

SYNOPSIS (CONTINUED)

<p><u>NAME OF SPONSOR/COMPANY:</u> Ortho-McNeil Pharmaceutical, Inc.</p> <p><u>NAME OF FINISHED PRODUCT:</u></p> <p><u>NAME OF ACTIVE INGREDIENT(S):</u> Levofloxacin® and Metronidazole®</p>	<p><u>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER</u></p> <p>Volume:</p> <p>Page:</p>	<p><u>(FOR NATIONAL AUTHORITY USE ONLY)</u></p>
<p>Patients were randomized to 1 of 2 treatment arms:</p> <ul style="list-style-type: none"> Patients received levofloxacin 750 mg IV (either a single 750-mg bag or combination of IV doses to total 750 mg) plus metronidazole 1500 mg IV (combination of IV doses to total 1500 mg) every 24 hours. Initially all patients were treated with IV therapy. Patients randomized to levofloxacin/metronidazole were permitted to switch after 48 hours of IV therapy at the discretion of the investigator from the above IV levofloxacin/metronidazole regimen to an oral regimen of levofloxacin/ metronidazole: levofloxacin 750 mg by mouth (either a single 750 mg tablet or combination of tablets to total 750 mg) every 24 hours and metronidazole 1500 mg by mouth (a combination of tablets to total 1500 mg) every 24 hours. Patients received piperacillin/tazobactam 3.375 grams IV every 6 hours. Patients randomized to IV piperacillin/tazobactam were permitted to switch after 48 hours of IV therapy at the discretion of the investigator from the above intravenous to an oral regimen of amoxicillin/clavulanate acid: amoxicillin/clavulanate 875 mg/125 mg by mouth every 12 hours. <p>Patients were evaluated daily while hospitalized. At the time of hospital discharge, the investigator prescribed the remaining required duration of study drug for the patient. Patients were evaluated 7-14 days post-therapy (Post-Therapy Visit) at which time they were assessed for clinical response and for the possibility of surgical complications. Additionally, long-term clinical response was assessed 30-34 days post-therapy (Post-Study Phone Contact).</p>		
<p>Number of Patients (planned and analyzed): The original plan was to enroll 144 clinically evaluable patients to each group. This required an estimated 420 randomized patients. However, the study was administratively terminated due to lack of enrollment. Despite repeated efforts to improve patient accrual the sponsor, Ortho-McNeil Pharmaceutical, Inc., decided to terminate enrollment due to slow accrual, as only 33% (139/420) of the planned cohort was randomized after 1 year and only 60% (83/139) of these had the diagnosis of complicated appendicitis.</p>		
<p>Diagnosis and Main Criteria for Inclusion: Patients who met entry criteria for the study were enrolled. Patients must have exhibited either of the following: at least 2 clinical signs and symptoms of appendicitis present for at least 24 hours or radiologic evidence demonstrating changes consistent with complicated appendicitis.</p>		
<p>Test Product, Dose, and Mode of Administration, Batch No.: Levofloxacin 750 mg intravenous or orally (IV/po) followed by metronidazole 1500 mg IV once daily for 4-14 days. Levofloxacin 750 mg intravenous batch nos.: R12145; Levofloxacin 750 mg orally batch nos.: R12146. Study drug was sent to 2 sites.</p>		
<p>Reference Therapy, Dose, and Mode of Administration, Batch No.: Piperacillin/tazobactam 3.375 grams IV every 6 hours for 4-14 days; after 48 hours, patients may have received amoxicillin/clavulanate 875/125 by mouth every 12 hours. Piperacillin/tazobactam and amoxicillin/clavulanate were open-stock medications from the individual institution pharmacies.</p>		
<p>Duration of Treatment: Patients were to receive study drug to complete a total of 4-14 days of therapy.</p>		

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<p>Criteria for Evaluation: The investigator determined a clinical response for each patient by comparing the patient's signs and symptoms of appendicitis at the Post-Therapy Visit to those recorded at admission. Patients were classified as: clinical cure, clinical improvement, clinical failure, or unable to evaluate. Safety evaluations included daily examination of the patients while they were hospitalized, as well as follow-up 7 to 14 days post-therapy (Post-Therapy Visit) and 30-34 days post-therapy (Post-Study Phone Contact). Changes in physical findings, including vital signs, and assessment of the presence of possible adverse events were performed by the investigator at study visits. Adverse events and antibiotic concomitant medications were collected at each Post-Therapy Visit and Post-Study Phone Contact.</p>		
<p>Statistical Methods: The primary efficacy endpoint was clinical success at the Post-Therapy Visit (7-14 days post-therapy) among the MITT and the clinically evaluable patients. Secondary efficacy endpoints included:</p> <ul style="list-style-type: none"> • Long-term clinical response at the Post-Study Phone Contact Visit among MITT and clinically evaluable patients; • Resolution or Improvement of clinical signs and symptoms of complicated appendicitis: Resolution of clinical symptom, i.e. symptom 'present' at admission and 'absent' at the Post-Therapy Visit; • Average length of hospital stay: The length of hospital stay was calculated for each patient as the Date of Hospital Discharge minus Date of Surgery + 1; • Duration (days) of IV therapy; • Duration (days) of oral therapy; • <i>In vitro</i> susceptibility of pathogens identified at the time of admission. <p>The <i>in vitro</i> susceptibility of pathogens identified at admission was summarized by pathogen and by treatment group. All other data were summarized by treatment group. Long term clinical response, symptoms (fever, nausea, chills and vomiting) of complicated appendicitis, resolution or improvement of clinical signs and symptoms (nausea, vomiting, fever and WBC), and <i>in vitro</i> susceptibility of pathogens were summarized with frequency counts and percentages. The average length of hospital stay and durations of IV and oral therapies were described with summary statistics.</p> <p>For the analysis of drug dispensing/administration costs, a site was selected which was believed to hold potential for high enrollment and which also had costs representative of the majority of sites.</p> <p>The clinical success rates were compared using a 2-sided 95% confidence intervals (CI) with continuity correction for the difference between treatment groups. The symptoms of appendicitis and surgery information were summarized by treatment group. The length of hospital stay was also summarized by treatment group.</p>		

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<p>Statistical Methods (continued):</p> <p>The frequency of each clinical response was presented for each treatment group. A 2-sided 95% CI (using normal approximation to the binomial with a continuity correction)²¹ was constructed for the difference of clinical success rates between the 2 treatment groups (piperacillin/tazobactam minus levofloxacin/metronidazole) at the Post-Therapy Visit for the MITT and Clinically Evaluable Populations. To claim that levofloxacin was at least as efficacious as the comparator, the upper bound of 95% CI had to be less than 15%.</p> <p>Safety analyses included examinations of the incidence, severity, relationship to study drug and type of adverse events and changes from baseline in vital signs and clinical laboratory tests. Safety data were summarized for the ITT Safety and the MITT Safety populations.</p>		
<p>SUMMARY - CONCLUSIONS</p>		
<p>EFFICACY RESULTS:</p> <p>A total of 139 patients were enrolled and randomized. Of the 73 patients randomized to the levofloxacin/metronidazole (levofloxacin arm) arm, 43 patients had complicated appendicitis and 30 had uncomplicated appendicitis. Of the 66 patients who were randomized to the piperacillin/tazobactam (comparator arm) arm, 40 patients had complicated appendicitis and 26 had uncomplicated appendicitis. Among those patients who had complicated appendicitis at the time of surgery:</p> <ul style="list-style-type: none"> • 36 patients in the levofloxacin arm and 32 patients in the comparator arm completed the 4 to 14 day treatment regimen; • 31 patients in the levofloxacin arm and 29 patients in the comparator arm completed the study through the Post-Therapy Visit; • 29 patients in the levofloxacin arm and 29 patients in the comparator arm completed the study through the Post-Study Phone Contact, respectively. <p>Patients ranged in age from 19 to 72 years, with a mean age of 39.9 years. The majority of the patients were male (62.7%). The mean Total Apache II Score was 4.3.</p> <p>The clinical success rates based on the MITT population were 72.1% for levofloxacin/metronidazole arm and 80.0% for piperacillin/tazobactam arm with a 95% CI (-11.6%, 27.4%) for the difference of clinical success rates between the 2 treatment groups. Similarly, the clinical success rates based on the Clinically Evaluable Population were 73.3% for levofloxacin/metronidazole arm and 88.9% for piperacillin/tazobactam arm with a 95% CI (-14.5%, 45.6%) for the difference of clinical success rates between the 2 treatment groups.</p> <p>Due to low patient numbers, no conclusion can be drawn from these findings. In the MITT population, a single patient's scoring in a different clinical success category would have made an approximately 2.5% difference in the percentages in his/her treatment group. In the Clinically Evaluable Population, a single patient's scoring in a different success category would have made an approximately 6% difference in the percentages in his/her treatment group.</p>		

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<p><u>EFFICACY RESULTS (continued):</u></p> <p>There is clinical evidence that random imbalances in distribution between these 2 small groups of MITT patients may have influenced the efficacy evaluation. Patients with more severe variants of complicated appendicitis may have been randomized to the levofloxacin/metronidazole treatment regimen. This is demonstrated in the invasiveness of the surgical procedure used, in the intraoperative surgical findings and the percentage of patients deemed eligible for primary closure of their surgical incision. While 30 (69.8%) of patients randomized to the levofloxacin/metronidazole regimen required an open incision procedure, this more invasive procedure was used in only 19 (47.5%) of the patients randomized to the piperacillin/tazobactam regimen; conversely, the less invasive laparoscopic procedure was deemed appropriate and used in 11 (25.6%) and 19 (47.5%) of randomized patients, respectively. Six (14.0%) of patients receiving the levofloxacin/metronidazole regimen had a gangrenous appendix with resultant abscess, only 3 (7.5%) of patients receiving the piperacillin/tazobactam regimen had these findings. The incidence of uncomplicated, gangrenous appendix was lower in the levofloxacin/metronidazole recipients: 12 (27.9%) vs. 14 (35.0%). Only 25 (58.1%) of patients receiving levofloxacin/metronidazole vs. 29 (72.5%) of piperacillin/tazobactam recipients were deemed to be at low enough risk for subsequent complications to warrant primary closure of their surgical incision.</p> <p>Both the median and mean APACHE II scores differed by ≥ 1 point in the piperacillin/tazobactam recipients vs. the levofloxacin/metronidazole recipients, with higher scores noted in the piperacillin/tazobactam group. This finding indicates that, in general, the piperacillin/tazobactam recipients actually may have appeared to be in somewhat more distress at the time that they presented (i.e., baseline) than the levofloxacin/metronidazole recipients.</p> <p>Based on these findings, efficacy favoring one of these treatment regimens over the other cannot be concluded.</p> <p><u>SAFETY RESULTS:</u></p> <p>In the MITT population, adverse events were reported by 74.4% of patients in the levofloxacin/metronidazole arm. In the comparator arm, adverse events were reported by 80.0% of patients. The majority of patients reported adverse events that were considered by the investigator to be unrelated to treatments. In both treatment arms, adverse events occurred most frequently in the gastrointestinal system, body as a whole, and metabolic and nutritional system. Respiratory system disorders, central and peripheral nervous system disorders, liver and biliary system disorders, red blood cell disorders, and urinary system disorders were also common.</p> <p>The majority of patients in the MITT population reported adverse events of mild or moderate severity. Adverse events of severe intensity in the levofloxacin arm were fever, diarrhea, diverticulitis, ileus, intestinal obstruction, neoplasm NOS, infection, and dyspnea. In the comparator arm, adverse events of severe intensity included ileus and abscess.</p>		

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<p>SUMMARY - CONCLUSIONS</p>		
<p><u>SAFETY RESULTS (continued):</u></p> <p>Treatment-related adverse events for the MITT population were reported by 10 patients in the levofloxacin and 7 patients in the comparator arm. In the levofloxacin arm, nausea was the most frequently reported treatment-related adverse event followed by vomiting, constipation, and diarrhea. In the comparator arm diarrhea and nausea were the most frequently reported treatment-related adverse events. Other treatment-related adverse events were reported in ≤2 patients in each treatment arm. In the MITT population, a total of 21 patients (12 patients in the levofloxacin arm and 9 patients in the comparator arm) discontinued or withdrew prematurely from therapy. The primary reasons for discontinuation in the levofloxacin arm were: discontinuation due to adverse events (7 patients), and lost to follow-up (3 patients). The primary reasons for discontinuation in the comparator arm were also adverse event (2 patients), lost to follow-up (3 patients), and protocol violation (3 patients).</p> <p>A total of 17 serious adverse events were reported in 15 patients, 10 in the levofloxacin arm and 5 in the comparator arm. The majority of serious adverse events were moderate to severe in intensity and considered by the investigator to be not related or to have an unlikely relationship to treatment. Five (5) serious adverse events (4 in the levofloxacin arm and 1 in the comparator arm) led to premature discontinuation of therapy. There were no deaths reported during the study nor any deaths that occurred up to 30-34 days after the last dose of study drug.</p> <p>In addition, concomitant medication data for anti-infectives was slightly greater for patients in the levofloxacin arm when compared to patients in the comparator arm (58.1% vs. 47.5%). This may or may not be clinically important as the medications in this category include all anti-infectives, including topical agents. This difference could also be due to the patients in the levofloxacin arm being more ill and or more complicated than those randomized to the comparator arm of the study. There was a greater number of patients in the levofloxacin arm that required an open incision or intraperitoneal lavage as part of their surgical procedure as compared to patients in the comparator arm.</p> <p>No unexpected findings or trends were noted in vital signs and clinical laboratory parameters over the treatment period with levofloxacin or comparator. There were no meaningful differences in safety between levofloxacin and comparator therapy.</p> <p><u>CONCLUSION:</u></p> <p>The following conclusions can be drawn from this administratively terminated study:</p> <ul style="list-style-type: none"> • No conclusion with respect to efficacy can be reached. • Levofloxacin/metronidazole combination therapy appears to be safe and well tolerated. 		
<p>Date of the report: 10 May 2005</p>		