# 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: CR005485**

**Title of Study:** A Multicenter, Randomized Study to Compare the Safety and Efficacy of Oral Levofloxacin with Amoxicillin/Clavulanate Potassium in the Treatment of Acute Sinusitis in Adults

**Investigators:** 28 principal investigators; all investigators enrolled subjects

**Study Centres:** 28 centers

**Publications (Reference):** None

**Studied Period:** 26 August 1993 - 11 July 1994 **Phase of development:** 3

**Objectives:**

The primary objective of this study was to compare the safety and efficacy of levofloxacin administered orally with that of amoxicillin/clavulanate administered orally in the treatment of acute bacterial sinusitis.

**Methodology:** This was a randomized, open-label, active-control, multicenter study conducted in the United States. Subjects were assigned to 1 of 2 treatment groups (levofloxacin or comparator) in a 1:1 ratio according to a computer-generated randomization schedule. The clinical signs and symptoms were assessed at admission (Day 1), on-therapy (Days 3-6), at posttherapy (2-5 days after last dose of study drug), and at poststudy (28-32 days after the last dose of study drug). The primary efficacy variable for this study was the clinical response to treatment (defined as cured, improved, or failed) as measured by reduction of pretreatment signs and symptoms and stabilization/improvement of radiographic results. 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: 490 subjects. Enrolled: 615 subjects evaluable for efficacy and safety; 306 subjects received levofloxacin treatment and 309 received amoxicillin/clavulanate.

**Diagnosis and Main Criteria for Inclusion:** Men and women aged 18 years of age or older with a diagnosis of acute bacterial sinusitis, as evidenced by: fever, headache, purulent nasal discharge, facial pain or malar tenderness, radiographic evidence supporting the diagnosis. Additional inclusion: appropriate candidates for oral therapy. Subjects with the followed were excluded from study entry: chronic sinusitis (defined as duration of current symptoms for more than 4 weeks or more than 2 other episodes of acute sinusitis within the previous 12 months), previous allergic or serious adverse reaction to quinolones; calculated creatinine clearance ≤20 mL/min; requirement of a second systemic antimicrobial agent; effective systemic antimicrobial therapy within 48 hours prior to study admission; seizure disorder; or condition requiring tranquilizers.

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

**Duration of Treatment:** 10-14 days for levofloxacin and for amoxicillin/clavulanate

**Reference Therapy, Dose and Mode of Administration:**
Amoxicillin/clavulanate 500/125 mg PO q8h

**Criteria for Evaluation:**

Efficacy:

- Clinical response and stabilization/improvement of radiographic results assessed posttherapy 2 to 5 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 physical examination.

| | | |
|---|---|---|
| **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: | |

**Statistical Methods:**

The primary efficacy variable was the clinical response to treatment (defined as cured, improved, or failed). The safety analyses involved the examination of the incidence, severity, and type of adverse events reported during the study and by changes in physical findings and clinical laboratory tests from pre- to posttherapy.

The clinical responses of cured and improved were combined and classified as a clinical success in order to perform interval estimation. A two-sided 95% confidence interval about the difference in clinical success rates between the two treatment groups was provided to assess clinical equivalence.

**SUMMARY – CONCLUSIONS**

EFFICACY RESULTS:

Among clinically evaluable subjects in the levofloxacin treatment group, 58.4% were cured and 30.0% were improved, compared with 58.6% and 28.7% in the amoxicillin/clavulanate treatment group. Thirty-one (11.6%) subjects in the levofloxacin treatment group and 34 (12.7%) subjects in the amoxicillin/ clavulanate treatment group failed treatment. In the modified-intent-to-treat group, levofloxacin treatment resulted in 54.2% cure, 30.4% improvement, and 11.1% failure; 4.2% of the subjects could not be evaluated; amoxicillin/clavulanate treatment resulted in 53.7% cure, 30.1% improvement, and 13.6% failure, 2.6% of subjects could not be evaluated.

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 88.4% clinical success and amoxicillin/clavulanate treatment resulted in 87.3% clinical success, with a 95% confidence interval of [-6.8, 4.6] for the difference (amoxicillin/clavulanate-levofloxacin) in success rates. All of the treatment differences in this confidence interval lie below the upper bound of 15%, thereby establishing the therapeutic equivalence of the two treatments. Confidence intervals computed for each study center with 10 or more evaluable subjects in each treatment group and for all other centers pooled demonstrate the consistency of results across centers. In the modified-intent-to-treat group, the clinical success rates for treatment with levofloxacin and amoxicillin/clavulanate were 84.6% and 83.8%, respectively. The individual confidence intervals for all the analysis groups are centered below zero and are consistent with the therapeutic equivalence of the two treatments regarding clinical success rates.

Clinical response rates at the poststudy evaluation are summarized and cross-tabulated against clinical response rates at posttherapy for clinically evaluable subjects who had a poststudy assessment. Of 233 levofloxacin-treated subjects who were cured or improved at the posttherapy evaluation two to five days after completing therapy, only five had relapsed by the time of the poststudy evaluation approximately four weeks later, including two (1.3%) of the 154 who had been cured and three (3.8%) of the 79 who had improved. Among amoxicillin/clavulanate-treated subjects, the relapse rates were 1.9% and 7.9%, respectively, for subjects who were cured or improved at posttherapy.

Of 262 clinically evaluable levofloxacin-treated subjects with abnormal admission radiographic findings who underwent posttherapy radiographic examination, 215 (82.1%) showed either resolution (35.9%) or improvement (46.2%); similarly, of 262 clinically evaluable amoxicillin/clavulanate-treated subjects, 215 (82.1%) showed either resolution (35.5%) or improvement (46.6%).

SAFETY RESULTS:

Five hundred ninety-nine (97.4%) of 615 subjects enrolled were evaluated for safety. Of the 599 subjects, 297 received levofloxacin and 302 received amoxicillin/clavulanate. Sixteen subjects (nine in the levofloxacin treatment group and seven in the amoxicillin/clavulanate potassium treatment group) were lost to follow-up with no postadmission information available and therefore were excluded from the safety analysis.

One hundred fourteen (38.4%) of 297 subjects evaluated for safety in the levofloxacin treatment group and 146 (48.3%) of 302 safety-evaluable subjects in the amoxicillin/clavulanate treatment group reported at least one treatment-emergent adverse event during the study, including events considered by the investigator as related or unrelated to study drug. This difference between treatments in the overall rate of adverse events was statistically significant (ie, the 95% confidence interval does not include zero). Body systems with the highest reported incidence of adverse events were the gastrointestinal (GI) system and the central and peripheral nervous system. The incidence of GI-related adverse events was greater in the amoxicillin/clavulanate group (31.8%) than in the levofloxacin group (15.8%), with the difference being statistically significant. Adverse events in the other body systems occurred in fewer than 10.0% of subjects and were comparable between the two treatment groups, except for a statistically significant difference in psychiatric disorders (4.0% in the levofloxacin group vs. 1.0% in the amoxicillin/clavulanate group). Psychiatric events in the levofloxacin group consisted primarily of insomnia (2.4% of subjects) in addition to isolated reports of agitation, anxiety, nervousness,

| | | |
|---|---|---|
| **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: | |

sleep disorder, and somnolence.

The most frequently reported adverse events were nausea, diarrhea, and headache; nausea and headache were reported by similar percentages of subjects in each treatment group (6.7% and 6.1% for levofloxacin and 6.6% and 6.0% for amoxicillin/clavulanate). In contrast, diarrhea was reported more frequently in the amoxicillin/clavulanate group (19.9%) compared to the levofloxacin group (6.4%). Vaginitis and genital moniliasis were also somewhat more prevalent in the amoxicillin/clavulanate group than the levofloxacin group.

A smaller percentage of subjects in the levofloxacin treatment group (7.4%) than in the amoxicillin/ clavulanate treatment group (21.2%) had adverse events considered by the investigator to be drug-related, ie, probably or definitely related to study drug. Drug-related adverse events reported by ≥1.0% of levofloxacin-treated subjects were nausea (1.7%), diarrhea (1.3%), vaginitis (1.1%), and abdominal pain (1.0%). Drug-related adverse events reported by ≥1.0% of amoxicillin/clavulanate-treated subjects were diarrhea (11.6%), vaginitis (4.1%), nausea (4.0%), genital moniliasis (3.3%), abdominal pain (1.7%), vomiting (1.7%), and flatulence (1.3%).

The majority of adverse events were assessed as mild or moderate in severity. Seven subjects in the levofloxacin treatment group reported one or more adverse events of marked severity, including three subjects in whom the adverse events (abdominal pain and diarrhea; constipation; and urticaria) were considered by the investigator to be probably related to study therapy. Fifteen subjects in the amoxicillin/clavulanate treatment group reported adverse events of marked severity, including six with GI-related symptoms (eg, abdominal pain, nausea, or diarrhea) considered probably or definitely related to study drug.

No deaths occurred during the study. Twenty-seven subjects discontinued the study drug due to adverse events, including 11 (3.7%) of the 297 subjects evaluable for safety in the levofloxacin treatment group and 16 (5.3%) of the 302 subjects evaluable for safety in the amoxicillin/clavulanate treatment group. In the levofloxacin group, the subjects who discontinued due to adverse events included four subjects with urticaria, rash, or pruritis, four subjects with GI-related adverse events, one subject with both skin- and GI-related adverse events, and one subject each with asthenia/dizziness and influenza-like symptoms. In the amoxicillin/clavulanate group, all adverse event discontinuations were due to GI-related complaints except one case (fatigue).

Two levofloxacin-treated subjects experienced a serious adverse event within one week after completing study therapy (anemia in one subject and two instances of chest pain in another). Both of these adverse events resulted in hospitalization and neither was considered by the investigator to be related to study drug administration.

There were no clinically significant treatment-emergent mean changes from admission to posttherapy for any laboratory analytes in either treatment group, with comparable results in both groups. The incidence of markedly abnormal test results for individual analytes within a given treatment group was low (≤1.1%) and similar across treatment groups. Sixteen subjects (six in the levofloxacin group and 10 in the amoxicillin/ clavulanate group) had a total of 19 markedly abnormal treatment-emergent test results. Overall, five subjects had abnormal glucose levels: one subject in the levofloxacin group had increased glucose levels and two had decreased glucose levels; two subjects in the amoxicillin/clavulanate group had decreased levels. Five subjects (two in the levofloxacin group and three in the amoxicillin/clavulanate group) had elevations in SGPT or SGOT. Five subjects in the amoxicillin/clavulanate group, but none in the levofloxacin group, had markedly abnormal hematologic tests.

There were no clinically significant mean changes in vital signs from admission to posttherapy in the levofloxacin-treated or amoxicillin/clavulanate-treated subjects, with comparable results across 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 sinusitis. The clinical responses in the levofloxacin treatment group were therapeutically equivalent to those observed in the amoxicillin/clavulanate treatment group. These data support the efficacy of levofloxacin for acute bacterial sinusitis.

**Date of Report:** 19 Jul 1995