





<p><u>NAME OF SPONSOR/COMPANY:</u>    <small>Unit of Ortho-McNeil, Inc.</small>  <u>NAME OF FINISHED PRODUCT:</u>  LEVAQUIN®  <u>NAME OF ACTIVE INGREDIENT(S):</u>  Levofloxacin</p>	<p><u>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER</u></p> <p>Volume:   Page:</p>	<p><u>(FOR NATIONAL AUTHORITY USE ONLY)</u></p>
<p><b>Protocol No.:</b> CAPSS-349</p>		
<p><b>Title of Study:</b> A Multicenter, Double-Blind, Randomized Study to Compare the Efficacy and Safety of Levofloxacin 750 mg Once Daily for Five Days Versus Ciprofloxacin Twice Daily for Ten Days in the Treatment of Complicated Urinary Tract Infection or Acute Pyelonephritis</p>		
<p><b>Principal Investigator:</b> 113 principal investigators enrolled subjects; 40 additional investigators did not enroll subjects (see <a href="#">Appendix 1.4.1</a>).</p>		
<p><b>Publication (Reference):</b> Kaul S, Khashab M, Fisher A, Peterson J, Kahn J. Treatment of complicated urinary tract infections (cUTI) or acute pyelonephritis (AP) with once-daily levofloxacin 750 mg for 5 days compared to ciprofloxacin twice daily for 10 days: a randomized, double-blind study [abstract]. International Conference on Surgical Infections, September 6-8, 2006; Stockholm, Sweden.</p>		
<p><b>Study Initiation/Completion Dates:</b> 03 November 2004 – 11 April 2006</p>	<p><b>Phase of development:</b> 3B</p>	
<p><b>Objectives:</b> The primary objective of this study was to show that a 5-day course of levofloxacin 750 mg intravenously (i.v.) and/or orally (p.o.) once daily (q.d.) was as efficacious as a 10-day course of ciprofloxacin 400 mg i.v. and/or ciprofloxacin HCl 500 mg p.o. twice daily (b.i.d.) in the treatment of complicated urinary tract infections (cUTI) or acute pyelonephritis (AP). The primary endpoint was microbiologic response of the subjects' infections at the Posttherapy Visit. The secondary objectives were to assess the microbiological response at the Poststudy Visit; to assess the clinical response at the Posttherapy and Poststudy Visits; and to confirm the safety of levofloxacin 750 mg.</p>		
<p><b>Methodology:</b> This was a multicenter, randomized, double-blind, Phase 3B non-inferiority study conducted in the United States involving outpatient or inpatient adults with cUTI or AP. Subjects were stratified into 6 strata as follows: Stratum 1: AP subjects treated in an institution; Stratum 2: AP subjects treated in the community; Stratum 3: chronically catheterized cUTI subjects treated in an institution; Stratum 4: chronically catheterized cUTI subjects treated in the community; Stratum 5: non-chronically catheterized cUTI subjects treated in an institution; and Stratum 6: non-chronically catheterized cUTI subjects treated in the community. Subjects were randomized 1:1 to receive either levofloxacin or ciprofloxacin. Study drug was given either i.v. or p.o. or i.v. transitioning to p.o. at the investigator's discretion. Total duration of study drug administration for both arms was 10 days. Subjects randomized to levofloxacin received active therapy i.v. or p.o. in the morning and placebo i.v. or p.o. in the evening for 5 days, followed by 5 days of placebo in the morning and the evening. Subjects randomized to ciprofloxacin received 10 days of active therapy i.v. and/or p.o. b.i.d. The subjects were assessed clinically and microbiologically at 4 visits: Visit 1 Study Entry (Study Day 1), Visit 2 End of Therapy (Study Day 11±1), Visit 3 Posttherapy Visit (Study Days 15-19), and Visit 4 Poststudy (Study Days 38-45). Efficacy evaluations included microbiologic and clinical responses to treatment. Safety evaluations included incidence of treatment-emergent adverse events (AEs) that began on-therapy or up to 14 days after the last dose of active study drug and changes from admission to posttherapy in clinical laboratory test results and vital signs.</p>		
<p><b>Number of Subjects (planned and analyzed):</b> Planned enrollment: up to 1200 subjects, to provide at least 262 microbiologically evaluable and 540 modified intent-to-treat (mITT) subjects across both treatment groups. Enrolled: 1109 subjects, including 546 in the levofloxacin group and 563 in the ciprofloxacin group. Received at least 1 dose of study drug and relayed on-therapy safety information (safety population): 1102 subjects, including 543 in the levofloxacin group and 559 in the ciprofloxacin group. Randomized and received at least one dose of study medication (intent-to-treat [ITT] population): 1093 subjects, including 537 in the levofloxacin group and 556 in the ciprofloxacin group; mITT population: 619 subjects, including 317 in the levofloxacin group and 302 in the ciprofloxacin group; and microbiologically evaluable population: 506 subjects, including 265 in the levofloxacin group and 241 in the ciprofloxacin group.</p>		

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<p><b>Diagnosis and Main Criteria for Inclusion:</b> Adult (18 years of age or older) male and female outpatients or inpatients (e.g., hospital, chronic care, nursing home, or rehabilitation facility) were eligible for enrollment if they had a clinical diagnosis of cUTI or AP and evidence of pyuria by at least 1 of the following: a positive dipstick test for leukocyte esterase, <math>\geq 5</math> white blood cells (WBCs) per high power field (hpf) examination of centrifuged urine sediment, or <math>\geq 10</math> WBCs/mm<sup>3</sup> of uncentrifuged urine. AP was defined as the presence of least 2 of the following: fever <math>\geq 38^{\circ}\text{C}</math> or <math>\geq 100.4^{\circ}\text{F}</math> at the Study Entry Visit, flank pain or costovertebral angle (CVA) tenderness, peripheral WBC <math>&gt; 12,500/\text{mm}^3</math> or <math>\geq 10\%</math> bands, and WBC casts in urine; AND at least one of the following: nausea, vomiting, dysuria, increased urinary frequency compared to historical baseline, or urgency. All UTIs in males were considered cUTI. For cUTI in females, at least one of the following complicating factors was required: history of neurogenic bladder or urinary retention, partial obstruction of the urinary tract (not complete obstruction requiring surgery), or intermittent catheterization. Subjects were excluded from study entry if they had a history of allergy to any member of the quinolone class of antibacterials; urinary tract surgery or lithotripsy within 7 days of study entry; symptoms limited to uncomplicated UTI (females only); any infection within the previous 30 days treated with a quinolone; infections known to be caused by a bacterial pathogen resistant to any of the study medications; complete obstruction of any portion of the urinary tract; acute bacterial prostatitis or epididymitis; history of chronic bacterial prostatitis with evidence of tender prostate gland; polycystic kidney disease; nephrostomy tubes in place; only one functional kidney; renal or peri-renal abscess; emphysematous pyelonephritis or chronic pyelonephritis; calculated creatinine clearance <math>&lt; 50</math> mL/min; neutropenia; documented infection with HIV with CD4 counts <math>&lt; 200</math> cells/mm<sup>3</sup>; life expectancy <math>&lt; 72</math> hours; or seizure disorder or a psychiatric condition requiring use of major tranquilizers; or were pregnant or nursing.</p>		
<p><b>Test Product, Dose and Mode of Administration, Batch No.:</b> Levofloxacin 750 mg p.o. and/or i.v. q.d. Levofloxacin 750 mg capsules (Lot No. PD1179, PD1261, and PD1518) as over-encapsulated 750 mg LEVAQUIN® commercial tablets were supplied by PriCara. Placebo capsules (Lot No. PD1199, PD1260, and PD1520) were included in the medication kits. LEVAQUIN® Injection single-use vials/premixed containers were supplied by the study site (Lot No. 4BP0108, 4CP0117, 4CP0120, 4DP0129, 4GP0137, 4HP0149, 4JP0150, 4KP0168, 3HP0020, and 14088FJ).</p>		
<p><b>Reference Therapy, Dose and Mode of Administration, Batch No.:</b> Ciprofloxacin HCl 500 mg p.o. and/or ciprofloxacin 400 mg i.v. b.i.d. Ciprofloxacin HCl 500 mg tablets as over-encapsulated 500 mg Cipro® commercial tablets (Lot No. PD1180, PD1262, and PD1519) were supplied by PriCara. Cipro® Solution for injection was supplied by the study site (Lot No. 5400K2H, 54002HJ, 54004TG, 54004TK, 54005RR, 54005TO, 54006JN, 5400653, 5400658, 540080g, 2500LCX, 2500LN6, 2500LN7, and 2500L84).</p>		
<p><b>Duration of Treatment:</b> 10 days for all subjects. Subjects in the levofloxacin group received active therapy i.v. or p.o. as the morning dose followed by placebo i.v. or p.o. in the evening for 5 days, followed by 5 days of placebo b.i.d. only. Subjects in the ciprofloxacin group received 10 days of active therapy i.v. and/or p.o.</p>		
<p><b>Criteria for Evaluation:</b></p> <p><u>Efficacy:</u></p> <p><b>Primary Endpoint:</b></p> <p>The primary endpoint was microbiologic eradication of subjects' infections at the Posttherapy Visit in mITT and microbiologically evaluable subjects. Responses were categorized as eradicated, persisted/presumed persisted, or unknown. Eradication of pathogens (categorized as eradicated, persisted, persisted with acquisition of resistance, or unknown) was also evaluated to assist in the interpretation of the primary endpoint.</p> <p><b>Secondary Endpoints:</b></p> <p><u>Clinical Outcomes:</u></p> <ul style="list-style-type: none"> <li>▪ Clinical response at the Posttherapy Visit, based on resolution of signs and symptoms observed on admission. Posttherapy clinical response was categorized as cure, improvement, failure, or unable to evaluate.</li> <li>▪ Clinical response at the Poststudy Visit in subjects who completed therapy and were cured or improved at the Posttherapy Visit. Poststudy clinical response was categorized as long-term cure, long-term improvement, long-term clinical failure, or unable to evaluate.</li> </ul>		

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<p><u>Efficacy (Continued):</u>  <u>Microbiologic Outcomes:</u></p> <ul style="list-style-type: none"> <li>• Microbiologic response at the Poststudy Visit for subjects who completed therapy and were cured or improved at the Posttherapy Visit. Poststudy microbiologic response was categorized as long-term eradication, microbiologic relapse, microbiologic persistence, new infection, or unknown.</li> </ul> <p><u>Safety:</u> Occurrence of treatment-emergent AEs during the study; changes from admission to posttherapy in clinical laboratory test results, physical examination findings, and vital signs.</p>		
<p><b>Statistical Methods:</b> The primary efficacy variable was microbiological eradication of subjects' infections at the Posttherapy Visit in the co-primary mITT and microbiologically evaluable efficacy analysis populations. A two-sided 95% confidence interval (CI) around the difference between treatment groups (comparator minus levofloxacin) was computed. To conclude that a 5-day course of levofloxacin 750 mg/day was at least as efficacious as a 10-day course of ciprofloxacin, the upper bound of the 95% CI had to be less than or equal to 15%.</p> <p>Secondary efficacy variables were: 1) microbiologic response by pathogen and by subject at the Poststudy Visit in microbiologically and mITT evaluable subjects; 2) clinical response at the Posttherapy Visit in microbiologically and mITT evaluable subjects; 3) clinical response at the Poststudy Visit in microbiologically and mITT evaluable subjects; and 4) clinical response at the Poststudy Visit in microbiologically and mITT evaluable subjects who were cured or improved at posttherapy and had all study entry pathogens microbiologically eradicated. Two-sided 95% CIs around the treatment differences in posttherapy clinical success (cured plus improvement) rates and microbiologic eradication rates of subjects' infections and for the most prevalent pathogens were computed.</p> <p>Descriptive statistics were used to summarize treatment-emergent AEs and pretherapy to posttherapy changes in laboratory test results and vital signs. Two-sided 95% CIs were calculated for the differences between the treatment groups in the rates of treatment-emergent AEs overall and within each body system.</p>		
<p><b>SUMMARY - CONCLUSIONS</b></p> <p><u>EFFICACY RESULTS:</u></p> <p><b>Primary Endpoint:</b></p> <p><u>By-Subject Eradication Rates:</u> At the Posttherapy Visit assessment (window expanded to 15 to 22 days after the first dose of study drug prior to unblinding), the overall (cUTI and AP) microbiologic eradication rate by subjects' infections in the microbiologically evaluable population was 86.0% in the levofloxacin group and 89.2% in the ciprofloxacin group; the two-sided 95% CIs around the difference (ciprofloxacin minus levofloxacin) was (-2.5, 8.9). The overall microbiologic eradication rate by subjects' infections in the mITT population was 75.7% in the levofloxacin group and 75.8% in the ciprofloxacin group; the 95% CI for treatment differences was (-6.6, 6.9). For each of these co-primary populations, the upper bound of the 95% CI was below 15%, which indicates that levofloxacin 750 mg/day p.o. and/or i.v. for 5 days is at least as efficacious as ciprofloxacin HCl 500 mg p.o. and/or ciprofloxacin 400 mg i.v. b.i.d. for 10 days for the treatment of cUTI and AP. The results for each separate diagnosis (cUTI and AP) were similar to the overall results.</p> <p><u>By-Pathogen Eradication Rates:</u> The overall microbiologic eradication rate by pathogen at the Posttherapy Visit was 85.9% for the levofloxacin group and 89.6% for the ciprofloxacin group for the microbiologically evaluable population; the 95% CI around the difference was (-1.9, 9.3). For the mITT population, the overall microbiologic eradication rates by pathogen were 75.5% and 76.3%, respectively, with a 95% CI of (-5.9, 7.3). The results for each separate diagnosis (cUTI and AP) were similar to the overall results. The eradication rates by pathogen support the primary endpoint of microbiologic eradication by subjects' infections and confirm comparability (upper bound &lt;15%) of treatments.</p>		

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<p><u>EFFICACY RESULTS (Continued):</u></p> <p><b>Secondary Endpoints:</b></p> <p><u>Clinical Results:</u> For the microbiologically evaluable and mITT populations at posttherapy, the clinical cure plus improvement rates were similar in the levofloxacin (86.4% and 81.1%, respectively) and ciprofloxacin (88.4% and 80.1%, respectively) groups overall. Similar clinical success rates between treatments were also seen for the subgroups of subjects with cUTI and AP. More than 75% of subjects experienced resolution of each study entry urinary sign and symptom by the posttherapy evaluation.</p> <p>At the poststudy follow-up assessment (38 to 45 days after the first dose of study drug), 8.1% of microbiologically evaluable subjects in the levofloxacin group and 8.6% of subjects in the ciprofloxacin group overall had experienced clinical relapses. The corresponding proportions of mITT subjects who were clinical relapses at poststudy were 8.7% and 8.6%.</p> <p><u>Microbiologic Results:</u> At poststudy, 6.0% of levofloxacin-treated subjects and 5.6% of ciprofloxacin-treated subjects in the microbiologically evaluable population had a response of relapsed (includes presumed relapsed). The corresponding microbiological relapse rates in the mITT population were 6.3% and 5.4%. Long-term eradication rates were similar in subjects with cUTI and AP in both treatment groups and for both efficacy populations.</p> <p><u>SAFETY RESULTS:</u> Levofloxacin 750 mg/day p.o. and/or i.v. q.d. for 5 days was safe and well-tolerated in subjects with cUTI or AP. Overall, 35.4% of subjects in the levofloxacin group and 33.1% of subjects in the ciprofloxacin group reported at least 1 treatment-emergent AE (beginning on-therapy or anytime up to 14 days after the last dose of active study drug). The 95% CI around the difference was (-7.9, 3.3), indicating that the overall rates of treatment-emergent AEs were comparable between the two treatment groups. The most commonly reported AEs in both the levofloxacin and ciprofloxacin groups were nausea (6.4% and 6.8% of subjects, respectively), headache (3.5% and 5.2%, respectively), and diarrhea (3.1% and 3.2%, respectively). There were no apparent differences in the rates of any individual AEs between the two treatment groups (i.e., &gt;2% difference). The types and rates of treatment-emergent AEs observed with the levofloxacin 750 mg/day p.o. and/or i.v. for 5 days regimen evaluated in this study are consistent with the known safety profile of levofloxacin.</p> <p>No notable differences were observed between the levofloxacin and ciprofloxacin groups in the incidence of serious adverse events (3.1% versus 2.7%, respectively). The percentage of subjects with AEs that resulted in the discontinuation of therapy was 5.2% in the levofloxacin group and 2.9% in the ciprofloxacin group, and the percentage of subjects with markedly severe AEs was 9.9% and 11.9%, respectively. One death occurred in each treatment group; the deaths were unrelated to study treatment. There were no unusual or unexpected treatment-emergent safety problems associated with the use of levofloxacin 750 mg/day to treat cUTI or AP.</p> <p><u>CONCLUSION:</u> Levofloxacin 750 mg administered p.o. and/or i.v. once daily for 5 days was well tolerated and at least as effective as the ciprofloxacin HCl 500 mg p.o. and/or ciprofloxacin 400 mg i.v. b.i.d. for 10 days for the treatment of cUTI and AP. The results of this study support the efficacy of levofloxacin 750 mg/day for 5 days in the treatment of subjects with cUTI or AP associated with the following susceptible pathogens: <i>Escherichia coli</i>, <i>Klebsiella pneumoniae</i>, <i>Enterococcus faecalis</i>, or <i>Proteus mirabilis</i>.</p> <p>Date of the report: 16 October 2006</p>		

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