 mg for 10 days in the treatment of mild to severe CAP. The rates were similar when the evaluation was based on results obtained at Posttherapy Visit 4: clinical success rates were 90.7% in the 750 mg group and 91.1% in the 500 mg group, with a 95% CI of (-5.5, 6.5).

At the posttherapy visit that occurred 7 to 14 days after the last dose of active medication, the clinical success rates were 87.5% for the 750 mg group and 81.3% for the 500 mg group in the intent-to-treat population, and 94.2% and 94.6%, respectively, in the microbiologically evaluable population. At Posttherapy Visit 4, the clinical success rates were 86.3% for the 750 mg group and 81.3% for the 500 mg group in the intent-to-treat population, and 92.9% and 94.6%, respectively, in the microbiologically evaluable population.

Microbiologic Results: For microbiologically evaluable subjects, the microbiologic eradication rates by infection (eradication of all admission pathogens for a subject) based on results obtained at the posttherapy visit that occurred 7 to 14 days after the last dose of active medication were 93.2% in the 750 mg group and 92.4% in the 500 mg group with a 95% CI of (–8.6, 7.0). The statistical results indicate that levofloxacin 750 mg for five days was at least as effective as levofloxacin 500 mg for 10 days in eradicating infections in subjects with CAP. The results were nearly identical (92.9% and 92.4%) based on Posttherapy Visit 4. The microbiologic eradication rates by admission pathogen were 92.5% (136/147) for the 750 mg group and 91.5% (118/129) for the 500 mg group (7 to 14 days posttherapy). The eradication rates with levofloxacin 750 mg were higher than those with levofloxacin 500 mg for gram-negative aerobic pathogens (96.2% versus 90.7%). The eradication rates were similar in the two treatment groups for gram-positive aerobic pathogens, pathogens in other categories, and specific pathogens isolated from five or more subjects in either group. The microbiologic results were similar in analyses based on Posttherapy Visit 4 for both groups.

SAFETY RESULTS:

Both levofloxacin regimens were safe and well-tolerated. Overall, 57.8% of subjects in the 750 mg group and 59.6% of subjects in the 500 mg group reported at least one treatment-emergent adverse event beginning up to 14 days after the last dose of active medication. The 95% CI around the difference was (-6.8, 10.5). The rates of all treatment-emergent adverse events, adverse events in individual body systems, markedly severe adverse events, serious adverse events, events resulting in discontinuation of treatment, and markedly abnormal laboratory findings were not notably different between treatments. Five (1.9%) subjects in the 750 mg group and nine (3.4%) subjects in the 500 mg group died, but none of the deaths were judged to be related to study medication. Mean changes in vital signs from admission to posttherapy were not clinically significant. There were no unusual or unexpected treatment-emergent safety problems.

CONCLUSION:

Levofloxacin 750 mg administered i.v. or p.o. once daily for five days was as well-tolerated and at least as effective as the levofloxacin regimen (500 mg once daily for 10 days) currently approved for the treatment of CAP. The results of this study support the efficacy of levofloxacin 750 mg/day for five days in the treatment of mild to severe CAP associated with the following pathogens: *Streptococcus pneumoniae, Haemophilus influenzae*, *Haemophilus parainfluenzae, Chlamydia pneumoniae, Legionella pneumophila,* and *Mycoplasma pneumoniae*.

Date of the report: 19 November 2002

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