

blood gas revealed marked metabolic acidosis. A chest x-ray revealed markedly reduced lung volumes. The patient was sent to the ICU where he became asystolic. His abdomen was reopened at bedside and 800 ml of blood and fluid were found in the abdominal cavity. The patient died after several attempts were made to resuscitate. The pathologist ruled out a pulmonary embolism as the cause of death. Acidosis was believed to be the cause of death. The reporting physician felt that the acute myocardial infarction, acidosis, asystole, and death were definitely not related to study drug therapy.

AN 5335

A 67-year-old female with syncopal episodes, severe abdominal pain, ascites, metastatic disease of diaphragm, liver and pelvic area, began IV therapy with MK-0826 for the treatment of peritonitis due to perforated gastroduodenal ulcer. After her abdominal surgery, the patient was treated with chemotherapy for her malignancy on Study Day 1. The patient received her last dose of study drug on Study Day 6. The patient's condition deteriorated quickly and the patient died on Study Day 32. The investigator felt that the malignant ovary neoplasm and death were definitely not study drug related.

AN 5340

A 76-year-old male with arthritis, atrial fibrillation, psoas abscess, and a history of gout, arrhythmia, and anemia began IV therapy with MK-0826 for the treatment of intra-abdominal infection. On Study Day 14, study drug therapy was completed and on Study Day 15, the patient was discharged from the hospital to a rehabilitation unit. During the rehabilitation the patient experienced intermittent confusion and constipation. On Study Day 34, the patient developed an intra-abdominal infection and on Study Day 35, the patient developed acute renal failure. A Hickman catheter was placed and hemodialysis was started. On Study Day 36, an exploratory laparotomy was performed with right hemicolectomy, psoas abscess drainage, and end-ileostomy with mucous fistula. The patient was found to have a cecal perforation (the end of the appendix was leaking). On Study Day 37, the patient suffered an anterior septal myocardial infarction (life threatening). The patient's family indicated that the patient should not be resuscitated. The patient expired on Study Day 51 due to myocardial infarction. The investigator felt that the intra-abdominal infection, myocardial infarction, renal failure, and death were definitely not study drug related.

AN 5609

A 36-year-old female with peritonitis, bacterial sepsis, gastric ulcer, duodenal ulcer and a history of peptic ulcer began IV therapy of MK-0826 for the treatment of an intra-abdominal infection following surgery for a perforated gastric ulcer with associated peritonitis. On Study Day 2, the patient developed worsening peritonitis. Study drug therapy was discontinued on Study Day 3. The worsening peritonitis reportedly led to worsening sepsis on Study Day 2. On Study Day 29, the patient died and the cause of death was sepsis. The reporting physician felt that the peritonitis and bacterial sepsis were definitely not related to study drug therapy.

AN 5644

A 66-year-old female with chronic body pain, tenderness over the entire abdomen, dehydration, history of foot ulcer, tonsillectomy and diabetes mellitus began IV therapy with MK-0826 following surgery for perforated duodenal ulcer. The patient was tachycardic and had low urine output upon admission and throughout the hospital stay. The emergency medical service had given the patient furosemide during transport to the hospital for rales heard in the lungs upon evaluation. Concomitant therapy included meperidine, cimetidine, glucose/potassium chloride preparation, calcium gluconate, magnesium sulfate, morphine sulfate, general anesthesia, ampicillin, metronidazole, and gentamicin. On Study Day 2, the patient experienced an episode of respiratory distress which was reported to be related to sepsis. The patient was intubated and transferred to the ICU. The patient was paralyzed for respiratory management. Study drug therapy was discontinued on Study Day 4 when a single isolate of *Candida* was identified in the patient's peritoneal fluid. On Study Day 19, the patient developed gradually worsening acute respiratory distress syndrome and was subsequently changed to "no code" status. The patient was kept comfortable on supportive care only. On Study Day 20, antibiotics, fluids, and ventilator support were discontinued and the patient subsequently died. The cause of death was reported to be related to respiratory distress. The reporting physician felt that the patient's respiratory distress and death were definitely not related to study drug therapy.

AN 5784

A 68-year-old male with urinary tract infection (infected with vancomycin resistant *Enterococcus*), diarrhea, pain, severe peripheral vascular disease, decubitus ulcer of the coccyx, infected amputation site, glaucoma, and a history

of colon carcinoma, colostomy, clostridium difficile toxin, above-the-knee amputation, axillofemoral-popliteal bypass, and pelvic ulcer disease began IV therapy of MK-0826 for the treatment of an intra-abdominal infection. While on study drug therapy, the patient continued to have signs of infection in the lower left quadrant of the abdomen. On Study Day 9, the patient's transaminases and phosphatase were "markedly abnormal" and the patient developed sepsis. On Study Day 9, the patient was discontinued from the study and placed on therapy with ciprofloxacin, metronidazole (Flagyl), and amphotericin B. On Study Day 11, the patient's ALT, AST and alkaline phosphatase were all considered normal. On Study Day 15, the patient received a transfusion. On the same day, the patient fell (nonserious) out of the bed onto the floor and seemed confused and unaware of his whereabouts. Two (2) hours later, the patient died. The study investigator felt that the transient elevations in the liver function tests were probably related to study drug therapy, but he felt that the patient's death was due to sepsis and definitely not related to study drug therapy.

AN 5947

A 68-year-old female with a history of pneumonia, colonic perforation, colectomy, colostomy, and progressive supranuclear palsy began IV therapy of MK-0826 for the treatment of intra-abdominal infection following drainage of a pelvic abscess. The patient was intubated. The patient's condition slowly improved and on Study Day 5 the patient was extubated. The patient remained febrile with coarse breath sounds. The abdominal wound was healing well with no obvious signs of infection. A follow-up abdominal CT scan revealed no further fluid collection. The patient was doing well on Study Day 6 at 2000 hours. On Study Day 7, the patient developed airway obstruction and at 2130 hours the patient was found to be unresponsive with no response to deep pain. The patient was pronounced dead at 2140 hours on Study Day 7. The investigator felt that the patient's airway obstruction and death were definitely not related to study drug.

***Medical Officer's Comment:** Additional information regarding this patient's death was requested from the Applicant and the Applicant submitted the requested information in their July 30, 2001 submission to the NDA. Additional useful information obtained from the patient's autopsy report included the pathologist's conclusion that the patient's death was secondary to acute and chronic aspiration, which was a complication of progressive supranuclear palsy and that contributing factors included: peritonitis, sepsis, and pelvic abscess.*

**MK-0826 1.5 Treatment Group**

AN 5103

A 65-year-old male with sepsis, diabetes mellitus, sacral decubiti, hypotension, low cardiac output, oliguria, metabolic acidosis, decreased temperature, congestive heart failure, decreased pulse, and a history of coronary artery disease and hyperlipidemia began IV therapy of MK-0826 for the treatment of an intra-abdominal infection due to anastomotic leak that resulted in peritonitis. Concomitant therapy included dopamine, amrinone, norepinephrine, heparin and sodium bicarbonate. On Study Day 8, atrial fibrillation was diagnosed, which was treated with procainamide. Additional symptoms of the arrhythmia (disabling and life threatening) were a decreased bicarbonate and left bundle branch block. Increased Blood Urea Nitrogen and creatinine were also noted on Study Day 8. The hospital's renal service was consulted and prerenal azotemia was diagnosed. The patient had a low cardiac index and a combination of amrinone and levophed was started. He became oliguric and diuretics were discontinued. A venous duplex on Study Day 8 revealed bilateral common femoral deep vein thrombosis which was treated with heparin. On Study Day 8, he was diagnosed with renal failure (life threatening) with additional symptoms of hypotension, red blood cells in his urine, and an increased sodium level. On Study Day 9, the patient was diagnosed with worsening congestive heart failure (life threatening) with symptoms of anasarca and tachypnea. Also on Study Day 9, the patient developed septic shock (life threatening) with hypotension which required therapy with fluid boluses and dopamine. A Computed Tomography scan performed on Study Day 10 demonstrated no new intra-abdominal collections but the patient had developed bilateral pulmonary effusions. The patient was placed on a furosemide drip. On Study Day 10, the patient's family had met with the attending physician and support measures were withdrawn. The patient died shortly thereafter. The cause of death was reported to be sepsis. The reporting physician felt that hypotension, atrial fibrillation, renal insufficiency, deep vein thrombosis, edema/swelling, arrhythmia, heart failure, left bundle branch block, ventricular tachycardia were definitely not related to study drug therapy and the oliguria/anuria, increased BUN, fever, idioventricular rhythm, septic shock and death were probably not related to study therapy.

***Medical Officer's Comment:*** Additional information regarding this patient's death was requested from the Applicant and the Applicant submitted the requested information in their July 30, 2001 submission to the NDA. Additional useful information obtained from the patient's hospital records included that the patient had a history of malignant cardiac arrhythmias for which the patient had an implanted defibrillator.

AN 5135

A 59-year-old male with end stage T-cell non-Hodgkin's lymphoma (Stage 20, insulin-dependent diabetes mellitus, small bowel perforation believed to be secondary to lymphoma, extensive ascites, bilateral pleural effusion, extensive arterial vascular calcification, and a history of broken hip, nasal and vocal cord polyps, and smoking, began IV therapy of MK-0826 for intra-abdominal infection. From Study Day 1 to Study Day 3, chest x-rays continued to show bilateral infiltrates and effusion. On Study Day 5, the patient's prognosis was reported to be 'extremely poor'. At the family's request, the patient was extubated at 14:45 and all medications were discontinued. The patient received only palliative care. On Study Day 6, the patient died of respiratory failure. The reporting physician felt that the patient's death was definitely not related to study drug therapy.

### **Piperacillin/tazobactam Treatment Groups**

AN 0270

A 35-year-old female with pulmonary hypertension began IV therapy with piperacillin/tazobactam for the treatment of an intra-abdominal infection. Study drug therapy ended on Study Day 15. On Study Day 23, the patient had elective surgery (heart surgery) and a left hepatectomy was performed due to hepatic left lobe atrophy. Less than 1 hour after completing surgery on Study Day 23, the patient developed sudden cardiorespiratory arrest due to arrhythmia and myocardial infarction (MI) and died. The cause of death was arrhythmia and MI. The reporting physician felt the patient's arrhythmia, myocardial infarction and death were definitely not related to study drug therapy.

AN 0454

A 56-year-old female with mechanical jaundice, subhepatic abscess, complex choledocho-duodenal and colon fistula, malnutrition, pneumonia, acute cardiac and pulmonary insufficiency began IV therapy with piperacillin/tazobactam for the treatment of an intra-abdominal infection. Concomitant therapy included insulin, strophanthin, prednisolone and isosorbide dinitrate. The patient received the last dose of study drug on Study Day 15. On Study Day 7, the surgeon noted that the patient's general condition was severe, but with some improvement. On Study Day 18, vesicular respiratory rales are audible over the lungs and there was a decrease of heart sounds. On Study Day 34, the patient had heart failure and died. The probably cause of death was cardiac insufficiency. The investigator felt that the heart failure and death were definitely not related to study drug therapy.

AN 0520

A 71-year-old male with a history of episodes of chest pain began IV therapy of piperacillin/tazobactam for a perforated appendicitis with peri-appendicular abscess. On Study Day 2, the patients began experiencing precordial pain and had an electrocardiogram performed. The cardiologist diagnosed stable angina. The patient began treatment with aspirin and nitroglycerin. Subsequently, the patient experienced cardiopulmonary arrest. The patient was transferred to the Coronary Unit where echocardiography showed an anterior left infarction. After additional resuscitation efforts, the patient died. The reporting physician felt that the angina, myocardial infarction, and death were definitely not related to study therapy.

AN 0532

A 92-year-old female with hypertension, gastroesophageal reflux, and dyspepsia began IV therapy with piperacillin/tazobactam for treatment of diffuse peritonitis. On Study Day 3, the patient experienced atrial fibrillation and heart failure with good response to diuretics and digoxin therapy. On Study Day 8, the patient received the last dose of IV study drug. The patient was discharged from the hospital on Study Day 21. On Study Day 36, the patient was admitted to the Emergency Room due to dehydration and malnutrition. On Study Day 50, the patient experienced heart failure and was diagnosed with bilateral nosocomial pneumonia. The patient was treated with empirical antibiotic therapy with no clinical response. On Study Day 59, the patient died due to

nosocomial pneumonia. The reporting physician felt that the atrial fibrillation, malnutrition, dehydration, heart failure, pneumonia, and death were definitely not related to study therapy.

AN 0695

A 56-year-old male with a history of sigmoid volvulus, began IV therapy with piperacillin/tazobactam for treatment of an intra-abdominal infection. On Study Day 2, the patient became anuric and IV study therapy was discontinued due to a worsening septic shock, septicemia, increased serum creatinine, and acute renal failure. On Study Day 5, the patient had positive blood cultures with *E. coli* isolated. On Study Day 6, the patient had an open laparotomy and *E. coli* was isolated from the peritoneal fluid. On Study Day 8, a repeat laparotomy revealed *Enterococcus* from the peritoneal fluid. The patient was placed on therapy with ciprofloxacin, amikacin, imipenem, and fluconazole. The patient was also subsequently placed on dialysis and received therapy with furosemide and sodium bicarbonate. The septic shock continued throughout the patient's clinical course. On Study Day 11, the patient experienced bradycardia. On Study Day 12, the patient died. The reporting physician felt that renal failure, bradycardia, increased serum creatinine, septicemia, septic shock, and death were definitely not related to study therapy.

AN 0732

A 74-year-old male with a history of diabetes mellitus, hypertension, and tuberculosis who had a laparotomy for a perforated sigmoid diverticulum began IV therapy with piperacillin/tazobactam for treatment of an intra-abdominal infection. The patient was receiving ipratropium bromide and fenoterol via inhalation. On Study Day 6, IV study medication was discontinued with resolution of the intra-abdominal infection. On Study Day 7, the patient experienced a sudden cardiac arrest. Resuscitation was unsuccessful. The possible cause of death was myocardial infarction. The reporting physician felt that the myocardial infarction and death were probably not related to study therapy.

AN 0922

An 81-year-old male with a history of diabetes mellitus, anemia, and recto-sigmoid cancer began IV therapy with piperacillin/tazobactam for treatment of peritonitis secondary to a perforation of the colon. On Study Day 1, the patient underwent surgery for a perforated sigmoid cancer with several liver metastasis. On Study Day 1, the patient was transferred to the ICU. The patient experienced hypotension and signs of myocardial ischemia requiring therapy with amiodarone, dopamine and noradrenalin. The patient subsequently died on Study Day 3. The reporting physician felt that the myocardial infarction and death were definitely not related to study therapy.

AN 5052

An 87-year-old male with active arteriosclerotic heart disease and previous inferior wall myocardial infarction, angina pectoris, congestive heart failure, dyspepsia, hypoalbuminemia, fever, pain, respiratory distress, hypotension, constipation, hypokalemia, and a history of hypertension began IV therapy with piperacillin/tazobactam following surgery for the treatment of a perforated gastroduodenal ulcer with diffuse peritonitis. On Study Day 1, based on the results of an electrocardiogram and cardiac enzymes, the patient developed a post-surgical acute myocardial infarction (life threatening) and had also aspirated. A chest x-ray examination [4.1.30] on Study Day 3 revealed bilateral infiltrates and the patient was diagnosed with pneumonia (life threatening). The patient remained in ICU in guarded condition. On day 5, the patient developed septic shock (life threatening). On Study Day 6, he developed respiratory failure and renal failure (both life threatening) and another myocardial infarction (life threatening). The patient died on Study Day 7 due to septic shock. The reporting physician felt that the patient's adverse experiences and death were definitely not related to study drug.

AN 5334

An 85-year-old female with dementia, asthma, chronic obstructive pulmonary disease (COPD), pain, hypokalemia, labile blood glucose, hypovolemia, pneumonia, insomnia, polyuria and congestive heart failure began IV therapy with piperacillin/tazobactam for the treatment of an intra-abdominal abscess following abscess drainage. After 1 week of study therapy her white blood cell count increased. On Study Day 8, she was removed from study therapy and placed on other antibiotics (gentamicin and piperacillin/tazobactam). Her pneumonia worsened during her hospital stay. On Study Day 15, she was made a Do Not Resuscitate and her family chose to withdraw all treatment due to her age and significant history. On Study Day 17, the patient was pronounced dead. The probable cause of death was reported as respiratory failure. The investigator felt that the pneumonia, hypoxemia, respiratory failure, and death were probably not study drug related.

AN 5394

An 83-year-old female with penicillin allergy, sulfa allergy, and amyotrophic lateral sclerosis (ALS) began IV therapy with piperacillin/tazobactam for the treatment of an intra-abdominal infection. Skin sensitivity tests to imipenem and piperacillin-tazobactam were negative upon study entry. On Study Day 2, the patient developed an extensive rash (reported as a nonserious adverse event of special interest). Study therapy was discontinued on that same day. The rash began to resolve shortly thereafter. On Study Day 9, the patient developed a worsening, rapid progression of amyotrophic lateral sclerosis (ALS). The patient was discharged to hospice care on Study Day 12 and died of multiple organ failure on Study Day 13. The investigator felt that the patient's rash was probably study drug related. Additionally, the investigator felt that the worsening ALS, multiple organ failure and death were definitely not related to study drug therapy.

AN 5399

A 54-year-old female with seizure disorder, pain, hypertension, hepatoencephalopathy and a history of alcohol abuse began IV therapy with piperacillin/tazobactam for the treatment of an intra-abdominal infection. Concomitant therapy included valproic acid sodium salt, sucralfate, phenobarbital, fentanyl, albuterol and thiamine. On Study Day 2, the patient had low serum magnesium value of 1.2 mg/dL (normal range 1.6 to 2.7 mg/dL). On Study Day 3, the patient experienced vaginal hemorrhage and stupor, and on Study Day 4 the patient had a seizure. It was reported that the left side of her mouth was twitching, her eyes rolled back and she had an elevated blood pressure and pulse. On Study Day 6, the patient had a wound infection and sinus arrest. On Study Day 7, the patient had a intraventricular conduction delay that lasted 4 minutes. On Study Day 10, the patient was noted to have swelling of her upper extremities. A doppler scan revealed a deep vein thrombosis of her left internal jugular vein. The patient did not have an internal jugular intravenous line in place. On Study Day 10, the patient had a mild supraventricular tachycardia that lasted 1 minute. Study drug therapy was discontinued on Study Day 12. On Study Day 22, the patient had ventricular tachycardia lasting 1 minute and on Study Day 23, the patient had atrial fibrillation, which also lasted 1 minute. The patient died on Study Day 29 due to unknown causes. The study investigator felt that the seizure was a result of the patient's history of a seizure disorder and definitely not related to study drug therapy. The investigator also felt that the hypomagnesemia, stupor, sinus arrest, wound infection, intraventricular conduction delay, supraventricular tachycardia, ventricular tachycardia, and atrial fibrillation were probably not study drug related. The investigator felt that the seizure, deep vein thrombosis, vaginal hemorrhage, and death were definitely not related to study drug therapy.

AN 5975

A 66-year-old male began IV therapy with piperacillin/tazobactam for the treatment of an intra-abdominal infection after surgery for perforated bowel and large fecal spillage. Study therapy was discontinued on Study Day 4 per the patient's request and he was transferred to the Veterans Administration Hospital. The patient received ciprofloxacin and metronidazole. The patient had improved and was scheduled to be discharged from the hospital with oral antibiotics. Before the time of discharge on Study Day 14, the patient was found in his room without a pulse. Cardiopulmonary resuscitation was performed but the patient could not be revived. The cause of death was determined to be a pulmonary embolus. The study investigator believed that the pulmonary embolus and death were definitely not related to study drug therapy.

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## PROTOCOL 018-Community Acquired Pneumonia

### **MK-0826 Treatment Group**

#### AN 6281

This 55-year-old male was admitted to the hospital complaining of increased dyspnea, productive cough with production of yellow sputum, and right lower lateral rib pain. The patient also had "gastrointestinal distress," COPD, hypotension, hiatal hernia, emphysema, asthma, and a history of anorexia and tobacco use. One day before starting study therapy a chest x-ray showed right middle- and lower-lobe infiltrates. A sputum culture grew *Streptococcus pneumoniae* and *Branhamella catarrhalis*. The patient was enrolled in the study and placed on therapy with MK-0826 IV 1 g daily for the treatment of pneumonia. He received 2 days of IV study therapy. On Study Day 2 the patient became increasingly short of breath and hypotensive, and he was transferred to the Intensive Care Unit. The patient's condition worsened and he developed acute respiratory failure and cardiac arrhythmia. The patient was treated with dopamine, ATROVENT™ (ipratropium bromide, Boehringer Ingelheim), and digoxin. The patient developed functional bradycardia and then asystole. The patient was defibrillated many times and intubated. Cardiopulmonary resuscitation (CPR) was performed. The patient was also treated with epinephrine, calcium gluconate, atropine, bretylium, adenosine, and lidocaine. The patient was pronounced dead on Study Day 3. The investigator reported that cardiac arrhythmia was the cause of death and that all of the patient's experiences were not related to study drug.

#### AN 6431

This 81-year-old female received MK-0826 therapy for CAP. She had congestive heart failure, Type 2 diabetes mellitus, interstitial lung fibrosis, and a history of arterial hypertension and coronary artery disease. On Study Day 5, the patient developed cyanosis. An arterial blood gas revealed hypoxemia and an increase in pCO<sub>2</sub> for which inhaled oxygen was increased to 50% by venturi mask. The patient progressed to respiratory failure and received mechanical ventilation. Study drug was discontinued on Study Day 5. On Study Day 6, the patient died. In the opinion of the investigator, the respiratory insufficiency and death were not related to study drug.

#### AN 7227

This 86-year-old female, who received MK-0826 therapy for CAP, had a history of heart failure, hypertension, chronic renal insufficiency, and hip surgery. On Study Day 2, she was transferred to the Intensive Care Unit because of worsening heart failure, acute respiratory insufficiency requiring mechanical ventilation, and worsening of her renal insufficiency. Study therapy was discontinued on Study Day 2. On Study Day 3, she had signs of respiratory ailure (decreased arterial pO<sub>2</sub>, increased pCO<sub>2</sub>, and acidosis). On Study Day 4, chest x-ray showed interstitial alveolar infiltrates. She died on Study Day 4, due to the worsening heart failure. In the opinion of the investigator, the patient's respiratory insufficiency, worsening renal insufficiency, worsening heart failure, and death were not related to study therapy.

#### AN 6376

This 88-year-old female, treated with MK-0826 for CAP had a history of abdominal aortic aneurysm, hypertension, previously excised melanoma, and gastric ulcer. Six (6) hours after receiving the first 1 gm dose of MK-0826 she died. A post-mortem was not performed. The cause of death was attributed to cardiac arrest. In the opinion of the investigator, the patient's experiences were not related to study drug.

#### AN 7079

This 75-year-old female, treated with MK-0826 for CAP, had chronic bronchitis, chronic gastritis, and a history of headache. She received 11 days of IV study therapy. On Study Day 9, she developed a hemorrhagic cerebrovascular accident (CVA). This presented with a seizure that a consulting neurologist reported was related to the CVA. She was placed on ventilator support. On Study Day 12, her physicians suspected a ventilator-associated pneumonia. Treatment with ceftazidime and vancomycin was started. On Study Day 17, she was placed on parenteral nutrition. On Study Day 18, she was still considered critically ill. On Study Day 22, the patient had a cardiac arrest, did not respond to resuscitation attempts, and died. The reporting physician felt that death was related to hemorrhagic CVA. The investigator reported that the patient's experiences were not related to study therapy.

AN 6624

This 58-year-old male was entered into the study and treated with MK-0826 for CAP. He also had diabetes mellitus and a history of colon carcinoma with anterior resection and hypertension. He received 3 days of IV study therapy. On Study Day 3, he was found to have hypoxemia and study therapy was discontinued because of his worsening clinical condition. On Study Day 4, he was diagnosed with worsening pneumonia and placed on therapy with ceftazidime and erythromycin. The patient's condition continued to deteriorate and the patient was admitted to the intensive care unit on Study Day 6. At this time, his antibiotic therapy included doxycycline 100 mg twice a day orally, vancomycin 1 g daily, ceftazidime, metronidazole 500 mg every 8 hours IV, and erythromycin. He was diagnosed with hypotension, acute respiratory distress syndrome (ARDS), acute renal failure, septic shock, and disseminated intravascular coagulopathy. He required mechanical ventilation, inotropic support, dialysis, and slow continuous ultrafiltration. Ciprofloxacin 200 mg twice a day orally, Amikacin 750 mg IV, and oral ethambutol 400 mg every other day were administered on Study Day 8 when an endotracheal aspirate specimen revealed acid fast bacilli. His condition continued to deteriorate and he died on Study Day 10. The investigator reported that the patient's experiences were not related to study drug.

AN 7055

This 76-year-old male was enrolled in the study and treated with MK-0826 for CAP. He had a history of chronic pulmonary disease, cardiac failure, and coronary failure. He received 9 days of IV study therapy. The patient did not return for his EFU visit. The investigator learned that the patient had a myocardial infarction and died on Study Day 12. In the opinion of the investigator, the patient's experience was not related to study drug.

AN 6272

This 57-year-old female was treated with MK-0826 for CAP. She had anxiety, osteoporosis, intestinal diverticulitis, chronic sinusitis, a productive cough, shortness of breath, upper respiratory congestion, and neck pain, and a history of COPD. She received 4 days of IV study drug and 11 days of oral amoxicillin/clavulanate. On Study Day 44, she was diagnosed with sepsis syndrome and began treatment with alatrovafloxacin, ampicillin/sulbactam, gentamicin, and vancomycin. On Study Day 48, treatment with metronidazole and an increased dose of vancomycin were initiated for treatment of *C. difficile* infection that was considered the cause of the sepsis syndrome diagnosed on Study Day 44. A fecal *C. difficile* toxin test done on Study Day 47 was positive. With a poor prognosis, prolonged mechanical ventilation, and the use of pressors, the patient wanted mechanical ventilation withdrawn. On Study Day 57, mechanical ventilation was withdrawn. On Study Day 58, she died. In the opinion of the investigator, the patient's experiences were not related to study drug.

### **Ceftriaxone Treatment Group**

AN 6312

This 78-year-old male, who received ceftriaxone for CAP, had COPD, cor pulmonale, hyponatremia, an elbow abscess, and a history of hypothyroidism, urethral trauma, and an arm lipoma. Diagnosis of pneumonia was confirmed by clinical signs and symptoms and chest x-ray. On Study Day 2, the patient experienced worsening of his cor pulmonale. On Study Day 7, he experienced worsening bilateral pneumonia, aspiration, and continued worsening of cor pulmonale. He demonstrated worsening respiratory function, chest x-ray findings and neurologic condition. Infiltrates extended to the left upper lobe. On Study Day 7, IV study therapy was discontinued. The patient's physician changed his antibiotic therapy to clindamycin and ceftriaxone. The patient's condition continued to decline and he died on Study Day 9. In the opinion of the investigator, the patient's experiences were not related to study drug.

AN 7082

This 35-year-old female was hospitalized with signs and symptoms of pneumonia and received ceftriaxone therapy for 8 days. During her hospitalization, she showed clinical signs of improvement. However, no significant radiographic changes were observed. A physical examination on Study Day 7 revealed evidence of cardiac tamponade. An echocardiogram revealed a significant pericardial effusion. On the same day, a pericardiocentesis was performed for relief of the cardiac tamponade. Approximately 400 cc of purulent fluid indicated a diagnosis of septic pericarditis. The patient subsequently underwent formal surgical drainage and was admitted to ICU. The patient died on Study Day 9; the cause of death was attributed to severe pneumococcal pneumonia, purulent bacterial pericarditis, cardiac tamponade, and septicemia. In the opinion of the investigator, the patient's experiences were not related to study drug.

AN 7077

This 73-year-old female, treated with ceftriaxone for CAP, also had COPD, and a history of rheumatoid arthritis and gastric ulcer. She received 7 days of IV study therapy. On Study Day 4, the patient experienced respiratory failure with a respiratory arrest of 3 minutes. She responded to resuscitation and showed spontaneous respiration. She was then sedated and intubated. The patient's respiratory failure persisted. On Study Day 5, the patient continued on mechanical ventilation with clinical improvement. On Study Day 6, diminished breath sounds in the right lung and worsening arterial blood gases with respiratory acidosis were reported. The endotracheal tube was changed and increased tracheal secretions were found. At this time the patient showed improvement. On Study Day 7, the patient continued having increased tracheal secretions that improved with tracheal suctioning. A bronchoscopy with endobronchial lavage was scheduled for the following day. Later on Study Day 7, she experienced hypotension and acute hemodynamic instability. On Study Day 8, the patient had a cardiac arrest and died. In the opinion of the investigator, the patient's experiences were not related to study drug.

AN 6795

This 86-year-old female was admitted to the hospital in respiratory distress. She was enrolled in the study and placed on therapy with ceftriaxone for CAP. She also had an electrolyte imbalance, depression, acid reflux, congestive heart failure, gout, pain, diabetes mellitus, COPD, nausea, and anxiety. She had a history of cholecystectomy, hysterectomy, appendectomy, tonsillectomy, and insomnia. She had a broken right forearm and had a plate inserted. She had pneumonia twice approximately 2 years prior to her participation in the study. On Study Day 2, the patient was noted to have loud wheezes in all fields. Later that same day, the patient was examined and was noted to have wheezing with a loose cough, rales, and shortness of breath. Her oxygen saturation was 94% on 4 liters of oxygen. The patient was alert and in moderate distress. She appeared to be more comfortable than on admission. She was encouraged to breathe deeply and clear secretions upon coughing. Her urinary output was low and she was administered furosemide. Study drug therapy was discontinued on Study Day 2. In the early morning of Study Day 3 the patient was asleep but appeared comfortable. Two hours later the patient was found to be apneic. A code was called and resuscitation attempts were not successful. The patient was pronounced dead on Study Day 3. The cause of death was recorded as respiratory failure. In the opinion of the investigator, the patient's experience was definitely not related to study drug therapy.

AN 6441

This 74-year-old male was diagnosed with pneumonia, enrolled in the study and treated with ceftriaxone for CAP. He also had COPD and a history of retinal detachment, milk intolerance, cataracts, and exposure to a toxic agent. He received 11 days of IV study therapy. Patient symptoms (cough, shortness of breath, and production of purulent sputum) improved as did the clinical signs (wheezing) on Study Day 4 and on Study Day 8. However, microbiology and laboratory tests did not show improvement. On Study Day 12, the patient presented with a clearly worsening clinical condition, chest x-ray, and laboratory results. On Study Day 12, study therapy was discontinued. His therapy was changed to ceftazidime and clindamycin. Also on Study Day 12, an adverse experience of general deterioration was reported. On Study Day 13, inotropic therapy and other support measures were started without response. Also on Study Day 13, he was diagnosed with pulmonary sepsis. On Study Day 17, he died due to his pulmonary sepsis. In the opinion of the investigator, these experiences were not study drug related.

AN 6197

This 77-year-old male was treated with ceftriaxone for CAP. He also had prostate cancer, insomnia, dyspnea, and pain. He received 3 days of IV study therapy followed by 5 days of oral amoxicillin/clavulanate. On Study Day 2, chest and abdominal x-rays revealed that he had atelectasis, a pulmonary radiodensity (suspicious for a malignant pleural neoplasm) and a hepatic lesion. He was discharged home on Study Day 4. He was rehospitalized on Study Day 7 with dyspnea and a large pleural effusion requiring further antibiotic therapy. He was discharged on Study Day 11 with a diagnosis of adenocarcinoma. The patient reported for his EFU visit on Study Day 17 and was found to have an increased potassium level, but refused a hospital admission. He returned to the emergency room later on Study Day 17 and was admitted for dehydration and acute renal failure. He was discharged on Study Day 20. The investigator reported that the patient's experiences were not related to study therapy.

**Medical Officer's Comment:** Additional information from the CRF for this patient includes:

*This patient was a 77 year-old male had a history remarkable for a history of remote subhepatic abscess, chronic pancreatitis status post Whipple procedure, prostate cancer, and tobacco abuse. He was treated for 3 days with IV ceftriaxone and 5 days with oral Augmentin and then switched to oral levofloxacin due to diagnosis of lung abscess. On study day 2 he had a CT of the chest and abdomen that revealed a pulmonary mass and multiple liver lesions consistent with metastatic cancer. On study day 1 he had a diagnostic thoracentesis performed and cytology from that procedure was consistent with adenocarcinoma of the lung. The patient died 21 days after completing parenteral and oral (augmentin) study drug therapy. The cause of death noted by the Investigator was pulmonary edema and adenocarcinoma of the lung. The Investigator considered the death as "Definitely Not" related to study medication.*

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## PROTOCOL 020-Community Acquired Pneumonia

### **MK-0826 Treatment Group**

#### AN 2964

*Medical Officer's Comment: A narrative was not provided for this patient by the Applicant. This patient was a 55 year old male with a history of gastritis, sinusitis, thoracotomy, hypertension, ETOH abuse, delerium tremens, and hallucinations. The patient completed the study through the EFU visit and was considered a clinical cure. The patient was rehospitalized, prior to the LFU visit, for methadone and alcohol overdose and died. The Investigator attributed the death to the overdose and considered the event unrelated to study therapy.*

#### AN 3272

A 64-year-old male with COPD, glaucoma, and osteomyelitis began IV therapy with MK-0826 for the treatment of CAP. On Study Day 6, the patient was switched as per protocol to oral therapy with amoxicillin/clavulanate, which was completed on Study Day 15. On Study Day 27, the patient was seen at a scheduled follow-up visit. The patient had an increased shortness of breath, cough, and carbon dioxide retention and a chest x-ray revealed new infiltrate. The patient was re-admitted to the hospital due to recurrent pneumonia and worsening of COPD. Therapy with clindamycin was started. On Study Day 28, the patient died due to pneumonia, respiratory failure, COPD, and carbon dioxide retention. In the opinion of the investigator, the recurrent pneumonia, respiratory failure, COPD, and carbon dioxide retention were definitely not related to the study drug therapy.

#### AN 3443

A 97-year-old male with multiple medical problems including Parkinson's disease, bronchoconstriction, chronic renal insufficiency, diabetes mellitus, and a history of cerebrovascular accident began IV therapy with MK-0826 for the treatment of CAP. On Study Day 4, the patient was switched per protocol to oral therapy with cefprozil. On Study Day 11, study drug therapy was completed and the patient was transferred to a nursing home. On Study Day 14, the patient developed dehydration, worsening renal insufficiency, electrolyte imbalance, and dysphagia and was readmitted to the hospital. The patient was diagnosed with aspiration pneumonia and on Study Day 15 was placed on therapy with metronidazole and levofloxacin. Due to the patient's overall poor clinical situation, a "do not resuscitate" status was established. The patient's condition continued to deteriorate and he died on Study Day 18 due to dehydration, worsening renal insufficiency, and electrolyte imbalance. In the opinion of the investigator, the dehydration, worsening renal insufficiency, electrolyte imbalance, dysphagia, and aspiration pneumonia were definitely not related to the study drug therapy.

#### AN 4200

An 82-year-old male with hypertension, congestive heart failure, benign prostate hyperplasia, anemia, cerebrovascular accident, and history of renal insufficiency and hepatic disorder began IV therapy with MK-0826 for the treatment of CAP. On Study Day 2, the patient had abdominal distension and tenderness, bowel sounds were decreased, and an abdominal ultrasound showed gallbladder increase and dilated biliary tract. The patient was diagnosed with acute cholecystitis and surgery was performed. The IV study therapy was discontinued and the patient was placed on therapy with ceftriaxone and metronidazole. The patient was in respiratory failure and was on placed mechanical ventilation. Subsequently, the endotracheal tube was withdrawn. After eating some food, the patient had severe dyspnea caused by aspiration pneumonia that rapidly developed to respiratory failure. On Study Day 22, the patient died due to respiratory failure and aspiration pneumonia. In the opinion of the investigator, the cholecystitis was possibly related to the study drug therapy and the respiratory failure and aspiration pneumonia were definitely not related to the study drug therapy.

#### AN 4254

A 74-year-old male with hypertension, COPD, and a history of renal failure began therapy with MK-0826 for the treatment of CAP. On Study Day 1, the patient had a worsening of COPD, requiring mechanical ventilation, and renal insufficiency. On Study Day 3, the patient suffered septic shock. The IV study therapy was discontinued on Study Day 3 due to clinical treatment failure. The patient died on Study Day 19 due to COPD worsening and septic shock/pneumonia. In the opinion of the investigator, the worsening COPD and septic shock were definitely not related to study drug therapy and the renal failure was probably not related to the study drug therapy.

### **Ceftriaxone Treatment Group**

#### AN 2753

A 65-year-old female with COPD, diabetes mellitus, hypertension, congestive heart failure, cardiomyopathy, dyspepsia, esophageal stricture, diarrhea, hypokalemia, and a history of atrial fibrillation and myocardial infarction began IV therapy with ceftriaxone for the treatment of CAP. On Study Day 8, IV study therapy was completed and as per protocol the patient was switched to oral therapy with amoxicillin/clavulanate. On Study Day 11, the patient's husband reported that the patient had died at home. The cause of death was unknown. In the opinion of the investigator, the death was definitely not related to the study drug therapy.

#### AN 2888

A 67-year-old female with a history of pituitary neoplasm, a hip fracture, contractures of both lower extremities, and a craniotomy began IV therapy with ceftriaxone for the treatment of CAP. The patient was considered an aspiration risk and on Study Day 3 was placed on a feeding tube. On Study Day 5, she was found in her room without a pulse due to respiratory arrest. Cardiopulmonary resuscitation (CPR) was initiated and the patient was intubated and placed on a ventilator. The IV study drug therapy continued through Study Day 11. The patient remained on the ventilator and desaturated several times; her blood pressure remained low and her urine output also decreased. A chest x-ray showed worsening pleural effusion, pleural edema, and development of acute respiratory distress syndrome. Due to the patient's overall poor clinical situation, a "do not resuscitate" status was established. On Study Day 22, the patient died due to respiratory distress. In the opinion of the investigator, the respiratory failure was definitely not related to study drug therapy.

#### AN 3191

A 70-year-old male with atrial fibrillation, COPD, hypertension, coagulation disorder, and a history of resected abdominal aortic aneurysm and carotid endarterectomy began IV therapy with ceftriaxone for the treatment of CAP. On Study Day 9, a chest x-ray showed worsening of pneumonia in the right lung and full involvement of the left lung (not seen on a previous chest x-ray). On Study Day 10, IV study drug therapy was discontinued and antibiotic therapy with cefotaxime and trovafloxacin was started for treatment of the pneumonia. On Study Day 15, at the request of the patient's family, he was withdrawn from supplemental oxygen and died. The cause of death was attributed to worsening pneumonia and bacteremia. In the opinion of the investigator, the patient's worsening pneumonia and bacteremia were definitely not related to the study drug therapy.

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## PROTOCOL 021-Complicated Urinary Tract Infections

### **MK-0826 Treatment Group**

#### 8569

An 89-year-old female with asthma, gastritis, diabetes mellitus, and a history of bronchitis and chronic obstructive pulmonary disease began IV ertapenem therapy for the treatment of complicated urinary tract infection. On Study Day 4, the patient was switched to oral ciprofloxacin 1 gram daily as per protocol and completed on Study Day 14. On Study Day 15, the patient developed severe pyloric stenosis, which was considered disabling and she was hospitalized. Subsequently, the patient recovered and was discharged from the hospital. The reporting physician felt that the patient's pyloric stenosis was probably not related to study drug therapy. Upon follow-up, the physician learned that the patient had suffered cardiac and respiratory arrest and had died on Study Day 32. The physician felt that the cardiac and respiratory arrest and death were probably not related to study drug therapy.

#### 8584

An 88-year-old male with bladder malignant neoplasm, diabetes mellitus, atrial fibrillation, renal insufficiency, cardiomyopathy, urinary incontinence, aspirin allergy, hypokalemia, hypertension, prostatic malignant neoplasm, and a history of prostatic surgery, biliary surgery, and osteotomy was hospitalized. The patient entered the study and began IV ertapenem therapy for the treatment of complicated urinary tract infection. On Study Day 2, the patient experienced worsening renal insufficiency, severe respiratory insufficiency, psychogenic musculoskeletal disorder, hypotension, and worsening hyperglycemia. No action was taken with regard to study drug therapy. The patient was given furosemide for his renal failure and hydrocortisone for his respiratory insufficiency. He also required respiratory assistance. An echocardiograph with doppler showed right cavity overload. The patient completed study IV therapy and was switched to oral ciprofloxacin 1 gram daily on Study Day 7 as per protocol. ~~On the same day, chest x ray revealed left lung pneumocele and the patient was diagnosed with severe atelectasis.~~ On Study Day 13, the patient developed severe parotiditis. These events were considered disabling and life-threatening, prolonging the patient's hospitalization. Oral ciprofloxacin therapy was completed on Study Day 14. On Study Day 15, the patient was placed on mechanical respiratory assistance. On the same day, the patient died of respiratory insufficiency. The reporting physician felt that the patient's worsening renal insufficiency, respiratory insufficiency, psychogenic musculoskeletal disorder, worsening hyperglycemia, hypotension, atelectasis, and parotiditis were definitely not related to study drug therapy.

#### 8586

A 47-year-old male with fever, nystagmus, anxiety, constipation, hypercholesterolemia, hypertension, abdominal pain, neoplasm, nausea, and a history of erysipelas, nephrectomy, ureteral surgery, bladder surgery, arrhythmia and appendectomy began IV ertapenem therapy for the treatment of complicated urinary tract infection. On Study Day 4, the patient was switched to oral ciprofloxacin 1 gram daily as per protocol and completed on Study Day 14. On Study Day 38, the patient developed fever and was hospitalized. He was given imipenem and vancomycin. On Study Day 39, the patient experienced mild delirium. On Study Day 42, he developed moderate erythema and a CT scan performed on Study Day 43 revealed paravertebral abscess which was subsequently drained. On Study Day 45, the patient developed urinary retention. These events continued and they were considered as disabling and life threatening prolonging the patient's hospitalization. The patient was considered to be at a terminal stage. On Study Day 71, the patient died. The investigator felt that the patient's fever, delirium, erythema, abscess, urinary retention and death were definitely not related to study drug therapy.

### **Ceftriaxone**

#### AN 8564

A 48-year-old male with, anemia, and a history of gastric malignant neoplasm, gastritis, and gastrectomy began IV ceftriaxone sodium therapy for the treatment of complicated urinary tract infection. Study IV therapy was completed on Study Day 7. On Study Day 17, the patient developed severe gastric hemorrhage and was hospitalized. The investigator considered the gastric hemorrhage as disabling and life threatening. On Study Day 18, the patient died of gastric hemorrhage. The reporting physician felt that patient's gastric hemorrhage and death were probably not related to the study drug therapy.

**PROTOCOL 023-Acute Pelvic Infections**

**MK-0826 Treatment Group**

**AN 7500**

A 42-year-old female with a history cervical malignant neoplasm and total pelvic exenteration was diagnosed with a pelvic abscess, and started study therapy with IV MK-0826. Cultures taken from the pelvic abscess isolated *Proteus mirabilis* and *Enterococcus*. Blood culture results showed *Escherichia coli*. On Study Day 3, the patient experienced bacteremia. On Study Day 4, the patient experienced septic shock, and respiratory distress. On Study Day 5, the patient was started on IV vancomycin for additional antimicrobial coverage. On Study Day 5, due to her respiratory distress, the patient received therapy with albuterol. On the same day, the patient received increasing doses of dobutamine. No action was taken with regard to study therapy. On Study Day 7, the patient died due to septic shock. The reporting physician felt that the bacteremia, septic shock, respiratory distress, and death were not related to study therapy.

**AN 8618**

A 17-year-old female with no significant prior history was placed on IV MK-0826 for endometritis. On Study Day 1, the patient was taken to surgery for an exploratory laparotomy and hysterectomy due to a diagnosis of sepsis. On Study Day 1, IV study therapy was discontinued and the patient was placed on ampicillin, gentamicin, and metronidazole. The patient's blood cultures were negative. The patient then experienced cardiac arrest with resolution after resuscitation measures. On Study Day 2, the patient experienced pulmonary edema with eventual death on the same day. The reporting physician felt that the sepsis, cardiac arrest, pulmonary edema, and death were not related to study therapy.

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**Piperacillin/Tazobactam Group**  
None Reported

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**Appendix 29**

**Medical Officer's Review of Study 029**

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### Phase IIB Intramuscular (IM) Dosing Study

1. Reviewer: Jean M. Mulinde, M.D.

2. Review Dates

2.1 CDER Stamp Date: 7/3/01

2.2 Review Begun: 8/10/01

2.3 Review Completed: 8/27/01

3.0 **Protocol 029:** A Prospective, multicenter, Double-Blind, Randomized, Comparative Study to Evaluate the Local tolerability of MK-0826 Versus Ceftriaxone Sodium Administered Intramuscularly

3.1 Objective/Rationale

The objectives of the study, as stated by the Applicant, were:

**Primary Objective**

1. After at least one dose, to evaluate the local tolerability of IM ertapenem in the treatment of patients with lower respiratory tract infection (LRTI), UTI, or skin infection.

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**Secondary Objectives**

1. After at least one dose, to compare the local tolerability of IM ertapenem with that of IM ceftriaxone sodium in the treatment of patients with LRTI, UTI, or skin infection.
2. To evaluate and compare the safety profile of ertapenem versus ceftriaxone sodium at the end of IM therapy with respect to the proportion of patients with any drug-related adverse experiences leading to discontinuation of study drug and also with respect to the proportion of patients with any drug-related serious adverse experiences.

**Exploratory Objective**

1. To report the efficacy of therapeutic regimens incorporating IM ertapenem and those incorporating IM ceftriaxone sodium.

***Medical Officer's Comment:** In the January 19, 2000 fax from the Division to the Sponsor, multiple discrepancies between current FDA Guidance documents and the study design as related to efficacy parameters were noted. In the Sponsor's response to these comments, submitted February 17, 2000, they noted that the primary objective of this study was to provide information regarding the safety and tolerability of IM dosing and not efficacy data, therefore it was not their intention to amend the protocol to make it consistent with FDA Guidances for the indications under study.*

3.2 Study Design

This was a double-blind, prospective, randomized, comparative study that evaluated the local tolerability of IM ertapenem versus IM ceftriaxone sodium in the treatment of lower respiratory tract infections (LRTIs), skin infections, and urinary tract infections (UTIs).

Nine centers participated in this study (2 sites in the United States and 7 sites internationally) and patients were enrolled between May 18, 2000 and October 2, 2000.

Patients with community acquired pneumonia (CAP), acute exacerbation of chronic bronchitis (AECB), complicated or uncomplicated skin and skin structure infections (cSSSI or uSSSI), and complicated or uncomplicated UTI (cUTI or uUTI) were enrolled in the study, if they were considered eligible based upon inclusion and exclusion criteria. Patients were randomized in a 3:1 ratio of ertapenem 1 gm IM every 24 hours to ceftriaxone sodium 1 gm IM every 24 hours, respectively. No attempt was made to stratify patients equally among the types of infections. The addition of a macrolide or azilide was allowed for patients with CAP in whom an "atypical" pathogen was suspected. Investigators had the option to switch therapy to an oral antimicrobial agent (the suggested oral antibiotic agent was AUGMENTIN™) if, after a minimum of 2 days of IM therapy, patients satisfied prespecified criteria for clinical improvement. The suggested total duration of therapy (IM and oral) in patients with LRTIs or skin infections was 5 to 14 days. The suggested total duration of therapy in patients with UTIs was 3 to 14 days.

Clinical assessment of the index infection was performed by the Investigators at prestudy, at the discontinuation of intramuscular therapy (DCIM), and at the test-of-cure (TOC) assessment, 7 to 14 days posttherapy. Microbiological response assessments were made separately for each pathogen identified at prestudy.

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The safety of IM MK-0826 and ceftriaxone was evaluated by determining the presence or absence of clinical or laboratory adverse experiences and local injection site tolerability. Patients were monitored for adverse experiences on a daily basis during the IM study antibiotic period, and for 14 days after the discontinuation of all study therapy (IM plus oral antimicrobial therapy). The schedule of clinical observations and laboratory measurements is displayed in the following table.

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Schedule of Clinical Observations and Laboratory Measurements

Assessment/Procedures	Eligibility Screening (524 Hours Prior to Study Therapy)	Daily While on IM Therapy	One-Therapy Assessment (Day 3, 4, or 5 of Study IM Therapy) <sup>1</sup>	Discontinuation of IM Therapy	Follow-Up (7 to 14 Days After Discontinuation of All Study Agents-IM and Oral)
Medical history	X		X	X	X
Physical examination, clinical signs and symptoms, and vital signs	X		X	X	X
Chest x-ray <sup>2</sup>	R		R <sup>1</sup>		R
Monitored for adverse experiences <sup>3</sup>					
Monitored for local intolerance <sup>4</sup>		X	X	X	X
Blood and urine for safety	X	X	X	X	X
Culture and susceptibility of respiratory menses for direct infection <sup>5</sup>	R		R	R	R
Blood culture and susceptibility	R <sup>1</sup>		R <sup>1</sup>	R <sup>1</sup>	R <sup>1</sup>
Respiratory test	X <sup>10</sup>				
Clinical culture evaluation					
Compliance with oral antibiotics					
Assessment of subcutaneous site <sup>6</sup>					
Only necessary if patient received 25 days of IM therapy. Otherwise, only discontinuation of IM therapy procedures needed to be done.				X <sup>11</sup>	X
For patients with lower respiratory tract infections.					
For patients with lower respiratory tract infections if clinical response was suboptimal.					
Monitored for adverse experiences daily during IM therapy and for 14 days after completion of all study therapy.					
If laboratory safety tests performed 1 day before the discontinuation of IM therapy were normal, then repeat blood samples were not required at IM discontinuation visit.					
For all patients with urinary tract infection quantitative urine cultures were requested on the indicated time points. Cultures in lower respiratory tract infection and skin infection should have been done as clinically indicated.					
If patient was hospitalized, 2 sets were recommended.					
Blood cultures (2 sets) were to be performed only if prestudy blood culture was positive, or if clinically indicated.					
Performed on all women of childbearing potential.					
Patients with pathogens isolated.					
For urinary tract infection patients with a pathogen isolated at present.					
X - Required.					
R - Recommended according to usual clinical practice.					
IM - Intramuscular.					

(Applicant's Table 1, July 3, 2001 submission, Volume 1 of 1, page 31)

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***Medical Officer's Comment:*** Due to the multiple discrepancies between the design of the current study and designs recommended in the FDA Guidances for these indications (regarding inclusion and exclusion criteria, methods of obtaining cultures, and documentation of infections), the efficacy data provided by this study was of limited utility from a regulatory perspective. While details of the protocol design will be further elaborated in the following section of this review, only deviations from recommended FDA Guidances that impact on analysis of safety and tolerability data will be commented on further by the Medical Officer (MO).

*Of note, because of a color difference between the 2 study drugs, designated unblinded personnel were used to prepare and administer the IM injections. These people then played no further role in the conduct of the study and neither the patient nor any blinded personnel were allowed to see the syringe or learn which treatment the patient received.*

### 3.3 Protocol Overview

#### 3.3.1 Population/Procedures

Inclusion and exclusion criteria were applied in order to enroll patients with CAP, AECB, uSSSI, cSSSI, uUTI, and cUTI that required at least 2 days of parenteral therapy and not more than 14 days of parenteral therapy. The following are noteworthy inclusion and exclusion criteria:

#### Inclusion Criteria:

#### **General Criteria**

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- 1) Patients, male or female, aged  $\geq 18$  years, with LRTI, skin or skin structure infection, or UTI, as defined below.
- 2) Females of childbearing potential with a negative urine pregnancy test were eligible for enrollment. However, they had to have a confirmatory negative serum pregnancy test. Use of adequate birth control measures were discussed with the investigator. Hormonal contraceptives were not used as the sole method of birth control because the effect of ertapenem on the efficacy of hormonal contraceptives had not yet been established. Nursing women could have participated if they agreed to defer breast-feeding until 5 days after completion of therapy to allow elimination of the drug from breast milk.
- 3) Patient's infection was of sufficient severity to require IM therapy and the patient was expected to require a minimum of 2 doses of IM therapy (i.e., 2 days), but, no more than 7 doses of IM therapy.
- 4) Patient's infection was known or thought by the investigator to be caused by microorganisms susceptible to the IM study antibiotics.
- 5) Patient's infection had been treated with  $< 24$  hours of systemic antibiotic therapy known to be effective against the presumed or documented etiologic pathogen(s) within the 72-hour period immediately prior to entry into the study. If a patient had received  $\geq 24$  hours of systemic antimicrobial therapy, there had to be clear evidence that the patient had failed this regimen. Such evidence included continued fever, and persistence or worsening of symptoms related to the index infection, and/or persistent laboratory or radiographic changes, or positive cultures.

### Criteria for Patients With Lower Respiratory Tract Infection

Patient had a clinically suspected bacterial LRTI (CAP or AECB), according to the following diagnostic criteria.

#### 1) Community-Acquired Pneumonia (CAP)

New onset of a clinical picture compatible with bacterial pneumonia with at least TWO of the following signs and symptoms:

- a) Cough;
- b) Production of purulent sputum or an increase or a change in the character of sputum;
- c) Auscultatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation (dullness on percussion, diminished breath sounds, bronchial breath sounds, rales, rhonchi, wheezing, or egophony);
- d) Dyspnea, tachypnea, hypoxemia, pleuritic chest pain, particularly if any or all of these were progressive in nature;

AND at least ONE of the following:

- ~~e) Organism consistent with a respiratory pathogen isolated from blood culture;~~
- f) Fever, defined as body temperature  $>38.0^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ) orally,  $>38.5^{\circ}\text{C}$  ( $101.2^{\circ}\text{F}$ ) tympanically, or  $>39.0^{\circ}\text{C}$  ( $102.2^{\circ}\text{F}$ ) rectally;
- g) An elevated total peripheral white blood cell (WBC) count  $>10,000/\text{mm}^3$ , or  $>15\%$  immature neutrophils (bands), regardless of total peripheral WBC, or leukopenia with total WBC  $<4500/\text{mm}^3$  provided the leukopenia was caused by the infection.

#### 2) Acute Exacerbation of Chronic Bronchitis

- a) History of chronic cough and sputum production for  $>2$  consecutive years and on most days for 3 consecutive months

and

- b) Evidence of acute exacerbation as indicated by some combination of increased cough and/or dyspnea, hypoxemia or worsened hypoxemia, increased sputum volume, or increased sputum purulence, in the absence of radiographic evidence of pneumonia.

### Criteria for Patients With Skin Infections

- 1) For a clinical diagnosis of skin or skin structure infection, patients had to have signs and symptoms of acute infection (present for  $\sim 7$  days or less) in the absence of associated indwelling foreign material (such as a central venous catheter, peripheral IV line, or pacemaker). Infections suitable for inclusion were:

- a) Infected wounds or skin lesions as evidenced by purulent drainage from or collection adjacent to the wound or lesion

OR

- b) Acute cellulitis (e.g., erythema, swelling, tenderness, warmth, induration)

Patients with uncomplicated skin infections such as impetigo, furunculosis, or carbunculosis could have been enrolled provided the infection was of sufficient severity to warrant parenteral therapy. Patients with complicated skin and skin structure infections were also eligible for inclusion. Because ceftriaxone lacks anaerobic coverage, patients with infections known or presumed to be caused by anaerobes were not allowed to be enrolled in this study.

#### Criteria for Patients With Urinary Tract Infections

Patients with suspected UTI based on the following criteria could have been enrolled:

- 1) Patients with recent onset of at least one of the following clinical symptoms of UTI:
- a) dysuria
  - b) urinary frequency or urgency
  - c) suprapubic pain
  - d) urine turbidity
- 

- 2) Urinalysis with WBC count  $\geq 10$  per high powered field in a midstream clean catch urine.

Patients with either complicated or uncomplicated UTI could have been enrolled, but in all cases patients had to have infection of sufficient severity to warrant parenteral therapy.

#### Noteworthy Exclusion Criteria

Patients were not eligible for enrollment if any of the following exclusion criteria applied:

#### General Criteria

- 1) History of coagulation disorder or patient on anticoagulation therapy.
- 2) Patients who had received any intragluteal IM therapy in the 48 hours prior to study entry.
- 3) Patients with any local pathology (e.g., cellulitis, abscess, ulcer) in the gluteal area.
- 4) Infections known at admission to be caused by pathogens resistant to either of the study drugs. This included patients at risk for anaerobic infections. Note: A macrolide could have been added for suspected "atypical" respiratory pathogens.
- 5) Patients who were hemodynamically unstable defined as:  
    Poorly perfused extremities.  
    or

Resting pulse >100 bpm and systolic blood pressure <90 mm Hg with the need for pressors or volume repletion.

- 6) Platelet count <100,000/mm<sup>3</sup>.
- 7) Coagulation (prothrombin time [PT] and partial thromboplastin time [PTT]) tests out of the range of normal values used by the laboratory performing the test. Patients who were on anticoagulant therapy should not have been enrolled. Patients with any evidence of a coagulation disorder were not to be enrolled.

#### Exclusion Criteria for Patients With Lower Respiratory Tract Infections

- 1) Patients on mechanical ventilation prior to onset of pneumonia (ventilator-associated pneumonia) or patients who were likely to require ventilatory support for their pneumonia.
- 2) Patients with cystic fibrosis.
- 3) Patients with neurologic disease preventing normal clearance of secretions (i.e., a fully or partially paralyzed patient due to a stroke), or who were at risk for recurrent episodes of aspiration. Patients with well-controlled seizure disorders were eligible.
- 4) Patients with known or suspected postobstructive pneumonia. (Patients who had chronic obstructive pulmonary disease [COPD] were eligible.)
- 5) Patients with primary lung cancer or another malignancy metastatic to the lungs.
- 6) Empyema.

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#### Exclusion Criteria for Patients With Skin Infections

- 1) Infected burn wounds.
- 2) Patients with necrotizing fasciitis.
- 3) Patients with evidence of osteomyelitis or septic arthritis.
- 4) Infections of prosthetic materials.
- 5) Patients whose wound contained concomitant gangrene or who were likely, in the opinion of the investigator, to require amputation of the infected area.
- 6) Patients with deep venous thrombosis.
- 7) Patients with infections known or presumed to be caused by anaerobes.

#### Exclusion Criteria for Patients With Urinary Tract Infections

- 1) Patients with complete obstruction of any portion of the urinary tract.
- 2) Patients with perinephric or intrarenal abscess.
- 3) Male patients with prostatitis.

#### 3.3.2 Evaluability Criteria

According to the Applicant, determinations of evaluability for the MITT populations were made prior to unblinding using the prespecified criteria stated in the Data Analysis Plan (DAP). The following criteria were used by the Applicant to define study populations for analysis:

##### Screened population

All patients who signed a consent form for the study. This population includes those patients who were not randomized to therapy and those patients who were randomized to therapy.

Randomized population

A subset of the screened population comprising patients who were randomized to 1 of the 2 study regimens.

Treated population

A population comprising patients who received at least 1 dose of study therapy. The primary hypothesis and other safety assessments were conducted in the treated population. In this study all randomized patients received therapy so the randomized and treated populations are identical.

Clinical MITT population

A subset of the treated population comprising patients with LRTI and skin infection that met the minimal disease definition. As the diagnosis of UTI was based on the isolation of a urine pathogen and not on clinical grounds, patients with UTI were not included in the clinical MITT population.

Microbiologic MITT population

A subset of the clinical MITT population and patients with UTI, comprising those patients who had a baseline pathogen identified, regardless of susceptibility to study agents, and who had a microbiologic response assessment.

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3.3.3 Endpoints

Efficacy was evaluated on the basis of "favorable" or "unfavorable" outcomes. Favorable clinical outcomes included "cure" and "improved" and favorable microbiologic outcomes included "eradication" and "presumptive eradication." The definitions of clinical and microbiological responses assigned by the Investigator at each study visit are displayed in the following tables.

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### Clinical Response Definitions

Clinical Response Definitions	
Cure	Complete or substantial resolution of signs and symptoms of active infection (with worsening of none), and no additional antibiotic therapy was required, and no prior assessment of failure.
Improvement	This assessment was only made at discontinuation of intramuscular therapy visit: improvement in most of the signs and symptoms of the index infection. Patient could have been switched to oral study therapy.
Failure	Failure could have been assessed at any time up to and including the follow-up visit: (a) death from any cause, (b) persistence, incomplete resolution, or worsening of entry signs and symptoms, and/or (c) emergence of new signs or symptoms of index infection, and/or (d) requirement for additional nonstudy antimicrobial therapy for index infection because of poor clinical response; this additional therapy was recorded.
Indeterminate	Study data were not available for evaluation of efficacy for any reason, including: (a) circumstances precluded classification as cure or failure. (b) patient was withdrawn for any reason before sufficient clinical data were obtained.

(Applicant's Table 6, July 3, 2001 submission, Volume 1 of 1, page 50)

### Microbiological Response Definitions

Microbiological Response	Definitions
Eradication	Original pathogen absent from the culture of an adequate specimen obtained from the original site of infection.
Presumptive eradication	No appropriate material (e.g., sputum) available for culture from the original site of infection, or collection of such a specimen would have caused the patient undue discomfort, in the setting of resolution or improvement of clinical signs and symptoms. This definition was not allowed for urinary tract infection (UTI).
Persistence	The continued presence of the original pathogen in cultures from the original site of infection obtained during or after completion of therapy up to the follow-up visit.
Persistence acquiring resistance	The continued presence of the original pathogen in cultures from the original site of infection during or after completion of therapy up to the test-of-cure visit, and the pathogen that was susceptible to study drug pretreatment became resistant to study drug posttreatment.
Presumed persistence	In patients who were judged to be clinical failures, and for whom a culture was not possible or was not done, it was presumed that there was persistence of the original pathogen. This definition was not allowed for UTI.
Indeterminate	(a) UTI: Follow-up cultures not available or microbiologic data insufficient to make an assessment. (b) Lower respiratory tract infection and skin infection: Follow-up cultures not available and the clinical assessment indeterminate. (c) Any other circumstance that made it impossible to define the microbiological response.
<b>For Pathogens First Isolated After the Entry Culture (Emergent Pathogens)</b>	
Suprainfection	Emergence of a new pathogen during therapy, either at the site of infection or at a distant site with emergence or worsening of signs and symptoms of infection.
New infection	Isolation of a new pathogen from a posttreatment culture from the same site or a distant site in a patient with signs and symptoms of infection.

(Applicant's Table 7, July 3, 2001 submission, Volume 1 of 1, page 51)

### 3.3.4 Statistical Considerations

#### Safety and Tolerability

The primary safety hypothesis was evaluated based on estimating the proportion of patients in the ertapenem group who experienced any moderate-to-severe local reactions after at least one intramuscularly administered dose. Assuming a total of 75 patients in the ertapenem group, if the true incidence rate of any moderate-to-severe local reactions after at least one IM dose was 10%, then the estimated incidence would be within  $\pm 7\%$  points (i.e., 95% confidence interval about an incidence rate of 10% is 3 to 17%). If no moderate-to-severe local reactions occurred after at least one IM dose for the 75 patients in the ertapenem group, then true incidence rate of moderate-to-severe local reactions would be  $< 2\%$  with 80% confidence and  $\leq 5\%$  with 98% confidence.

To address the secondary safety hypothesis, the two treatment groups were compared for the proportion of patients who experienced any study drug-related adverse experiences that led to discontinuation of IM study drug and for the proportion of patients with any IM study drug-related serious adverse experiences during treatment. The relative risk and the 95% confidence interval about the relative risk (ertapenem over ceftriaxone sodium) in proportions were displayed.

The relative risk and p-values associated with testing the secondary hypothesis that the relative risk is equal to one were also provided. If the values of the proportions were such that the relative risk ratio could not be calculated, Fisher's exact test was used to assess the treatment difference. For all other adverse experiences, including adverse experiences of special interest, the counts and percentages by treatment group are displayed but no comparative analyses were performed. Summary statistics (mean, median, and standard deviation) at baseline, DCIM, and follow-up were provided for hematology and blood chemistry parameters.

#### Efficacy

To address the IM efficacy exploratory objective, a modified intent-to-treat (MITT) approach was used. Overall efficacy was based on clinical response for LRTIs and skin infections and microbiological response for UTIs. The proportions of patients with favorable outcomes were reported by type of infection and also by overall infections combined. The efficacy analysis was performed only at the TOC visit. In the Applicant's original MITT analyses, if the follow-up assessment was missing the discontinuation of IM therapy assessment was carried forward. A second, more conservative approach to the efficacy analysis was also presented by the Applicant, in which, a patient who had a missing assessment at follow-up, was counted as a failure in the MITT analyses. The 95% confidence intervals were computed for the cure rates using the exact method.

### 3.4 Study Efficacy Results

3.4.1 Evaluability

A total of 117 patients from 9 study sites were randomized into 1 of the 2 treatment groups: 87 patients were randomized to receive MK-0826 and 30 patients were randomized to receive ceftriaxone. As all the randomized patients received at least 1 dose of therapy, the randomized and treated populations are identical. An accounting of treated patients in the study and the reasons patients discontinued from the study are presented in the following table.

Patient Accounting  
(Treated Population)

	Ertapenem 1 g		Ceftriaxone 1 g		Total	
ENTERED:	87		30		117	
Male (age range)	25	(19 to 89)	12	(24 to 65)	37	(19 to 89)
Female (age range)	62	(19 to 82)	18	(22 to 76)	80	(19 to 82)
COMPLETED THERAPY:	77		28		105	
DISCONTINUED THERAPY:	10		2		12	
Clinical adverse experience	4		0		4	
Laboratory adverse experience	0		0		0	
Lost to follow-up	2		2		4	
Deviation from protocol	2		0		2	
Clinical/microbiologic failure	1		0		1	
Patient withdrew consent	1		0		1	
COMPLETED STUDY:	81		28		109	
DISCONTINUED STUDY:	6		2		8	
Clinical adverse experience	1		0		1	
Laboratory adverse experience	0		0		0	
Lost to follow-up	4		2		6	
Deviation from protocol	0		0		0	
Patient withdrew consent	1		0		1	

(Applicant's Table 9, July 3, 2001 submission, Volume 1 of 1, page 62)

The number and percent of patients by type of infection in the MITT clinically evaluable and MITT microbiologically evaluable populations and the reasons that patients were considered to be non-evaluable for the MITT analyses are displayed in the following table.

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Patient Accounting of Evaluability  
(Treated Population)

Reasons Not Evaluable	Ertapenem 1 g		Ceftriaxone 1 g	
	n	(%)	n	(%)
<b>LRTI Patients</b>	<b>(N=30)</b>		<b>(N=6)</b>	
Clinical MITT evaluable	30	(100)	6	(100)
Clinical MITT non-evaluable	0	(0.0)	0	(0.0)
Microbiologic MITT evaluable	10	(33.3)	3	(50.0)
Microbiologic MITT non-evaluable	20	(66.7)	3	(50.0)
Baseline microbiology-no pathogen isolated	20	(66.7)	3	(50.0)
<b>Skin Infection Patients</b>	<b>(N=29)</b>		<b>(N=13)</b>	
Clinical MITT evaluable	29	(100)	13	(100)
Clinical MITT non-evaluable	0	(0.0)	0	(0.0)
Microbiologic MITT evaluable	8	(27.6)	4	(30.8)
Microbiologic MITT non-evaluable	21	(72.4)	9	(69.2)
Baseline microbiology-no pathogen isolated	21	(72.4)	9	(69.2)
<b>UTI Patients</b>	<b>(N=28)</b>		<b>(N=11)</b>	
Microbiologic MITT evaluable	20	(71.4)	9	(81.8)
Microbiologic MITT non-evaluable	8	(28.6)	2	(18.2)
Baseline microbiology-no pathogen isolated	8	(28.6)	2	(18.2)
LRTI = Lower respiratory tract infection.				
N = Number of treated patients in each indication:				
MITT = Modified intent-to-treat.				
UTI = Urinary tract infection.				

(Applicant's Table 11, July 3, 2001 submission, Volume 1 of 1, page 65)

The numbers of patients randomized into the study by investigator and treatment group are displayed in the following table.

Number of Patients Entered by Investigator and Treatment Group  
(Treated Population)

Study Number	Investigator	Location	Ertapenem 1 g (N=87)	Ceftriaxone 1 g (N=30)	Total (N=117)
029001	Bettis, Robert B.	Edmonds, WA	4	1	5
029002	Schwartz, Robert	Ft. Myers, FL	3	2	5
029003	Cambronero-Hernandez	Costa Rica	8	4	12
029004	Quintero Perez, Nora	Mexico	8	4	12
029006	Legua, Pedro	Peru	20	6	26
029007	Lema Osos, Juan Jo	Peru	20	6	26
029008	Ortiz Ruiz, Guillermo	Columbia	13	3	16
029009	Hincapie, Gustavo Ad	Colombia	7	3	10
029010	Perdomo, Pedro	Venezuela	4	1	5

(Modified Applicant's Table 10, July 3, 2001 submission, Volume 1 of 1, page 63)

3.4.2 Demographics

The table below displays baseline characteristics for the treated population.

Baseline Patient Characteristics by Treatment Group  
(Treated Population)

	Ertapenem 1 g (N=87)	Ceftriaxone 1 g (N=30)	Total (N=117)
	n (%)	n (%)	n (%)
<b>Gender</b>			
Male	25 (28.7)	12 (40.0)	37 (31.6)
Female	62 (71.3)	18 (60.0)	80 (68.4)
<b>Race</b>			
Black	1 (1.1)	1 (3.3)	2 (1.7)
Caucasian	6 (6.9)	2 (6.7)	8 (6.8)
Hispanic	62 (71.3)	18 (60.0)	80 (68.4)
Mestizo	17 (19.5)	9 (30.0)	26 (22.2)
Other	1 (1.1)	0 (0.0)	1 (0.9)
<b>Age (Years)</b>			
18 to 40	33 (37.9)	9 (30.0)	42 (35.9)
41 to 64	24 (27.6)	19 (63.3)	43 (36.8)
65 to 74	20 (23.0)	1 (3.3)	21 (17.9)
> 74	10 (11.5)	1 (3.3)	11 (9.4)
Mean	48.9	46.3	48.2
SD	20.4	14.8	19.1
Median	47.0	45.0	47.0
Range	19 to 89	22 to 76	19 to 89
<b>LRTI Patients</b>			
	(N=30)	(N=6)	(N=36)
Exacerbation of chronic bronchitis	21 (24.1)	2 (6.7)	23 (19.7)
Community-acquired pneumonia	9 (10.3)	4 (13.3)	13 (11.1)
<b>Skin Infection Patients</b>			
	(N=29)	(N=13)	(N=42)
Uncomplicated	22 (25.3)	8 (26.7)	30 (25.6)
Complicated	7 (8.0)	5 (16.7)	12 (10.3)
<b>UTI Patients</b>			
	(N=28)	(N=11)	(N=39)
Uncomplicated	16 (18.4)	8 (26.7)	24 (20.5)
Complicated	12 (13.8)	3 (10.0)	15 (12.8)
LRTI = Lower respiratory tract infection.			
SD = Standard deviation.			
UTI = Urinary tract infection.			

(Applicant's Table 12, July 3, 2001 submission, Volume 1 of 1, page 66)

**Medical Officer's Comment:** A larger percentage of patients in the ertapenem group were female.

The table below displays the extent of exposure to study drugs (duration) by treatment group for the treated population.

Extent of Exposure (Duration of Therapy) by Treatment Group  
(Treated Population)

	Ertapenem 1 g (N=87)	Ceftriaxone 1 g (N=30)	Total (N=117)
<b>Days on Study Therapy</b>			
n	87	30	117
Mean	10.1	9.7	10.0
SD	2.9	3.1	2.9
Median	10.0	10.0	10.0
Range			
<b>Days on IM Therapy</b>			
n	87	30	117
Mean	4.1	3.8	4.0
SD	1.9	1.2	1.8
Median	4.0	4.0	4.0
Range			
<b>Days on Oral Therapy</b>			
n	84	28	112
Mean	6.2	6.3	6.2
SD	2.5	2.6	2.5
Median	6.0	6.5	6.0
Range			
<p>† One patient (AN 0017), because of an artifact of the database, appears to have received 15 days of IM therapy when the patient actually received 6 days of IM and 9 days of oral therapy without missing any days of therapy. No patients received more than 7 days of IM therapy.</p> <p>IM = Intramuscular. N = Total number of patients in each treatment group. n = Number of patients in category. SD = Standard deviation.</p>			

(Applicant's Table 16, July 3, 2001 submission, Volume 1 of 1, page 72)

**Medical Officer's Comment:** *The 2 treatment groups appeared similar with respect to extent of exposure to study drug.*

3.4.3 Efficacy

3.4.3.1 Overall MITT Efficacy

The Applicant's more conservative analysis ("Alternate MITT"), in which an assessment of failure was assigned for all patients missing the TOC visit, regardless of outcome at the DCIM visit, is displayed below.

Proportion of Patients With Favorable Response Assessments  
(Alternative MITT Population)

Indication (Response Type)	Treatment Group			
	Ertapenem 1g (N=79)		Ceftriaxone 1g (N=28)	
	n/m	Response % (95% CI)	n/m	Response % (95% CI)
Lower Respiratory Tract (clinical)	27/30	90.0	6/6	100
Skin (clinical)	20/29	69.0	11/13	84.6
Urinary Tract (microbiologic)	15/20	75.0	7/9	77.8
Overall (clinical or microbiologic)	62/79	78.5 (67.8, 86.9)	24/28	85.7 (67.3, 96.0)

MITT = Modified intent to treat.  
N = Number of MITT patients in each treatment group.  
n/m = Number of patients with favorable response assessment/number of MITT patients per indication.  
CI = Confidence interval, calculated using an exact method.  
All patients who missed the follow-up visit are counted as failures.

(Applicant's Table 68, July 3, 2001 submission, Volume 1 of 1, page 168)

*Medical Officer's Comment: The outcome trend for each indication was worse for the ertapenem group, particularly for skin infections; however, the design of this study and the small sample size enrolled in each indication make it difficult to draw any definitive conclusions regarding the efficacy of IM ertapenem versus comparator.*

3.4.3.2 Microbiologic MITT Efficacy

The Applicant's more conservative analysis, in which an assessment of failure was assigned for all patients missing the TOC visit, regardless of outcome at the DCIM visit, is displayed below.

Proportion of Patients With Favorable Microbiological Response Assessments  
(Alternative Microbiological MITT Population)

Infection Type	Treatment Group			
	Ertapenem 1g (N=38)		Ceftriaxone 1g (N=16)	
	n/m	Response % (95% CI)	n/m	Response % (95% CI)
Lower Respiratory Tract	10/10	100	3/3	100
Skin	3/8	37.5	4/4	100
Urinary Tract	15/20	75.0	7/9	77.8
Overall	28/38	73.7 (56.9, 86.6)	14/16	87.5 (61.7, 98.5)

MITT = Modified intent to treat.  
N = Number of microbiological MITT patients in each treatment group.  
n/m = Number of patients with favorable microbiological response assessment/number of microbiological MITT patients.  
CI = Confidence interval, calculated using an exact method.  
All patients who missed the follow-up visit are counted as failures.

(Applicant's Table 69, July 3, 2001 submission, Volume 1 of 1, page 169)

**Medical Officer's Comment:** The outcome for patients with skin infections in the microbiologic MITT population was worse in the ertapenem group. Of the 5 patients that were failures in the ertapenem group, 1 of the patients was lost to follow-up (AN 0016) and 4 of the patients were treatment failures (ANs 0066, 0093, 0098, and 0151). The Applicant's narratives for these 4 treatment failures are provided in the following table. The design of this study and the small sample size enrolled in each indication, however, make it difficult to draw any definitive conclusions regarding the efficacy of IM ertapenem versus comparator.

AN	Narrative
0066	A 70-year-old female began IM therapy with ertapenem for the treatment of a right thigh infection. The initial size of the lesion was 8 cm x 7 cm x 0.4 mm. <i>Staphylococcus aureus</i> was isolated and was susceptible to ertapenem and amoxicillin/clavulanate. On Study Day 4 after receiving 4 days of IM therapy, the patient developed an abscess at the site of infection requiring drainage. A repeat culture was performed and <i>S. aureus</i> was isolated again. The patient's therapy was switched to amoxicillin/clavulanate for 7 days. The investigator assessed the patient as a cure at follow-up but the sponsor considered this to be a failure.
0093	A 49-year-old female with diabetes mellitus and a history of cellulitis of the right leg began IM therapy with ertapenem for the treatment of cellulitis of the left leg. This was considered a complicated skin infection. The size of the affected area was recorded as 24 cm x 33 cm x 2.5 cm. <i>Aeromonas hydrophila</i> was isolated as the pathogen and was susceptible to ertapenem but resistant to amoxicillin/clavulanate. The patient received 7 days of IM therapy and 7 days of ciprofloxacin. On Study Day 15, the patient had developed a fistula with purulent drainage close to the site of the original skin lesion and was deemed a failure by the investigator. The size of the fistula was 2.5 cm x 2 cm x 1 cm. Cultures at this time showed no growth. The patient continued on ciprofloxacin and clindamycin phosphate was added for 17 additional days of therapy.
0098	A 32-year-old male began IM therapy with ertapenem for the treatment of a wound of the left leg. The size of the wound was 10 cm x 6 cm x 0.3 cm. <i>S. aureus</i> was isolated as the pathogen and was sensitive to ertapenem and amoxicillin/clavulanate. The patient received 3 days of IM therapy and 7 days of amoxicillin/clavulanate. On Study Day 12, the patient returned and was deemed a failure by the investigator. However, the size of the wound had decreased to 1.5 cm x 1.5 cm x 0.5 cm. The culture again grew <i>S. aureus</i> , which was susceptible to ertapenem but now resistant to amoxicillin/clavulanate. The patient began ciprofloxacin therapy for 10 additional days of therapy.
0151	A 20-year-old male with a history of eczema began IM therapy with ertapenem for the treatment of a furuncle (uncomplicated) located on his back. The initial size of the wound was 3 cm x 2 cm x 1/2 cm. <i>Propionibacterium</i> was identified as a pathogen but no susceptibility testing was performed. On Study Day 3, after receiving 2 days of IM therapy, the depth of the wound had increased to 2 cm and the investigator discontinued study therapy due to failure. The patient's therapy was switched to cephalixin for 10 days. There were no repeat cultures performed.

### 3.4.3.3 By Pathogen

The Applicant's more conservative analysis ("Alternate MITT"), in which an assessment of failure was assigned for all patients missing the TOC visit, regardless of outcome at the DCIM visit, is displayed below.

Proportion of Favorable Microbiological Response Assessments  
Displayed by Baseline Pathogen  
(Alternative Microbiologically MITT Population—Total Isolates)

Total Isolates	Treatment Group	
	Ertapenem 1g (N=38)	Ceftriaxone 1g (N=16)
	n/m	n/m
<b>Gram-Positive Aerobic Cocci</b>	<b>5/9</b>	<b>3/3</b>
<i>Staphylococcus aureus</i>	2/4	2/2
<i>Staphylococcus haemolyticus</i>		1/1
<i>Streptococcus</i>	1/1	
<i>Streptococcus pneumoniae</i>	2/3	
<i>Streptococcus pyogenes</i>	0/1	
<b>Gram-Negative Aerobic Rods</b>	<b>26/31</b>	<b>9/11</b>
<i>Aeromonas hydrophila</i>	1/1	
<i>Escherichia coli</i>	11/15	7/8
<i>Haemophilus</i>	1/1	
<i>Haemophilus influenzae</i>	2/2	
<i>Haemophilus parainfluenzae</i>	2/2	
<i>Klebsiella oxytoca</i>	3/3	
<i>Klebsiella pneumoniae</i>		1/1
<i>Moraxella catarrhalis</i>	2/2	1/1
<i>Pantoea agglomerans</i>	4/5	0/1
<b>Gram-Negative Aerobic Cocci</b>		<b>1/1</b>
<i>Neisseria sicca</i>		1/1
<b>Gram-Positive Anaerobic Rods</b>	<b>0/1</b>	
<i>Propionibacterium</i>	0/1	
<b>Gram-Positive Anaerobic Cocci</b>	<b>0/1</b>	<b>1/1</b>
<i>Peptostreptococcus anaerobius</i>		1/1
<i>Peptostreptococcus prevotii</i>	0/1	
<b>Gram-Negative Anaerobic Rods</b>	<b>0/2</b>	
<i>Fusobacterium necrophorum</i>	0/1	
<i>Fusobacterium nucleatum</i>	0/1	

N = Number of microbiological MITT patients in each treatment group.  
n/m = Number of pathogens with associated favorable assessment/number of pathogens with an assessment.  
All patients who missed the follow-up visit are counted as failures.

(Applicant's Table 70, July 3, 2001 submission, Volume 1 of 1, page 170)

**Medical Officer's Comment:** The small number of pathogens indentified per species in this study make any meaningful conclusions regarding by-pathogen data impossible.

3.5 Review of Safety

Adverse experiences were recorded during IM study therapy, oral study therapy, and for 14 days after the end of study therapy (safety follow-up period). The

parenteral study therapy period is the primary focus of the Applicant's safety discussion; however, the Applicant also provided analyses of the adverse experiences that occurred during the total study therapy (parenteral plus oral) plus 14-day follow-up period.

All of the 117 randomized patients (87 in the ertapenem group and 30 in the ceftriaxone group) received at least one dose of IM study therapy and are included in the analyses of adverse experiences. The tables below provide an overall summary of clinical and laboratory safety during the parenteral therapy period and total study period (parenteral therapy plus oral therapy and the 14-day follow-up periods).

Clinical and Laboratory Adverse Experience Summary

Clinical Adverse Experiences Number (%) of patients	Parenteral Study Period				Parenteral plus Oral Therapy And 14 Day Follow-up Period			
	Ertapenem 1 g (N=87)		Ceftriaxone 1 g (N=30)		Ertapenem 1 g (N=87)		Ceftriaxone 1 g (N=30)	
	n	(%)	n	(%)	n	(%)	n	(%)
with one or more adverse experiences	26	(29.9)	10	(33.3)	43	(49.4)	12	(40.0)
with no adverse experience	61	(70.1)	20	(66.7)	44	(50.6)	18	(60.0)
with drug-related <sup>†</sup> adverse experiences	14	(16.1)	5	(16.7)	18	(20.7)	6	(20.0)
with serious adverse experiences	2	(2.3)	0	(0.0)	4	(4.6)	0	(0.0)
with serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	1	(1.1)	0	(0.0)	1	(1.1)	0	(0.0)
discontinued due to an adverse experience	1	(1.1)	0	(0.0)	4	(4.6)	0	(0.0)
discontinued due to a drug-related adverse experience	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)
discontinued due to a serious adverse experience	1	(1.1)	0	(0.0)	2	(2.3)	0	(0.0)
discontinued due to a serious drug-related adverse experience	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Laboratory Adverse Experiences Number (%) of patients	Ertapenem 1 g (N=84)		Ceftriaxone 1 g (N=30)		Ertapenem 1 g (N=86)		Ceftriaxone 1 g (N=30)	
	n	(%)	n	(%)	n	(%)	n	(%)
with one or more adverse experiences	40	(47.6)	10	(33.3)	43	(50.0)	10	(33.3)
with no adverse experience	44	(52.4)	20	(66.7)	43	(50.0)	20	(66.7)
with drug-related <sup>†</sup> adverse experiences	31	(36.9)	7	(23.3)	35	(40.7)	7	(23.3)
with serious adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
with serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to an adverse experience	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a drug-related adverse experience	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious adverse experience	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse experience	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

<sup>†</sup> Determined by investigator to be possibly, probably, or definitely drug related.

N = Number of treated patients with at least one laboratory test postbaseline.

n = Number of patients with a laboratory adverse experience.

(Modified Applicant's Tables 25, 27, 36, and 38, July 3, 2001 submission, Volume 1 of 1, pages 89, 94, 112, and 117)

**Medical Officer's Comment:** While the incidence of clinical serious adverse experiences were higher in the ertapenem group, serious drug-related adverse experiences were not reported in either group.

*Overall the incidence of clinical and laboratory adverse experiences were similar in the 2 treatment groups.*

3.5.1 Extent of Exposure

The table below shows the extent of exposure to parenteral therapy by dose and duration for all patients who received at least 1 dose of study therapy. The number of patients who received each total daily dose of parenteral therapy is displayed. The protocol allowed a one-time adjustment in dosing interval between the first and second parenteral study drug doses, to accommodate local medication administration schedules; 2 patients in the MK-0826 group and 0 patients in the ceftriaxone group had this dosing interval adjustment and received two 1 gm doses within the first 24 hour period (i.e., Day 1 of therapy).

Extent of Exposure by Dose and Duration  
(Treated Population)

Treatment Group	Number of Days on Parenteral Therapy <sup>†</sup>					Total Patients	Range	Total Days	Mean
	≤2	3 to 4	5 to 6	7 to 8					
<b>Ertapenem</b>									
Any dose	14	45	20	8	87	—	347	4.0	
1 g	14	46	19	8	87	—	345	4.0	
2 g	2	0	0	0	2	—	2	1.0	
<b>Ceftriaxone</b>									
Any dose	5	13	12	0	30	—	115	3.8	
1 g	5	13	12	0	30	—	115	3.8	

<sup>†</sup> The table displays the number of patients receiving exactly the specified number of days of therapy.

(Applicant's Table 24, July 3, 2001 submission, Volume 1 of 1, page 88)

**Medical Officer's Comment:** *The 2 treatment groups were similar with respect to extent of exposure to parenteral therapy by dose and duration. As was displayed in the demographics section of this review, the extent of exposure to oral therapy after IM therapy was also similar in the 2 treatment groups.*

3.5.2 Deaths

There was one death (AN 0060) in the ertapenem group and no deaths in the ceftriaxone group among patients enrolled in Protocol 029. The single death occurred during the parenteral study period. Neither the death, nor the adverse experiences associated with the death, were considered study-drug related, by the Investigator or Applicant. The Applicant's narrative for this death (AN 0060) is as follows:

“A 76-year-old male with acute exacerbation of chronic bronchitis and a history of COPD and cor pulmonale began IM therapy with ertapenem for the treatment of an LRTI. On Study Day 4, he had a sudden cardiac arrest that did not respond to cardiopulmonary resuscitation. The probable cause

of the cardiac arrest was cor pulmonale and pulmonary hypertension. The investigator determined that the adverse experiences were not related to study drug therapy.”

No additional deaths occurred during the remainder of the entire study period.

**Medical Officer's Comment:** *The Case Report Form for this patient was reviewed and the MO is in agreement that this patient's death was most likely related to underlying disease.*

**3.5.3 Other Serious Adverse Events**

In addition to patient AN 0060 discussed above, one other patient (AN 0014) in the ertapenem group experienced serious clinical adverse events during the parenteral therapy period and 2 other patients (ANs 0048 and 0093) in the ertapenem group experienced serious clinical adverse events during the entire study period, but after parenteral therapy. No serious clinical adverse experiences were reported in the ceftriaxone group. No serious drug-related clinical adverse experiences were reported in either treatment group. The following table displays patients with serious clinical adverse experiences occurring during the study therapy and follow-up period.

**Listing of Patients With Serious Clinical Adverse Experiences  
During Study Therapy and Follow-Up Period  
(Treated Population)**

AN	Study Number	Gender	Race	Age	Daily Dose <sup>1</sup>	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Intensity	Drug Relationship	Action Taken <sup>2</sup>	Outcome
<b>Ertapenem 1 g</b>												
0014	029004	F	Mestizo	80	Ertapenem 1 g Amoxicillin/clavulanate 1750 mg	5	Bronchoconstriction	4 days	Severe	Definitely not	None	Recovered
0048	029007	F	Hispanic	48	Off drug Amoxicillin/ clavulanate 1 g	22 10	CVA Necrosis	13 days 11 days	Moderate Moderate	Definitely not Probably not	None Discontinued	Still present Recovered
0093	029007	F	Mestizo	49	Off drug	15	Fistula	17 days	Mild	Definitely not	None	Recovered
0060	029008	M	Hispanic	76	Ertapenem 1 g Ertapenem 1 g Ertapenem 1 g Ertapenem 1 g	4 4 4 4	Death Cardiac arrest Hypertension, pulmonary Cor pulmonale	30 minutes 30 minutes 30 minutes	Severe Severe Severe	Probably not Probably not Probably not	None Discontinued Discontinued	Recovered Still present Still present
<sup>1</sup> Displays any change of daily dose that occurred within the duration of the adverse experience. <sup>2</sup> Action taken with regard to study drug therapy.												

**Medical Officer's Comment:** *Although there appears to be an imbalance in the serious clinical adverse events between treatment groups, the MO has reviewed the Case Report Forms for these patients and agrees with the Applicant's assessment that the serious clinical adverse events that occurred are most likely due to patients' underlying diseases (ANs 0060 and 0014) or failure of study therapy (ANs 0048 and 0093).*

**3.5.4 Dropouts**

Four patients in the ertapenem group and no patients in the ceftriaxone group discontinued from study therapy. One of these patients (AN 0060), who was previously discussed in the death section of this review, discontinued during parenteral therapy. The remaining three patients (ANs 0123, 0048, and 0054) discontinued therapy while receiving oral therapy with amoxicillin/clavulanate.

AN 0123 discontinued due to stomatitis considered related to study therapy by the Investigator. AN 0054 discontinued therapy due to dysphagia and AN 0048 discontinued due to therapy failure; in both cases these events were considered unrelated to study therapy by the Investigators.

3.5.5 Other Treatment Emergent Adverse Events

Overall 26 patients [29.9%] in the ertapenem group and 10 patients [33.3%] in the ceftriaxone group had a drug-related adverse experience during the parenteral therapy period and 43 patients [49.4%] in the ertapenem group and 12 patients [40.0%] in the ceftriaxone group had a drug-related adverse experience during the entire study period. The Applicant's table displaying overall and drug-related adverse events for the entire study period is displayed below.

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Number (%) of Patients With Specific Clinical Adverse Experiences  
(Incidence >0% in One or More Treatment Groups) by Body System  
During Study Therapy and Follow-Up Period  
(Treated Population)  
Total and Drug Related

	Ertapenem 1 g (N=87)			Ceftriaxone 1 g (N=30)		
	Total		DR	Total		DR
	n	(%)	n	n	(%)	n
Patients with one or more adverse experiences	43	(49.4)	18	12	(40.0)	6
Patients with no adverse experience	44	(50.6)	--	18	(60.0)	--
<b>Body as a Whole/Site Unspecified</b>	<b>18</b>	<b>(20.7)</b>	<b>6</b>	<b>6</b>	<b>(20.0)</b>	<b>2</b>
Asthenia/fatigue	1	(1.1)	0	1	(3.3)	0
Death	1	(1.1)	0	0	(0.0)	0
Ecchymosis, injection site	2	(2.3)	0	1	(3.3)	1
Edema/swelling	2	(2.3)	0	0	(0.0)	0
Fistula	1	(1.1)	0	0	(0.0)	0
Induration, injection site	2	(2.3)	0	0	(0.0)	0
Necrosis	1	(1.1)	0	0	(0.0)	0
Pain/tenderness/soreness, injection site	4	(4.6)	3	2	(6.7)	1
Pain, abdominal	6	(6.9)	2	1	(3.3)	0
Pain, chest	0	(0.0)	0	1	(3.3)	0
Pain, pelvic	1	(1.1)	0	0	(0.0)	0
Pruritus, injection site	1	(1.1)	0	0	(0.0)	0
Rash, injection site	1	(1.1)	1	0	(0.0)	0
<b>Cardiovascular System</b>	<b>7</b>	<b>(8.0)</b>	<b>0</b>	<b>1</b>	<b>(3.3)</b>	<b>0</b>
Cardiac arrest	1	(1.1)	0	0	(0.0)	0
Cardiovascular disorder	0	(0.0)	0	1	(3.3)	0
Cor pulmonale	1	(1.1)	0	0	(0.0)	0
CVA	1	(1.1)	0	0	(0.0)	0
Hypertension, pulmonary	1	(1.1)	0	0	(0.0)	0
Infused vein complication	2	(2.3)	0	0	(0.0)	0
Phlebitis/thrombophlebitis	2	(2.3)	0	1	(3.3)	0
Tachycardia	3	(3.4)	0	0	(0.0)	0
<b>Digestive System</b>	<b>13</b>	<b>(14.9)</b>	<b>6</b>	<b>1</b>	<b>(3.3)</b>	<b>0</b>
Cholelithiasis	1	(1.1)	0	0	(0.0)	0
Diarrhea	6	(6.9)	3	0	(0.0)	0
Dyspepsia	2	(2.3)	2	0	(0.0)	0
Dysphagia	1	(1.1)	0	0	(0.0)	0
Nausea	3	(3.4)	0	1	(3.3)	0
Stomatitis	1	(1.1)	1	0	(0.0)	0
Vomiting	4	(4.6)	0	0	(0.0)	0
<b>Musculoskeletal System</b>	<b>3</b>	<b>(3.4)</b>	<b>1</b>	<b>2</b>	<b>(6.7)</b>	<b>2</b>
Arthralgia	1	(1.1)	1	0	(0.0)	0
Bursitis	1	(1.1)	0	0	(0.0)	0
Pain, foot	0	(0.0)	0	1	(3.3)	1
Pain, leg	1	(1.1)	0	0	(0.0)	0
Stiffness	0	(0.0)	0	1	(3.3)	1
<b>Nervous System and Psychiatric Disorder</b>	<b>4</b>	<b>(4.6)</b>	<b>1</b>	<b>4</b>	<b>(13.3)</b>	<b>1</b>
Dizziness	1	(1.1)	0	0	(0.0)	0
Dream abnormality	0	(0.0)	0	1	(3.3)	0
Headache	2	(2.3)	1	2	(6.7)	1
Paresthesia	0	(0.0)	0	1	(3.3)	0
Spasm	1	(1.1)	0	0	(0.0)	0

Number (%) of Patients With Specific Clinical Adverse Experiences  
(Incidence >0% in One or More Treatment Groups) by Body System  
During Study Therapy and Follow-Up Period  
(Treated Population)  
Total and Drug Related

	Ertapenem 1 g (N=87)			Ceftriaxone 1 g (N=30)		
	Total		DR	Total		DR
	n	(%)	n	n	(%)	n
<b>Respiratory System</b>	<b>11</b>	<b>(12.6)</b>	<b>2</b>	<b>2</b>	<b>(6.7)</b>	<b>0</b>
Bronchitis	1	(1.1)	0	0	(0.0)	0
Bronchoconstriction	3	(3.4)	2	0	(0.0)	0
Cough	2	(2.3)	0	0	(0.0)	0
Hemoptysis	2	(2.3)	0	0	(0.0)	0
Infection, respiratory, upper	2	(2.3)	0	0	(0.0)	0
Pharyngitis	1	(1.1)	0	0	(0.0)	0
Rales/rhonchi	2	(2.3)	0	1	(3.3)	0
Rhinitis, allergic	1	(1.1)	1	0	(0.0)	0
Rhinorrhea	3	(3.4)	0	1	(3.3)	0
Sinusitis	1	(1.1)	0	0	(0.0)	0
Wheezing	3	(3.4)	0	0	(0.0)	0
<b>Skin and Skin Appendage</b>	<b>8</b>	<b>(9.2)</b>	<b>1</b>	<b>1</b>	<b>(3.3)</b>	<b>0</b>
Abscess	1	(1.1)	0	0	(0.0)	0
Ecchymosis	0	(0.0)	0	1	(3.3)	0
Erythema	1	(1.1)	0	0	(0.0)	0
Herpes simplex	2	(2.3)	0	0	(0.0)	0
Infection, skin	1	(1.1)	0	0	(0.0)	0
Infection, wound	1	(1.1)	0	0	(0.0)	0
Pruritus vulvae	1	(1.1)	0	0	(0.0)	0
Rash	2	(2.3)	1	0	(0.0)	0
Sweating	1	(1.1)	0	0	(0.0)	0
<b>Special Senses</b>	<b>1</b>	<b>(1.1)</b>	<b>0</b>	<b>0</b>	<b>(0.0)</b>	<b>0</b>
Pain, ear	1	(1.1)	0	0	(0.0)	0
<b>Urogenital System</b>	<b>5</b>	<b>(5.7)</b>	<b>3</b>	<b>1</b>	<b>(3.3)</b>	<b>1</b>
Candiduria	1	(1.1)	1	0	(0.0)	0
Dysuria	1	(1.1)	0	0	(0.0)	0
Vaginitis	1	(1.1)	1	0	(0.0)	0
Vulvovaginitis	2	(2.3)	1	1	(3.3)	1

N = All treated patients.  
n = Number of patients reporting clinical adverse experiences.  
DR = Number of patients reporting clinical adverse experiences, determined by the investigator to be possibly, probably, or definitely drug related.  
Only adverse experiences that occurred during study drug therapy and 14 days after the discontinuation of study drug therapy are counted. Adverse experiences reported more than 14 days after the discontinuation of study drug therapy (parenteral and oral) are not counted.  
Although a patient may have had 2 or more adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.  
All body systems are listed in which at least 1 patient had an adverse experience.

(Applicant's Table 28, July 3, 2001 submission, Volume 1 of 1, pages 95-98)

**Medical Officer's Comment:** The overall incidence of clinical adverse experiences and drug-related adverse experiences was similar between the 2 treatment groups. The incidence of drug-related diarrhea was greater in the ertapenem group during both the parenteral therapy period (3.4% ertapenem group versus 0% ceftriaxone group) and during the entire study period (6.9% ertapenem group versus 0% ceftriaxone group). Given the broader antimicrobial spectrum of ertapenem, patients in the ertapenem group may have experienced a greater perturbation of the normal gastrointestinal tract flora.

3.5.6 Laboratory Findings

Of the patients in the treated population, 40 (47.6%) in the ertapenem group and 10 (33.3%) in the ceftriaxone group had a laboratory adverse experience during

parenteral therapy and 43 (50.0%) in the ertapenem group and 10 (33.3%) in the ceftriaxone group had a laboratory adverse experience during the entire study period. The most common laboratory adverse experiences were increased CPK, increased ALT and AST concentrations, increased alkaline phosphatase, increased eosinophil count, and increased platelet count. The tables below display the number (percent) of patients with specific laboratory adverse experiences and drug-related laboratory adverse experiences with an incidence >0% in one or more treatment groups, occurring during the parenteral study period.

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**Number (%) of Patients With Specific Laboratory Adverse Experiences  
(Incidence >0% in One or More Treatment Groups) by Laboratory Test Category  
During Study Therapy and 14-Day Follow-Up Period  
(Treated Population)**

	Ertapenem 1 g (N=87)			Ceftriaxone 1 g (N=30)		
	Total		DR	Total		DR
	n/m	(%)	n/m	n/m	(%)	n/m
Patients with one or more adverse experiences	43/86	(50.0)	35/86	10/30	(33.3)	7/30
Patients with no adverse experience	43/86	(50.0)	--	20/30	(66.7)	--
<b>Blood Chemistry</b>	<b>32/86</b>	<b>(37.2)</b>	<b>23/86</b>	<b>10/30</b>	<b>(33.3)</b>	<b>6/30</b>
Alkaline phosphatase increased	8/86	(9.3)	8/86	1/30	(3.3)	1/30
ALT increased	8/86	(9.3)	8/86	1/30	(3.3)	1/30
AST increased	6/86	(7.0)	6/86	3/30	(10.0)	3/30
Direct serum bilirubin increased	3/78	(3.8)	1/78	0/28	(0.0)	0/28
Indirect serum bilirubin increased	4/78	(5.1)	2/78	0/28	(0.0)	0/28
Serum bicarbonate increased	1/83	(1.2)	0/83	0/28	(0.0)	0/28
Serum calcium increased	1/86	(1.2)	0/86	0/30	(0.0)	0/30
Serum CPK increased	19/83	(22.9)	10/83	6/29	(20.7)	2/29
Serum creatinine increased	1/86	(1.2)	0/86	0/30	(0.0)	0/30
Serum glucose decreased	1/86	(1.2)	0/86	0/30	(0.0)	0/30
Serum glucose increased	2/86	(2.3)	0/86	0/30	(0.0)	0/30
Serum potassium decreased	1/86	(1.2)	0/86	0/30	(0.0)	0/30
Serum potassium increased	2/86	(2.3)	1/86	0/30	(0.0)	0/30
Serum sodium increased	1/86	(1.2)	1/86	0/30	(0.0)	0/30
Total serum bilirubin increased	4/86	(4.7)	2/86	1/30	(3.3)	1/30
<b>Hematology</b>	<b>21/86</b>	<b>(24.4)</b>	<b>19/86</b>	<b>5/30</b>	<b>(16.7)</b>	<b>5/30</b>
Eosinophils increased	10/86	(11.6)	10/86	2/30	(6.7)	2/30
Platelet count increased	7/86	(8.1)	7/86	0/30	(0.0)	0/30
PTT increased	0/86	(0.0)	0/86	1/30	(3.3)	1/30
Segmented neutrophils decreased	4/86	(4.7)	4/86	2/30	(6.7)	2/30
Segmented neutrophils increased	2/86	(2.3)	0/86	0/30	(0.0)	0/30
WBC count decreased	2/86	(2.3)	2/86	1/30	(3.3)	1/30
WBC decreased	2/86	(2.3)	2/86	0/30	(0.0)	0/30
WBC increased	1/86	(1.2)	0/86	0/30	(0.0)	0/30
<b>Urinalysis</b>	<b>4/85</b>	<b>(4.7)</b>	<b>3/85</b>	<b>0/30</b>	<b>(0.0)</b>	<b>0/30</b>
Urine bacteria increased	1/84	(1.2)	1/84	0/28	(0.0)	0/28
Urine WBCs increased	1/84	(1.2)	0/84	0/28	(0.0)	0/28
Urine yeast, nondiagnostic	2/2	(100.0)	2/2	0/0	(0.0)	0/0

N = Total number of patients per treatment group.  
n/m = Number of patients with laboratory adverse experience/number of patients with laboratory test.  
DR = Number of patients reporting laboratory adverse experiences, determined by the investigator to be possibly, probably, or definitely drug related.  
Although a patient may have had 2 or more adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.  
All categories are listed in which at least 1 patient had an adverse experience.

(Applicant's Table 39, July 3, 2001 submission, Volume 1 of 1, page 119)

**Medical Officer's Comment:** The number of events was similar in the parenteral therapy only period. Transaminase elevations and increased eosinophil and platelet counts appeared to occur more often in the ertapenem group. Elevated transaminases will be further addressed later in this review in the Adverse Events of Special Interest section. While the Applicant's table lists eosinophilia as occurring in

11.6% (10/86 patients) of ertapenem patients and 6.7% (2/30 patients) of ceftriaxone patients, when the Applicant's data were further reviewed and absolute eosinophil counts were calculated, 7.0% (6/86 patients) in the ertapenem group and 6.7% (2/30 patients) in the ceftriaxone group actually developed eosinophil counts >500 cells/uL while on study. Therefore the frequency at which patients developed significant eosinophilia appears similar between treatment groups.

3.5.7 Assessment of Tolerability

An assessment of tolerability at the IM study drug injection site was performed daily by Investigators while patients were on study therapy. The intensity of each specific injection-related sign or symptom was rated as mild, moderate, or severe. If local intolerance was felt by the Investigator to reach the level of a clinical adverse experience, the adverse experience was reported as a clinical syndrome (e.g. local phlebitis/thrombophlebitis) and was displayed as "infused vein complication" in the counts of clinical adverse experiences. A clinical adverse experience of "infused vein complication" was reported for 2/87 (2.3%) patients in the ertapenem group and none of the patients in the ceftriaxone group. The following table displays the number and percent of patients reporting local reaction symptoms of any intensity.

Number (%) of Patients With Local Reaction Symptoms  
of Any Intensity—During Intramuscular Therapy  
(Treated Population)

	Ertapenem 1 g (N=87)		Ceftriaxone 1 g (N=30)	
	n/m	%	n/m	%
<b>Patients With One or More Symptoms†</b>	<b>31/87</b>	<b>35.6</b>	<b>13/30</b>	<b>43.3</b>
Erythema	1/87	1.1	0/30	0.0
Induration	2/87	2.3	1/30	3.3
Local Phlebitis	0/87	0.0	0/30	0.0
Pain	15/87	17.2	7/30	23.3
Pruritis	0/87	0.0	0/30	0.0
Swelling	0/87	0.0	0/30	0.0
Tenderness	21/87	24.1	5/30	16.7
Ulceration	0/87	0.0	0/30	0.0
Warmth	0/87	0.0	0/30	0.0
Other: ecchymosis	1/87	1.1	0/30	0.0
Other: ecchymosis, injection site	1/87	1.1	1/30	3.3
Other: hematoma, injection site	1/87	1.1	0/30	0.0
Other: rash, papular, injection	1/87	1.1	0/30	0.0
Other: stiffness	0/87	0.0	1/30	3.3

† Patients with more than one symptom are counted only once in the overall count.  
N = The number of patients in the treatment group.  
n = Number of patients reporting the intolerability symptom.  
m = Number of patients with an assessment.

(Applicant's Table 40, July 3, 2001 submission, Volume 1 of 1, page 121)

The number and percentages of patients who experienced one or more local reactions of moderate to severe intensity at the injection site were 1 of 87 (1.1%) in the ertapenem group and 3 of 30 (10.0%) in the ceftriaxone group. Pain was the only symptom of moderate-to-severe intensity reported in either treatment group. To address the primary hypothesis, the differences in incidence of intolerability symptoms of moderate to severe intensity between the 2 treatment groups was analyzed by the Applicant and the results of this analysis is displayed in the following table.

**Number (%) of Patients With Local Reaction Symptoms During Parenteral Therapy (Treated Population)**

	Treatment Groups						Difference (A-B) (95% CI)
	Ertapenem 1 g (A) (N=87)			Ceftriaxone 1 g (B) (N=30)			
	n/m	%	(95% CI)	n/m	%	(95% CI)	
Patients with one or more symptoms of moderate-to-severe intensity	1/87	1.1	(0.0, 6.2)	3/30	10.0	(2.1, 26.5)	-8.9 (-31.1, 3.3)
Patients with one or more symptoms of any intensity	31/87	35.6		13/30	43.3		-7.7

N - Number of patients in each treatment group who received at least one intramuscular dose.  
n/m = Number of patients reporting at least one intolerability symptom/number of patients with an assessment.  
CI - Confidence interval calculated using an exact method.

(Applicant's Table 42, July 3, 2001 submission, Volume 1 of 1, page 123)

**Medical Officer's Comment:** *When compared to intramuscular administration of ceftriaxone, intramuscular administration of ertapenem appears to be at least as well tolerated and possibly better tolerated.*

**3.5.8 Adverse Events of Special Interest**

Four adverse experiences were prespecified for more detailed review because of preclinical findings (neutropenia), adverse experiences associated with  $\beta$ -lactam antibiotics as a class (liver function elevations and rash), and adverse experiences associated with other carbapenem antimicrobials (seizures).

Seizures

No seizures were reported in this study.

Neutropenia/Liver Enzyme Elevations

In addition to reviewing investigator-reported laboratory adverse experiences, the Applicant performed an assessment of the relative laboratory safety of each treatment group by using predefined Clinically Significant Laboratory Abnormalities (CSLAs) for specified tests and identifying patients whose worst

laboratory value represented a worsening from baseline and met the criteria for a CSLA. In order to be considered in the analysis for CSLAs, patients had to have a baseline laboratory value, at least 1 postbaseline laboratory test and have normal ranges in the database. For platelet count, absolute neutrophil count, hematocrit, and hemoglobin the CSLA criteria were defined in terms of a fixed bound. For creatinine, total bilirubin, direct bilirubin, ALT, AST, and alkaline phosphatase, the CSLA criteria were defined in terms of a fixed bound greater than the upper limit of normal (ULN). The following table displays CSLAs for neutropenia and liver function assays during the parenteral therapy period and during the total study therapy plus the follow-up period.

**Number (%) of Patients With a Clinically Significant Laboratory Abnormality (CSLA) by Treatment Group**

Laboratory Test	CSLA Criteria	During Parenteral Therapy				During Study Therapy and Follow-up			
		Number (%) with CSLA				Number (%) with CSLA			
		Ertapenem (N=87)		Ceftriaxone (N=30)		Ertapenem (N=87)		Ceftriaxone (N=30)	
Absolute neutrophils (cells/ $\mu$ L)	<1800	n/m	(%)	n/m	(%)	n/m	(%)	n/m	(%)
	<1000	4/84	4.8	0/30	0.0	5/86	5.8	0/30	0.0
ALT (U/L)	>2.5 x ULN	3/82	3.7	0/30	0.0	5/84	6.0	0/30	0.0
	>5 x ULN	0/82	0.0	0/30	0.0	0/84	0.0	0/30	0.0
AST (U/L)	>2.5 x ULN	2/82	2.4	0/30	0.0	2/84	2.4	0/30	0.0
	>5 x ULN	0/82	0.0	0/30	0.0	0/84	0.0	0/30	0.0
Direct serum bilirubin (mg/dL)	>1.5 x ULN	2/74	2.7	0/28	0.0	5/75	6.7	0/28	0.0
	>2.5 x ULN	0/74	0.0	0/28	0.0	1/75	1.3	0/28	0.0
Hematocrit (%)	<24	0/84	0.0	0/30	0.0	0/86	0.0	0/30	0.0
Hemoglobin (g/dL)	<8	0/84	0.0	0/30	0.0	1/86	1.2	0/30	0.0
Platelet count (cells/ $\mu$ L)	<75,000	0/84	0.0	0/30	0.0	0/86	0.0	0/30	0.0
	<50,000	0/84	0.0	0/30	0.0	0/86	0.0	0/30	0.0
Serum alkaline phosphatase (U/L)	>2.5 x ULN	5/82	6.1	0/30	0.0	7/84	8.3	0/30	0.0
	>5 x ULN	1/82	1.2	0/30	0.0	1/84	1.2	0/30	0.0
Serum creatinine (mg/dL)	>1.5 x ULN	0/83	0.0	0/30	0.0	0/85	0.0	0/30	0.0
	>3 x ULN	0/83	0.0	0/30	0.0	0/85	0.0	0/30	0.0
Total serum bilirubin (mg/dL)	>1.5 x ULN	0/82	0.0	0/30	0.0	2/84	2.4	0/30	0.0
	>2.5 x ULN	0/82	0.0	0/30	0.0	0/84	0.0	0/30	0.0

N = The total number of patients in treatment group.

n/m = Number of patients with CSLA/number of patients with laboratory test at baseline and postbaseline.

(Modified Applicant's Tables 43 and 44, July 3, 2001 submission, Volume I of I, pages 126 and 129)

### Rash

Rash occurred in 3 patients in the ertapenem group and no patients in the ceftriaxone group during study therapy or the 14-day follow-up period. Of the rashes, 2 occurred during parenteral therapy reported (of mild intensity in AN 0063 and moderate intensity in AN 0042) and were considered drug-related. The third patient (AN 0166) experienced a rash of mild intensity while off therapy that was considered to be definitely not drug related by the investigator. Therapy was not discontinued in either patient whose rash occurred during parenteral therapy.

***Medical Officer's Comment:** Based on the MO's review of the Applicant's data, 4 patients (ANs 0051, 0131, 0132, and 0167) in the ertapenem group developed an absolute neutrophil count  $<1.8 \text{ THS/mm}^3$  during the parenteral phase and 1 additional patient (AN 0124) in the ertapenem group developed an absolute neutrophil count  $<1.8 \text{ THS/mm}^3$  during the follow-up period. However, no patient developed an absolute neutrophil count  $<1000 \text{ THS/mm}^3$  during the parenteral study period or the entire study period, nor did any clinical adverse events occur in the patients that developed transient absolute neutrophil counts  $<1800 \text{ THS/mm}^3$ . Therefore, the MO does not believe that clinically significant neutropenia occurred in this study.*

*The degree of transaminase elevations was also generally mild and reversible in this study and did not suggest that clinical hepatic toxicity occurred in either treatment group.*

### 3.6 Reviewer's Comments/Conclusion of Study

In adult patients with lower respiratory tract infections (AECB or CAP), skin and skin structure infections (uncomplicated or complicated), and urinary tract infections (uncomplicated or complicated) treated with intramuscular ertapenem 1 gm per day, with an oral antibiotic switch option (Augmentin suggested) after clinical improvement, the following conclusions can be drawn:

1. Ertapenem 1 gm per day diluted in 1% lidocaine and administered intramuscularly for up to 7 days is generally well tolerated.
2. The adverse event profile of intramuscularly administered ertapenem 1 gm per day is similar to that of intramuscularly administered ceftriaxone 1 gm per day.
3. Regarding the efficacy of ertapenem 1 gm per day given intramuscularly compared to ceftriaxone 1 gm per day given intramuscularly, there was a trend for lower cure rates in the ertapenem group within each type of infection in the overall MITT analysis, and a trend for a lower cure rate in the ertapenem group with skin and skin structure infections in the microbiologic MITT analysis. However, this study was not designed or powered to demonstrate equivalence and no conclusions regarding the efficacy of intramuscular ertapenem can be made based on the efficacy data provided by this study.

30 page(s) of  
revised draft labeling  
has been redacted  
from this portion of  
the review.