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.: LOFBIV-PNOP-001 (CR005557)

Title of Study: A multicenter, randomized open-label study to compare the safety and efficacy of levofloxacin with that of imipenem/cilastatin in the treatment of nosocomial pneumonia

Investigators: 96 principal investigators; 29 investigators did not enroll subjects

Study Centre(s): 67 centers

Publication (Reference): None

Studied Period (years): 12 December 1997 - 07 June 2001

Phase of development: 3B

Objectives: The primary objective of this study was to compare the safety and efficacy of levofloxacin with that of imipenem/cilastatin in the treatment of nosocomial pneumonia due to susceptible organisms. A secondary objective of this study was to evaluate the pharmacokinetics/pharmacodynamics of levofloxacin in this subject population.

Methodology: This was a multicenter, randomized, open-label Phase 3B study conducted in the United States and Canada. Subjects were assigned to one of two treatment groups (levofloxacin or comparator) in a 1:1 ratio according to a computer-generated randomization schedule stratified by study center and by a subject's requirement for respiratory tract intubation. Efficacy evaluations included assessments of posttherapy (5 to 7 days [expanded to 3 to 15 days] following last dose of study medication) clinical response rates, posttherapy microbiologic response rates by pathogen and subject, poststudy (one month following completion of study drug) clinical relapse/new infection rates, and poststudy microbiologic relapse rates by pathogen and by subject in those subjects with a response of cured or improved at posttherapy. The clinical success rate (defined as cured and improved) in the group of subjects evaluable for microbiologic efficacy was the primary efficacy variable for this study. 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 subjects with a minimum of 80 in each treatment group to provide 160 clinically and microbiologically evaluable subjects. Enrolled 438 subjects: 187 evaluable for microbiologic efficacy (levofloxacin, 93; comparator, 94); 438 evaluable for safety.

Diagnosis and Main Criteria for Inclusion: Men and women aged 18 years of age or older with a diagnosis of nosocomial (hospital-acquired) pneumonia based on the following evidence: protocol-specified hospitalization stay during which the infection was acquired, radiographic evidence of acute pulmonary infiltrate due to infectious process, an Apache II score of ≤35, and either abnormal temperature or abnormal peripheral white blood cell count. Specimens from the respiratory tract and blood for culture were required for entry into the study. Additional criteria for subjects who failed previous antimicrobial therapy (≥72 hours systemic therapy prior to study entry) included repeat culture specimen obtained by bronchoscopy, needle aspirate, or biopsy and either continued fever or worsening of infiltrate by x-ray. Subjects with infections due to organisms resistant to either study drug, diagnosis of cystic fibrosis or prior diagnosis of bronchiectasis, empyema, calculated creatinine clearance <20 mL/min, neutropenia, documented infection with HIV with CD4 counts ≤200 cells/mm^3, or a pre-infection terminal illness for whom the episode of pneumonia was very likely to be a life-ending event were excluded from study entry.

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

Intravenous levofloxacin 25 mg/mL FD 25213-097-D-45 (Batch Numbers R6821, R9423, R10030)
Oral levofloxacin 500 mg FD 25213-097-AA-22 (Batch Numbers R6476, R8166, R9422, R10028)
Oral levofloxacin 250 mg FD 25213-097-AB-22 (Batch Numbers R6616, R10029)

SYNOPSIS (CONTINUED)

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)

Duration of Treatment: 7 to 15 days for both regimens (levofloxacin and reference therapy) as clinically indicated.

Reference Therapy, Dose and Mode of Administration, Batch No.: Imipenem/cilastatin 500 mg-1 g q6-8h i.v. After 72 hours of imipenem/cilastatin i.v., subjects could be switched to oral ciprofloxacin 750 mg q12h at the investigator's discretion.

imipenem/clavulanate NDC 0006-3516-59 (Batch Numbers R7322, R9404, R10026, R10347, 4096E, 4415H)
ciprofloxacin NDC 0026-8514-48 (Batch Numbers R7323, R9405, R10027, 7ADS, 8DEZ)

Criteria for Evaluation:

Efficacy:

- Clinical response assessed posttherapy (test of cure) 5 to 7 days (expanded to 3 to 15 days) following last dose of therapy. Posttherapy clinical response categorized as cure, improvement, failure, or unable to evaluate.
- Clinical relapse/new infection assessed poststudy (one month following completion of study drug) for subjects with a successful (cure or improvement) clinical outcome at the posttherapy visit. Poststudy clinical response was categorized as cure, clinical relapse/new infection, or unable to evaluate.

Microbiologic outcomes:

- Microbiologic response assessed posttherapy by pathogen, categorized as eradicated, presumed eradicated, persisted, presumed persisted, persisted with acquisition of resistance, or unknown.
- Microbiologic response assessed posttherapy by subject's infection, categorized as eradicated/presumed eradicated, persisted/presumed persisted, or unknown.
- Microbiologic response assessed posttherapy by blood pathogen, categorized as eradicated, persisted, presumed persisted, or unknown.
- Microbiologic relapse assessed poststudy by pathogen, categorized as eradicated, persisted, presumed persisted, microbiologic relapse, presumed microbiologic relapse, or unknown.
- Microbiologic relapse assessed poststudy by subject's infection, categorized as eradicated, persisted, 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 clinical response at the posttherapy (test-of-cure) visit based on the group of subjects evaluable for microbiologic efficacy. Secondary efficacy variables were: 1) the posttherapy and poststudy microbiologic responses by pathogen and by subject based on microbiologically evaluable subjects; 2) the posttherapy and poststudy (clinical relapse/new infection) clinical response based on the group of subjects evaluable for microbiologic and clinical efficacy; 3) the relationship between clinical and microbiologic response based upon subjects evaluable for microbiologic and clinical efficacy; 4) mortality due to or associated with nosocomial pneumonia; 5) time to normalization of temperature; 6) time to normalization of WBC count; 7) time to normalization of APACHE II score (<10); and 8) adjunctive therapy utilization. Two-sided 95% confidence intervals around the treatment difference (comparator minus levofloxacin) in posttherapy (test-of-cure) clinical success rates (cured and improved) were computed to assess therapeutic equivalence. Two-sided 95% confidence intervals around the treatment difference in posttherapy infection eradication rates overall and for the most prevalent pathogens were computed. Gehan's Generalized Wilcoxon test was used to compare times to normalization of temperature, WBC count, and APACHE II score between treatment groups.

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 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.

SYNOPSIS (CONTINUED)

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)

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Clinical Results: The posttherapy clinical success rate (cured and improved) for microbiologically evaluable subjects was 58.1% for levofloxacin-treated subjects and 60.6% for comparator-treated subjects (95% CI [-12.0, 17.2]). The 95% upper bound confidence interval is within 20% and statistically the clinical success rates for both treatment groups indicate that levofloxacin is at least as effective as comparator in the treatment of nosocomial pneumonia. The results were generally comparable among all efficacy analysis populations, with clinical success rates ranging from 58.1% to 66.2% in the levofloxacin treatment group and from 60.6% to 69.4% in the comparator treatment group.

Microbiologic Results: The posttherapy microbiologic response rates by infection (eradication of all admission pathogens for a subject) for microbiologically evaluable subjects were 66.7% in the levofloxacin treatment group and 60.6% in the comparator treatment group (95% CI [-20.3, 8.3]), indicating that levofloxacin is at least as effective as comparator in microbiologic eradication. The microbiologic eradication rates by admission pathogen were similar in the two treatment groups in both the ITT and microbiologically evaluable analysis populations. In microbiologically evaluable subjects, eradication rates for the 139 admission pathogens in each treatment group were 70.5% after levofloxacin treatment and 68.3% after comparator treatment (95% CI [-13.3, 9.0]). For the more prevalent category of admission respiratory pathogens in both treatment groups, the gram-negative aerobes (71.9% of pathogens in both groups), eradication rates were also higher in levofloxacin-treated subjects (73.0%) versus comparator-treated subjects (68.0%) (95% CI = [-18.1, 8.1]).

SAFETY RESULTS:

Both levofloxacin and imipenem/cilastatin followed by ciprofloxacin were safe and well-tolerated. The type and frequency of treatment-emergent adverse effects reported were consistent with the known safety profiles of these agents. Overall, 71.4% of subjects in the levofloxacin treatment group and 72.5% of subjects in the comparator treatment group reported at least one treatment-emergent adverse event during the study (95% CI [-7.5, 9.8]). The incidence 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 the occurrence of markedly abnormal laboratory findings were not notably different between treatments. Most were mild or moderate in severity and the majority was assessed as unrelated to the study drug. Deaths due to serious adverse events occurred with an incidence of 17.3% in the levofloxacin group and 14.7% in the comparator group; no deaths were considered treatment-related. For clinical laboratory test results, the observed mean changes were similar in direction in the two treatment groups and not clinically significant. Mean changes in vital signs from admission to posttherapy were not clinically significant. There were no unusual or unexpected treatment-emergent adverse events.

CONCLUSION:

Levofloxacin 750 mg administered i.v./oral once daily was shown to be as well tolerated and at least as effective as imipenem/cilastatin 0.5-1 g i.v. q6-8h (switched to ciprofloxacin 750 mg p.o. q12h) in the treatment of nosocomial pneumonia. The results of this study support the efficacy of levofloxacin in the treatment of nosocomial pneumonia associated with the following pathogens: *Staphylococcus aureus* (not methicillin-resistant), *Pseudomonas aeruginosa*, *Serratia marcescens*, *Escherichia coli*, *Enterobacter aerogenes*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*.

Date of the report: 14 December 2001

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.