SYNOPSIS

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

Protocol No: CR005494

Title of Study: A Multicenter, Active-Controlled, Randomized Study to Evaluate the Safety and Efficacy of Oral Levofloxacin Versus Cefaclor in the Treatment of Acute Bacterial Exacerbation of Chronic Bronchitis in Adults

Investigators: 27 principal investigators; 6 investigators did not enroll subjects; 1 investigator did not receive drug

Study Centres: 20 centers

Publications (Reference): None

Studied Period: 07 January 1992 - 13 July 1994	**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 cefaclor administered orally in the treatment of acute bacterial exacerbation of chronic bronchitis due to susceptible organisms in adult outpatients.

Methodology:
This was a randomized, open-label, active-control, multicenter study conducted in the United States, Canada, and Mexico. 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 of posttherapy microbiologic response rates by pathogen and by subject in those subjects with a response of cured or improved posttherapy and clinical response rates posttherapy (5-7 days following last dose of study drug). The primary efficacy variable for this study was the microbiologic response to treatment. The secondary efficacy variable was clinical response to treatment (defined as cured, improved, or failed) based on change in signs and symptoms and chest examination. Safety evaluations included incidence of treatment-emergent adverse events, and changes from admission to posttherapy in clinical laboratory test results and in physical examination.

Number of Subjects (planned and analyzed): Planned enrollment: 380 subjects for a minimum of 226 clinically and microbiologically evaluable subjects. Enrolled 373; subjects evaluable for efficacy and safety 372: 187 subjects received levofloxacin and 185 subjects received cefaclor.

Diagnosis and Main Criteria for Inclusion: Men and women aged 18 years of age or older with a diagnosis of acute bacterial exacerbation of chronic bronchitis based upon the following evidence: history of and physical findings consistent with chronic obstructive lung disease (chronic bronchitis and/or emphysema), recent increase in cough, and change in character and/or increase in production of sputum. Additional inclusions: subjects who received previous antimicrobial therapy for ≤24 hours and subjects who received previous antimicrobial therapy for >24 hours without improvement or stabilization.

Test Product, Dose and Mode of Administration:
Levofloxacin 488 mg oral q24h.

Duration of Treatment: 5 to 7 days for levofloxacin and 7 to 10 days for cefaclor

Reference Therapy, Dose and Mode of Administration:
Cefaclor 250 mg oral q8h.

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Criteria for Evaluation:

Microbiologic outcomes:

- Microbiologic response assessed posttherapy by pathogen and by subject.

Efficacy:

- Clinical response assessed posttherapy (5 to 7 days following last dose of therapy). Posttherapy clinical response categorized as cured, improved, failed, or unable to evaluate.

Safety:

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

Statistical Methods:

The primary efficacy variable was the microbiologic response to treatment and the secondary efficacy variable was clinical response to treatment (defined as cured, improved, or failed). 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. For microbiological response, two-sided 95% confidence intervals about the difference in eradication rates between levofloxacin and cefaclor were used to estimate equivalence.

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 physical examination. The proportion of subjects in each treatment group reporting at least one adverse event were compared using a two-sided 95% confidence interval about the difference in proportions. Similar confidence intervals were calculated for adverse events occurring within body systems of interest.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Clinical Results: Among clinically evaluable subjects in the levofloxacin treatment group, 72.1% were cured and 19.5% were improved, compared with 64.5% and 27.1% in the cefaclor treatment group, respectively. In each treatment group 13 (8.4%) subjects failed treatment. When the clinical response categories "cured" and "improved" were combined into a single category of "clinical success," levofloxacin and cefaclor treatment each resulted in 91.6% clinical success, with a 95% confidence interval of [-6.5, 6.6] for the difference (cefaclor minus levofloxacin) in success rates. The upper limit of this confidence interval lies below the confidence interval upper bound of 10%, thereby supporting clinical equivalence of the two treatments. Clinical response rates were generally comparable across analysis groups and centers.

Microbiologic Results: The overall microbiologic eradication rates by pathogen in the levofloxacin and cefaclor treatment groups were 95.0% and 86.5%, respectively, with a 95% confidence interval of [-16.4, -0.4], for the difference between treatments (cefaclor minus levofloxacin), assuming independence of multiple pathogens and multiple strains within a subject. The eradication rates by subject in the levofloxacin and cefaclor treatment groups were 94.2% and 86.5%, respectively, with a confidence interval of [-16.6, 1.3]. Using a confidence interval upper bound of 10% for eradication rates greater than 90%, this interval establishes therapeutic equivalence between the two treatments. Confidence intervals computed for each study center with 10 or more microbiologically evaluable subjects in each treatment group and for all other centers pooled demonstrate the consistency of results across centers. The most prevalent pathogens for both levofloxacin and cefaclor treatment groups were gram-negative aerobes (84.2% and 86.5% of pathogens for the levofloxacin and cefaclor groups, respectively); the remaining pathogens were gram-positive aerobes (15.8% and 13.5% of pathogens in the two treatment groups, respectively). The microbiologic eradication rates for gram-negative and gram-positive aerobes in the levofloxacin treatment group were 95.7% and 90.9%, respectively and in the cefaclor treatment group were 86.7% and 85.7%, respectively. There was 100% eradication of the most common pathogen (*H. influenzae)*, 94.7% eradication of the second most common pathogen (*M. [Branhamella] catarrhallis*), and 90.0% eradication of *S. pneumoniae* in the levofloxacin treatment group versus 70.8%, 100%, and 85.7% eradication in the cefaclor treatment group, respectively.

SAFETY RESULTS:

All except one of the 373 subjects enrolled were evaluated for safety. Of the 372 evaluable subjects, 187 received levofloxacin and 185 received cefaclor. No data were available from one cefaclor-treated subject who was lost to follow-up with no postadmission data available and who was therefore excluded from the safety analysis.

Sixty-four (34.2%) of 187 evaluable subjects in the levofloxacin treatment group and 62 (33.5%) of 185 evaluable subjects in the cefaclor treatment group reported at least one treatment-emergent adverse event during the study,

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including events considered by the investigator as related or unrelated to study drug. Body systems with the highest reported incidence of adverse events were the gastrointestinal system, the central and peripheral nervous system, and the body as a whole. Gastrointestinal adverse events were the most common adverse events in both treatment groups (17.1% for levofloxacin and 15.1% for cefaclor). Although not statistically significantly different, a higher percentage of levofloxacin-treated subjects (5.9% and 9.1%) compared with cefaclor-treated subjects (3.8% and 5.4%) reported psychiatric or central and peripheral nervous system adverse events; adverse events in these body systems consisted primarily of reports of headache, dizziness, and insomnia.

The most commonly reported individual adverse events were nausea, diarrhea, headache, and abdominal pain. The nature and frequency of individual adverse events were generally comparable across the two treatment groups, except for a higher incidence of insomnia in the levofloxacin group (4.3%) than in the cefaclor group (1.1%) and small differences between treatments in some specific gastrointestinal events.

Thirteen (7.0%) subjects in the levofloxacin treatment group and nine (4.9%) subjects in the cefaclor treatment group had adverse events considered by the investigator to be drug-related, i.e., probably or definitely related to study drug. Treatment-related adverse events reported by ≥1.0% of levofloxacin-treated subjects were nausea (2.1%), flatulence (1.6%), insomnia (1.1%), abdominal pain (1.1%), and diarrhea (1.1%). Treatment-related adverse events reported by ≥1.0% of cefaclor-treated subjects were diarrhea (2.2%), vaginitis (1.3%), and abdominal pain (1.1%).

The majority of adverse events were assessed as mild in severity. Seven subjects in the levofloxacin treatment group reported one or more adverse events of marked severity but no marked adverse event of a specific type was reported by more than one subject. Nine subjects in the cefaclor treatment group reported one or more marked adverse events, including respiratory disorders (exacerbation of COPD or respiratory insufficiency) in four subjects and diarrhea in two subjects. Of the two subjects with marked treatment-related adverse events, one was in the levofloxacin treatment group (abdominal pain) and one was in the cefaclor treatment group (diarrhea).

Eighteen (4.8%) subjects discontinued the study drug due to adverse events, including 12 (6.4%) subjects in the levofloxacin treatment group and six (3.2%) subjects in the cefaclor treatment group. In the levofloxacin group, all of the adverse events leading to discontinuation emerged within the first five days of therapy; these adverse events included primarily gastrointestinal complaints or central and peripheral nervous system-related symptoms. Treatment-limiting adverse events in the cefaclor group most frequently consisted of gastrointestinal complaints. One levofloxacin-treated subject and one cefaclor-treated subject died approximately three weeks after completing study therapy due to progression of their underlying disease.

Two subjects in the levofloxacin treatment group and eight subjects in the cefaclor treatment group reported a serious or potentially serious adverse event during or up to approximately one week after completing study therapy. Of the 10 subjects with serious or potentially serious adverse events, three withdrew from the study because of the adverse event. In all cases, the serious or potentially serious adverse event was considered by the investigator to be unrelated or remotely related to the study drug and, in many cases, appeared to be related to the subject's underlying respiratory condition.

There were no clinically significant treatment-emergent mean changes from admission to posttherapy for any laboratory analytes in either treatment group, and there were comparable results in both groups. The incidence of markedly abnormal test results for individual analytes within a given treatment group was low (≤3.2% for all analytes except lymphocyte count) and comparable across treatment groups. Thirty-four subjects (14 in the levofloxacin group and 20 in the cefaclor group) had a total of 39 markedly abnormal test results after the start of therapy. Eight (5.1%) subjects in the levofloxacin group and 11 (7.2%) in the cefaclor group had markedly decreased lymphocytes. Nine subjects had markedly abnormal glucose levels: one levofloxacin-treated and two cefaclor-treated subjects had increased glucose levels and one levofloxacin-treated and five cefaclor-treated subjects had decreased glucose levels. Two subjects in each treatment group had markedly abnormal liver function tests (elevations in SGOT, SGPT, or alkaline phosphatase).

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

CONCLUSIONS:

Levofloxacin was safe, well-tolerated, and effective in the treatment of subjects with acute bacterial exacerbation of chronic bronchitis. The microbiologic eradication rates in the levofloxacin treatment group were equivalent to those observed in the cefaclor group, as were the clinical response rates. These data support the efficacy of levofloxacin for acute bacterial exacerbation of chronic bronchitis due to *H. influenzae*, *H. parainfluenzae*, *M. (Branhamella) catarrhalis*, *S. pneumoniae*, and *S. aureus*.

Comparable results were seen across analysis groups for both clinical and microbiologic endpoints. In addition, there was

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concordance between the clinical and microbiologic responses based on a cross-tabulation of clinical response versus microbiologic response, further confirming the consistency of the clinical and microbiologic responses.		
Date of Report: 19 Jul 1995		

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