



## Absorption

Ertapenem, reconstituted with 1% lidocaine HCl injection, USP (in saline without epinephrine), is almost completely absorbed following intramuscular (IM) administration at the recommended dose of 1 g. The mean bioavailability is approximately 90%. Following 1 g daily IM administration, mean peak plasma concentrations (C<sub>max</sub>) are achieved in approximately 2.3 hours (T<sub>max</sub>). Distribution

Ertapenem is highly bound to human plasma proteins, primarily albumin. In healthy young adults, the protein binding of ertapenem decreases as plasma concentrations increase, from approximately 95% bound at an approximate plasma concentration of <100 micrograms (mcg)/mL to approximately 85% bound at an approximate plasma concentration of 300 mcg/mL.

The apparent volume of distribution at steady state (V<sub>ss</sub>) of ertapenem in adults is approximately 0.12 liter/kg, approximately 0.2 liter/kg in pediatric patients 3 months to 12 years of age and approximately 0.16 liter/kg in pediatric patients 13 to 17 years of age.

The concentrations of ertapenem achieved in suction-induced skin blister fluid at each sampling point on the third day of 1 g once daily IV doses are presented in Table 10. The ratio of AUC<sub>0-24</sub> in skin blister fluid/AUC<sub>0-24</sub> in plasma is 0.61.

0.5 hr	1 hr	2 hr	4 hr	8 hr	12 hr	24 hr
7	12	17	24	24	21	8

## Metabolism

In healthy young adults, after infusion of 1 g IV radiolabeled ertapenem, the plasma radioactivity consists predominantly (94%) of ertapenem. The major metabolite of ertapenem is the inactive ring-opened derivative formed by hydrolysis of the beta-lactam ring.

Ertapenem is eliminated primarily by the kidneys. The mean plasma half-life in healthy young adults is approximately 4 hours and the plasma clearance is approximately 1.5 L/hour. The mean plasma half-life in pediatric patients 13 to 17 years of age is approximately 4 hours and approximately 2.5 hours in pediatric patients 3 months to 12 years of age.

Following the administration of 1 g IV radiolabeled ertapenem to healthy young adults, approximately 80% is recovered in urine and 10% in feces. Of the 80% recovered in urine, approximately 38% is excreted as unchanged drug and approximately 37% as the ring-opened metabolite.

In healthy young adults given a 1 g IV dose, the mean percentage of the administered dose excreted in urine was 17.4% during 0-2 hours postdose, 5.4% during 4-6 hours postdose, and 2.4% during 12-24 hours postdose.

## Special Populations

### Renal Impairment

Total and unbound fractions of ertapenem pharmacokinetics were investigated in 26 adult subjects (31 to 80 years of age) with varying degrees of renal impairment. Following a single 1 g IV dose of ertapenem, the unbound AUC increased 1.5-fold and 2.3-fold in subjects with mild renal impairment (CL<sub>CR</sub> 60-90 mL/min/1.73 m<sup>2</sup>) and moderate renal impairment (CL<sub>CR</sub> 31-59 mL/min/1.73 m<sup>2</sup>), respectively, compared with healthy young subjects (25 to 45 years of age). No dosage adjustment is necessary in patients with CL<sub>CR</sub> ≥31 mL/min/1.73 m<sup>2</sup>. The unbound AUC increased 4.4-fold and 76-fold in subjects with advanced renal impairment (CL<sub>CR</sub> 5-30 mL/min/1.73 m<sup>2</sup>) and end-stage renal disease (CL<sub>CR</sub> <10 mL/min/1.73 m<sup>2</sup>), respectively, compared with healthy young subjects. The effects of renal impairment on AUC of total drug were of smaller magnitude. The recommended dose of ertapenem in adult patients with CL<sub>CR</sub> ≥30 mL/min/1.73 m<sup>2</sup> is 0.5 grams every 24 hours. Following a single 1 g IV dose given immediately prior to a 4 hour hemodialysis session in 5 adult patients with end-stage renal disease, approximately 30% of the dose was recovered in the dialysate. Dose adjustments are recommended for patients with severe renal impairment and end-stage renal disease *[see Dosage and Administration (2.4)]*. There are no data in pediatric patients with renal impairment.

### Hepatic Impairment

The pharmacokinetics of ertapenem in patients with hepatic impairment have not been established. However, ertapenem does not appear to undergo hepatic metabolism based on *in vitro* studies and approximately 10% of an administered dose is recovered in the feces *[see Clinical Pharmacology (12.3) and Dosage and Administration (2.6)]*.

### Gender

The effect of gender on the pharmacokinetics of ertapenem was evaluated in healthy male (n=8) and healthy female (n=8) subjects. The differences observed could be attributed to body size when body weight was taken into consideration. No dose adjustment is recommended based on gender.

### Geriatric Patients

The impact of age on the pharmacokinetics of ertapenem was evaluated in healthy male (n=7) and healthy female (n=7) subjects ≥65 years of age. The total and unbound AUC increased 37% and 67%, respectively, in elderly adults relative to young adults. These changes were attributed to age-related changes in creatinine clearance. No dosage adjustment is necessary for elderly patients with normal (for their age) renal function.

### Pediatric Patients

Plasma concentrations of ertapenem are comparable in pediatric patients 13 to 17 years of age and adults following a 1 g once daily IV dose.

Following the 20 mg/kg dose (up to a maximum dose of 1 g), the pharmacokinetic parameter values in patients 13 to 17 years of age (N=6) were generally comparable to those in healthy young adults.

Plasma concentrations at the midpoint of the dosing interval following a single 15 mg/kg IV dose of ertapenem in patients 3 months to 12 years of age are comparable to plasma concentrations at the midpoint of the dosing interval following a 1 g once daily IV dose in adults *[see Clinical Pharmacology (12.3)]*. The plasma clearance (mL/min/kg) of ertapenem in patients 3 months to 12 years of age is approximately 2-fold higher as compared to that in adults. At the 15 mg/kg dose, the AUC value (doubled to model a twice daily dosing regimen, i.e., 30 mg/kg/day exposure) in patients 3 months to 12 years of age was comparable to the AUC value in healthy adults receiving a 1 g IV dose of ertapenem.

### Drug Interactions

When ertapenem is co-administered with probenecid (500 mg p.o. every 6 hours), probenecid competes for active tubular secretion and reduces the renal clearance of ertapenem. Based on total ertapenem concentrations, probenecid increased the AUC of ertapenem by 25%, and reduced the plasma and renal clearance of ertapenem by 20% and 35%, respectively. The half-life of ertapenem was increased from 4.0 to 4.8 hours.

*In vitro* studies in human liver microsomes indicate that ertapenem does not inhibit metabolism mediated by any of the following cytochrome p450 (CYP) isoforms: 1A2, 2C8, 2C19, 2D6, 2E1 and 3A4.

*In vitro* studies indicate that ertapenem does not inhibit P-glycoprotein-mediated transport of digoxin or vinblastine and that ertapenem is not a substrate for P-glycoprotein-mediated transport.

## 12.4 Microbiology

### Mechanism of Action

Ertapenem has *in vitro* activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria. The bactericidal activity of ertapenem results from the inhibition of cell wall synthesis and is mediated through ertapenem binding to penicillin binding proteins (PBPs). In *Escherichia coli*, it has strong affinity toward PBPs 1a, 1b, 2, 3, 4 and 5 with preference for PBPs 2 and 3.

### Resistance

Ertapenem is stable against hydrolysis by a variety of beta-lactamases, including penicillinases, and cephalosporinases and extended spectrum beta-lactamases. Ertapenem is hydrolyzed by metallo-beta-lactamases.

### Antimicrobial Activity

Ertapenem has been shown to be active against most isolates of the following microorganisms both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section:

#### Gram-positive bacteria:

*Staphylococcus aureus* (methicillin susceptible isolates only)  
*Streptococcus agalactiae*  
*Streptococcus pneumoniae* (penicillin susceptible isolates only)  
*Streptococcus pyogenes*

#### Gram-negative bacteria:

*Escherichia coli*  
*Haemophilus influenzae* (beta-lactamase negative isolates only)  
*Klebsiella pneumoniae*  
*Moraxella catarrhalis*  
*Proteus mirabilis*

## Anaerobic bacteria:

*Bacteroides fragilis*  
*Bacteroides distasonis*  
*Bacteroides ovatus*  
*Bacteroides thetaiotaomicron*  
*Bacteroides uniformis*  
*Clostridium clostridioforme*  
*Eubacterium lentum*  
*Peptostreptococcus species*  
*Porphyromonas asaccharolytica*  
*Prevotella bilinearis*

The following *in vitro* data are available, **but their clinical significance is unknown**. At least 90% of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for ertapenem. However, the efficacy of ertapenem in treating clinical infections due to these bacteria has **not been** established in adequate and well-controlled clinical trials:

#### Gram-positive bacteria:

*Staphylococcus epidermidis* (methicillin susceptible isolates only)  
*Streptococcus pneumoniae* (penicillin-intermediate isolates)

#### Gram-negative bacteria:

*Citrobacter freundii*  
*Citrobacter koseri*  
*Enterobacter aerogenes*  
*Enterobacter cloacae*  
*Haemophilus influenzae* (beta-lactamase positive isolates only)  
*Haemophilus parainfluenzae*  
*Klebsiella oxytoca* (excluding ESBL producing isolates)

*Morganella morganii*  
*Proteus vulgaris*  
*Providencia rettgeri*  
*Providencia stuartii*  
*Serratia marcescens*

## Anaerobic bacteria:

*Bacteroides vulgatus*  
*Clostridium perfringens*  
*Fusobacterium spp.*

## Susceptibility Testing

For specific information regarding susceptibility testing methods, interpretive criteria, and associated test methods and quality control standards recognized by FDA for ertapenem, please see: <https://www.fda.gov/STC>.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### Carcinogenesis and Mutagenesis

No long-term studies in animals have been performed to evaluate the carcinogenic potential of ertapenem.

Ertapenem was not genotoxic in *in vitro* or *in vivo* assays, including: an alkaline elution/rat hepatocyte assay, a chromosomal aberration assay in Chinese hamster ovary cells, a TK6 human lymphoblastoid cell mutagenesis assay and a mouse micronucleus assay.

#### Impairment of Fertility

In rats, intravenous dosages up to 700 mg/kg/day (approximately 1.2 times the human exposure at the recommended human dose of 1 g based on plasma AUC) did not impair fertility.

### 13.2 Animal Toxicology and/or Pharmacology

In repeat-dose studies in rats, treatment-related neutropenia occurred at every dose-level tested, including the lowest dose of 2 mg/kg (approximately 2% of the human dose on a body surface area basis).

Studies in rabbits and Rhesus monkeys were inconclusive with regard to the effect on neutrophil counts.

## 14 CLINICAL STUDIES

### 14.1 Adults

#### Complicated Intra-Abdominal Infections

Ertapenem was evaluated in adults for the treatment of complicated intra-abdominal infections in a randomized, double-blind, non-inferiority clinical trial. This trial compared ertapenem (1 g intravenously once a day) with piperacillin/tazobactam (3.375 g intravenously every 6 hours) for 5 to 14 days and enrolled 665 patients with localized complicated appendicitis, and any other complicated intra-abdominal infection including colonic, small intestinal, and biliary infections and generalized peritonitis. The combined clinical and microbiologic success rates in the microbiologically evaluable population at 4 to 6 weeks posttherapy (test-of-cure) were 83.6% (163/195) for ertapenem and 80.4% (152/189) for piperacillin/tazobactam.

#### Complicated Skin and Skin Structure Infections

Ertapenem was evaluated in adults for the treatment of complicated skin and skin structure infections in a randomized, double-blind, non-inferiority clinical trial. This trial compared ertapenem (1 g intravenously once a day) with piperacillin/tazobactam (3.375 g intravenously every 6 hours) for 7 to 14 days and enrolled 540 patients including patients with deep soft tissue abscess, posttraumatic wound infection and cellulitis with purulent drainage. The clinical success rates at 10 to 21 days posttherapy (test-of-cure) were 83.9% (141/168) for ertapenem and 85.3% (145/170) for piperacillin/tazobactam.

#### Diabetic Foot Infections

Ertapenem was evaluated in adults for the treatment of diabetic foot infections without concomitant osteomyelitis in a multicenter, randomized, double-blind, non-inferiority clinical trial. This trial compared ertapenem (1 g intravenously once a day) with piperacillin/tazobactam (3.375 g intravenously every 6 hours). Test-of-cure was defined as clinical response between treatment groups in the clinically evaluable population at the 10-day posttherapy follow-up visit. The trial included 295 patients randomized to ertapenem and 291 patients to piperacillin/tazobactam. Both regimens allowed the option to switch to oral amoxicillin/clavulanate for a total of 5 to 28 days of treatment (parenteral and oral). All patients were eligible to receive appropriate adjunctive treatment methods, such as debridement, as is typically required in the treatment of diabetic foot infections, and most patients received these treatments. Patients with suspected osteomyelitis could be enrolled if all the infected bone was removed within 2 days of initiation of study therapy, and preferably within the prestudy period. Investigators had the option to add open-label vancomycin if enterococci or methicillin-resistant *Staphylococcus aureus* (MRSA) were among the pathogens isolated or if patients had a history of MRSA infection and additional therapy was indicated in the opinion of the investigator. Two hundred and four (204) patients randomized to ertapenem and 202 patients randomized to piperacillin/tazobactam were clinically evaluable. The clinical success rates at 10 days posttherapy were 75.0% (153/204) for ertapenem and 70.8% (143/202) for piperacillin/tazobactam.

#### Community-Acquired Pneumonia

Ertapenem was evaluated in adults for the treatment of community acquired pneumonia in two randomized, double-blind, non-inferiority clinical trials. Both trials compared ertapenem (1 g parenterally once a day) with ceftriaxone (1 g parenterally once a day) and enrolled a total of 866 patients. Both regimens allowed the option to switch to oral amoxicillin/clavulanate for a total of 10 to 14 days of treatment (parenteral and oral). In the first trial the primary efficacy parameter was the clinical success rate in the clinically evaluable population and success rates were 92.3% (168/182) for ertapenem and 91.0% (183/201) for ceftriaxone at 7 to 14 days posttherapy (test-of-cure). In the second trial the primary efficacy parameter was the clinical success rate in the microbiologically evaluable population and success rates were 91% (91/100) for ertapenem and 91.8% (45/49) for ceftriaxone at 7 to 14 days posttherapy (test-of-cure).

#### Complicated Urinary Tract Infections Including Pyelonephritis

Ertapenem was evaluated in adults for the treatment of complicated urinary tract infections including pyelonephritis in two randomized, double-blind, non-inferiority clinical trials. Both trials compared ertapenem (1 g parenterally once a day) with ceftriaxone (1 g parenterally once a day) and enrolled a total of 850 patients. Both regimens allowed the option to switch to oral ciprofloxacin (500 mg twice daily) for a total of 10 to 14 days of treatment (parenteral and oral). The microbiological success rates (combined trials) at 5 to 9 days posttherapy (test-of-cure) were 89.5% (229/256) for ertapenem and 91.1% (204/224) for ceftriaxone.

#### Acute Pelvic Infections Including Endometriometritis, Septic Abortion and Post-Surgical Gynecological Infections

Ertapenem was evaluated in adults for the treatment of acute pelvic infections in a randomized, double-blind, non-inferiority clinical trial. This trial compared ertapenem (1 g intravenously once a day) with piperacillin/tazobactam (3.375 g intravenously every 6 hours) for 3 to 10 days and enrolled 412 patients including 350 patients with obstetric/postpartum infections and 45 patients with septic abortion. The clinical success rates in the clinically evaluable population at 2 to 4 weeks posttherapy (test-of-cure) were 93.9% (153/163) for ertapenem and 91.5% (140/153) for piperacillin/tazobactam.

## Prophylaxis of Surgical Site Infections Following Elective Colorectal Surgery

Ertapenem was evaluated in adults for prophylaxis of surgical site infection following elective colorectal surgery in a multicenter, randomized, double-blind, non-inferiority clinical trial. This trial compared a single intravenous dose of ertapenem (1 g) versus cefotetan (2 g) administered over 30 minutes, 1 hour before elective colorectal surgery. Test-of-prophylaxis was defined as no evidence of surgical site infection, post-operative anastomotic leak, or unexplained antibiotic use in the clinically evaluable population up to and including at the 4-week posttreatment follow-up visit. The trial included 500 patients randomized to ertapenem and 502 patients randomized to cefotetan. The modified intent-to-treat (MITT) population consisted of 451 ertapenem patients and 450 cefotetan patients and included all patients who were randomized, treated, and underwent elective colorectal surgery with adequate bowel preparation. The clinically evaluable population was a subset of the MITT population and consisted of patients who received a complete dose of study therapy no more than two hours prior to surgical incision and no more than six hours before surgical closure. Clinically evaluable patients had sufficient information to determine outcome at the 4-week follow-up assessment and had no confounding factors that interfered with the assessment of that outcome. Examples of confounding factors included prior or concomitant antibiotic violations, the need for a second surgical procedure during the study period, and identification of a distant site infection with concomitant antibiotic administration and no evidence of subsequent wound infection. Three-hundred forty-six (346) patients randomized to ertapenem and 339 patients randomized to cefotetan were clinically evaluable. The prophylactic success rates at 4 weeks posttreatment in the clinically evaluable population were 70.5% (244/346) for ertapenem and 57.2% (194/339) for cefotetan (difference 13.3%, [95% C.I.: 6.1, 20.4], p<0.001). Prophylaxis failure due to surgical site infections occurred in 18.2% (63/346) ertapenem patients and 31.0% (105/339) cefotetan patients. Post-operative anastomotic leak occurred in 2.9% (10/346) ertapenem patients and 4.1% (14/339) cefotetan patients. Unexplained antibiotic use occurred in 8.4% (29/346) ertapenem patients and 7.7% (26/339) cefotetan patients. Though patient numbers were small in some subgroups, in general, clinical response rates by age, gender, and race were consistent with the results found in the clinically evaluable population. In the MITT analysis, the prophylactic success rates at 4 weeks posttreatment were 68.8% (263/451) for ertapenem and 48.9% (220/450) for cefotetan (difference 9.4%, [95% C.I.: 2.9, 15.9], p=0.002). A statistically significant difference favoring ertapenem over cefotetan with respect to the primary endpoint has been observed at a significance level of 5% in this trial. A second adequate and well-controlled trial to confirm these findings has not been conducted; therefore, the clinical superiority of ertapenem over cefotetan has not been demonstrated.

### 14.2 Pediatric Patients

Ertapenem was evaluated in pediatric patients 3 months to 17 years of age in two randomized, multicenter clinical trials.

The first trial enrolled 404 patients and compared ertapenem (15 mg/kg intravenous IV) every 12 hours in patients 3 months to 12 years of age, and 1 g IV once a day in patients 13 to 17 years of age) to ceftioxone (50 mg/kg/day IV in two divided doses in patients 3 months to 12 years of age and 50 mg/kg/day IV as a single daily dose in patients 13 to 17 years of age) for the treatment of complicated urinary tract infection (UTI), skin and soft tissue infection (SSTI), or community-acquired pneumonia (CAP). Both regimens allowed the option to switch to oral amoxicillin/clavulanate for a total of up to 14 days of treatment (parenteral and oral). The microbiological success rates in the evaluable per protocol (EPP) analysis in patients treated for UTI were 87.0% (40/46) for ertapenem and 90.0% (18/20) for ceftioxone. The clinical success rates in the EPP analysis in patients treated for SSTI were 85.6% (64/67) for ertapenem and 100% (26/26) for ceftioxone, and in patients treated for CAP were 96.1% (74/77) for ertapenem and 96.4% (27/28) for ceftioxone.

The second trial enrolled 112 patients and compared ertapenem (15 mg/kg IV every 12 hours in patients 3 months to 12 years of age, and 1 g IV once a day in patients 13 to 17 years of age) to ticarcillin/clavulanate (50 mg/kg for patients <60 kg or 3.0 g for patients ≥60 kg, 4 or 6 times a day) up to 14 days for the treatment of complicated intra-abdominal infections (IAI) and acute pelvic infections (API). In patients treated for IAI (primarily patients with perforated or complicated appendicitis), the clinical success rates were 83.7% (36/43) for ertapenem and 83.6% (7/11) for ticarcillin/clavulanate in the EPP analysis. In patients treated for API (post-operative or spontaneous obstetrical endometriometritis, or septic abortion), the clinical success rates were 100% (23/23) for ertapenem and 100% (4/4) for ticarcillin/clavulanate in the EPP analysis.

### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 16.1 How Supplied

Ertapenem for injection is supplied as a sterile lyophilized powder in single dose vials containing ertapenem for intravenous infusion or for intramuscular injection as follows:  
NDC 42023-222-110 in trays of 10 vials.

#### 16.2 Storage and Handling

##### Before reconstitution

Do not store lyophilized powder above 25°C (77°F).

##### Reconstituted and infusion solutions

The reconstituted solution, immediately diluted in 0.9% Sodium Chloride Injection *[see Dosage and Administration (2.7)]*, may be stored at room temperature (25°C) and used within 6 hours or stored for 24 hours under refrigeration (5°C) and used within 4 hours after removal from refrigeration. Solutions of ertapenem for injection should not be frozen.

### 17 PATIENT COUNSELING INFORMATION

#### 17.1 Instructions for Patients

Patients should be advised that allergic reactions, including serious allergic reactions could occur and that serious reactions may require immediate treatment. Advise patients to report any previous hypersensitivity reactions to ertapenem for injection, other beta-lactams or other allergens.

Patients should be counseled to inform their physician if they are taking valproic acid or divalproex sodium. Valproic acid concentrations in the blood may drop below the therapeutic range upon co-administration with ertapenem for injection. If treatment with ertapenem for injection is necessary and continued, alternative or supplemental anti-convulsant medication to prevent and/or treat seizures may be needed.

Patients should be counseled that antibacterial drugs including ertapenem for injection should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When ertapenem for injection is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ertapenem for injection or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

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