CLASSES

Carbapenems

DEA CLASS

Rx

DESCRIPTION

IV or IM broad-spectrum carbapenem antibiotic stable against beta-lactamases
Used to treat UTI, skin, pelvic, intraabdominal infections and community-acquired pneumonia; used for colorectal surgical prophylaxis
Once-daily dosing may be advantageous, but no P. aeruginosa activity

COMMON BRAND NAMES

Invanz

HOW SUPPLIED

Ertapenem/Invanz Intramuscular Inj Pwd F/Sol: 1g
Ertapenem/Invanz Intravenous Inj Pwd F/Sol: 1g

DOSAGE & INDICATIONS

For the treatment of community-acquired pneumonia, including cases with concurrent bacteremia.

Intravenous or Intramuscular dosage

Adults

1 g IV or IM once daily for 10 to 14 days. Consider transitioning to an appropriate oral therapy after at least 3 days of parenteral therapy, once clinical improvement has been demonstrated.[30920]

Adolescents

1 g IV or IM once daily for 10 to 14 days. Consider transitioning to an appropriate oral therapy after at least 3 days of parenteral therapy, once clinical improvement has been demonstrated.

Infants and Children 3 months to 12 years

15 mg/kg/dose IV or IM twice daily (Max: 1 g/day) for 10 to 14 days. Consider transitioning to an appropriate oral therapy after at least 3 days of parenteral therapy, once clinical improvement has been demonstrated.

Infants 1 to 2 months†

15 mg/kg/dose IV or IM twice daily.

For the treatment of complicated intraabdominal infections.

Intravenous or Intramuscular dosage

Adults

1 g IV or IM once daily for 5 to 14 days. Guidelines recommend ertapenem for 4 to 7 days for mild-to-moderate community-acquired infections, including perforated or abscessed appendicitis.

Adolescents

1 g IV or IM once daily for 5 to 14 days. Guidelines recommend ertapenem for 4 to 7 days for community-acquired infections.

Infants and Children 3 months to 12 years

15 mg/kg/dose IV or IM twice daily (Max: 1 g/day) for 5 to 14 days. Guidelines recommend ertapenem for 4 to 7 days for community-acquired infections.

For the treatment of complicated skin and skin structure infections, including diabetic foot infections (diabetic foot ulcer).

Intravenous or Intramuscular dosage

Adults

1 g IV or IM once daily for 7 to 14 days. Guidelines recommend ertapenem for mixed necrotizing infections. Surgical intervention is the primary therapeutic intervention. Antibiotic therapy should be administered until further debridement is not necessary, the patient has improved clinically, and fever has been absent for 48 to 72 hours. Ertapenem is also recommended for incisional surgical site infections of the intestinal or genitourinary tract. In setting of a cat or dog bite, preemptive antimicrobial therapy is recommended for 3 to 5 days for patients who are immunocompromised, asplenic, have advanced liver disease, have edema of the bite area, have moderate to severe injuries, particularly of the hand or face, or have penetrating injuries to the periosteum or joint capsule. Ertapenem is suggested as an option for moderate to severe diabetic wound infections. Most patients with skin and soft tissue infections do well with 1 to 2 weeks of therapy.

Adolescents

1 g IV or IM once daily for 7 to 14 days. Guidelines recommend ertapenem for mixed necrotizing infections. Surgical intervention is the primary therapeutic intervention. Antibiotic therapy should be administered until further debridement is not necessary, the patient has improved clinically, and fever has been absent for 48 to 72 hours.

Infants and Children 3 months to 12 years

15 mg/kg/dose IV or IM twice daily (Max: 1 g/day) for 7 to 14 days. Guidelines recommend ertapenem for mixed necrotizing infections. Surgical intervention is the primary therapeutic intervention. Antibiotic therapy should be administered until further debridement is not necessary, the patient has improved clinically, and fever has been absent for 48 to 72 hours.

For the treatment of complicated urinary tract infection (UTI) (pyelonephritis), including cases with concurrent bacteremia.

Intravenous or Intramuscular dosage

Adults

1 g IV or IM once daily for 10 to 14 days. Consider transitioning to an appropriate oral therapy after at least 3 days of parenteral therapy, once clinical improvement has been demonstrated.

Adolescents

1 g IV or IM once daily for 10 to 14 days. Consider transitioning to an appropriate oral therapy after at least 3 days of parenteral therapy, once clinical improvement has been demonstrated.

Infants and Children 3 months to 12 years

15 mg/kg/dose IV or IM twice daily (Max: 1 g/day) for 10 to 14 days. Consider transitioning to an appropriate oral therapy after at least 3 days of parenteral therapy, once clinical improvement has been demonstrated.

For the treatment of acute pelvic infections, including postpartum endomyometritis, septic abortion, and postsurgical gynecologic infections.

Intravenous or Intramuscular dosage

Adults

1 g IV or IM once daily for 3 to 10 days.

Adolescents

1 g IV or IM once daily for 3 to 10 days.

Infants and Children 3 months to 12 years

15 mg/kg/dose IV or IM twice daily (Max: 1 g/day) for 3 to 10 days.

For surgical infection prophylaxis for elective colorectal surgery.

Intravenous dosage

Adults

1 g IV as a single dose within 60 minutes prior to surgical incision. No intraoperative redosing and duration of prophylaxis less than 24 hours are suggested by clinical practice guidelines.

Infants†, Children†, and Adolescents†

15 mg/kg/dose IV as a single dose (Max: 1 g/dose) within 60 minutes prior to surgical incision. No intraoperative redosing and duration of prophylaxis less than 24 hours are suggested by clinical practice guidelines.

MAXIMUM DOSAGE

Adults

1 gram/day IV/IM.

Elderly

1 gram/day IV/IM.

Adolescents

1 gram/day IV/IM.

Children

30 mg/kg/day or 1 gram/day IV/IM.

Infants

>= 3 months: 30 mg/kg/day or 1 gram/day IV/IM.
< 3 months: Safety and efficacy have not been established.

DOSING CONSIDERATIONS

Hepatic Impairment

No dosage guidelines are available; it appears no dosage adjustment is needed.

Renal Impairment

No data are available regarding use in pediatric patients with renal impairment.
FDA-approved dosage in renal failure for adults:
CrCl > 30 mL/min: No dosage adjustment needed.
CrCl <= 30 mL/min: 500 mg IV or IM once a day.

Other dosage adjustment guidelines for adults:
CrCl > 10 mL/min: No dosage adjustment needed.
CrCl < 10 mL/min: 500 mg IV or IM once a day.

Intermittent hemodialysis
Give recommended dose of 500 mg IV or IM once a day. If ertapenem is given 6 hours or more prior to hemodialysis, no supplemental dosing is required. If ertapenem is given within 6 hours of hemodialysis, a supplementary dose of 150 mg is recommended following the hemodialysis session.

Peritoneal dialysis
Administer 500 mg IV or IM once a day.

Continuous renal replacement therapy (CRRT)
No dosage adjustment is necessary unless anticipated clearance is < 30 mL/min.

ADMINISTRATION

Injectable Administration

Visually inspect parenteral products for particulate matter and discoloration prior to administration whenever solution and container permit. Ertapenem solution is colorless to pale yellow; variations of color within this range do not affect the potency of the product.

Intravenous Administration

Reconstitution:
Reconstitute each 1 g vial with 10 mL of 0.9% Sodium Chloride Injection, Sterile Water for Injection, or Bacteriostatic Water for Injection using a syringe equipped with a 21-gauge or smaller diameter needle. Use with a needless IV system is not recommended.
Shake well to dissolve.
Further dilution is necessary for IV infusion.
Storage: Immediately transfer the appropriate amount of the reconstituted vial to diluent.[30920]

Dilution:
For 1 g dose: Dilute the entire contents of the reconstituted vial in 50 mL of 0.9% Sodium Chloride Injection.
For less than 1 g dose: Dilute the appropriate volume of the reconstituted solution (based on body weight) in 0.9% Sodium Chloride Injection to a concentration of 20 mg/mL or less.
Storage: Use within 6 hours if stored at room temperature (25 degrees C). The diluted solution may be refrigerated for up to 24 hours (5 degrees C) and used within 4 hours after removal from refrigeration. Do not freeze.[30920]

Intermittent IV infusion:
Complete the infusion within 6 hours of reconstitution.
Infuse IV over 30 minutes.
Do not co-infuse with other medications.[30920]

Intramuscular Administration

Reconstitution:
Reconstitute the 1 g vial with 3.2 mL of 1% lidocaine injection (without epinephrine). Agitate well to form a solution.
Storage: Use within 1 hour after preparation.

Intramuscular injection:
The IM reconstituted formulation is not for IV use.
May consider IM administration as an alternative to IV administration in the treatment of infections where IM therapy is appropriate; however, only administer via IM injection for 7 days.
Immediately withdraw the appropriate dose and inject deeply into a large muscle (i.e., upper outer quadrant of the gluteus maximus or lateral part of the thigh).
Storage: Use within 1 hour after preparation.

STORAGE

Invanz:
- Discard product if it contains particulate matter, is cloudy, or discolored
- Store reconstituted product in accordance with package insert instructions
- Store unreconstituted product at or below 77 degrees F

CONTRAINDICATIONS / PRECAUTIONS

Viral infection

This drug is not an effective treatment for a viral infection (e.g., common cold). Prescribing ertapenem in the absence of a proven or strongly suspected bacterial infection or for a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. Patients should be told to complete the full course of treatment, even if they feel better earlier.

Amide local anesthetic hypersensitivity

Lidocaine is the diluent for IM administration of ertapenem. IM use is contraindicated in patients with an amide local anesthetic hypersensitivity.

Carbapenem hypersensitivity, cephalosporin hypersensitivity, penicillin hypersensitivity

Ertapenem is contraindicated in any patient who has exhibited hypersensitivity to ertapenem, other drugs in the same class (e.g., carbapenem hypersensitivity) or in patients who have demonstrated anaphylactic reactions to beta-lactams. Prior to initiating ertapenem therapy, the patient should be carefully questioned about previous penicillin hypersensitivity, cephalosporin hypersensitivity, allergic reactions to other beta-lactams (e.g., aztreonam) and other allergens. Patients who have experienced anaphylactic reactions to penicillins or cephalosporins should not receive ertapenem. Ertapenem is structurally similar to the penicillins and cephalosporins and these patients may be more susceptible to hypersensitivity reactions. If an allergic reaction occurs, discontinue the drug and initiate appropriate emergency treatment with epinephrine, oxygen, IV steroids, intubation or other therapy as indicated.

Dialysis, renal failure, renal impairment

Patients with renal impairment or renal failure (CrCl <= 30 mL/min) will require a dosage adjustment of ertapenem. A supplemental dose may or may not be required following dialysis.

Brain tumor, myoclonic seizures, seizures

During clinical studies, seizures occurred in 0.5% of patients receiving 1 gram a day and during a 14-day follow-up. Patients at greater risk for seizures may include: patients with CNS disorders (brain tumor or brain lesions; history of seizure disorders) and/or patients with compromised renal function. Anticonvulsive therapy should be continued in patients with a known seizure disorder. If focal tremor or myoclonic seizures occur, patients should be evaluated neurologically. Anticonvulsant therapy should be initiated if indicated and the dose of ertapenem should be re-evaluated based on the patient's renal function.

Colitis, diarrhea, GI disease, inflammatory bowel disease, pseudomembranous colitis, ulcerative colitis

Almost all antibacterial agents have been associated with pseudomembranous colitis (antibiotic-associated colitis) which may range in severity from mild to life-threatening. In the colon, overgrowth of Clostridia may exist when normal flora is altered subsequent to antibacterial administration. The toxin produced by Clostridium difficile is a primary cause of pseudomembranous colitis. It is known that systemic use of antibiotics predisposes patients to development of pseudomembranous colitis. Consideration should be given to the diagnosis of pseudomembranous colitis in patients

presenting with diarrhea following antibacterial administration. Ertapenem should be prescribed with caution to patients with inflammatory bowel disease such as ulcerative colitis or other GI disease. If diarrhea develops during therapy, the drug should be discontinued. Following diagnosis of pseudomembranous colitis, therapeutic measures should be instituted. In milder cases, the colitis may respond to discontinuation of the offending agent. In moderate to severe cases, fluids and electrolytes, protein supplementation, and treatment with an antibacterial effective against Clostridium difficile may be warranted. Products inhibiting peristalsis are contraindicated in this clinical situation. Practitioners should be aware that antibiotic-associated colitis has been observed to occur over two months or more following discontinuation of systemic antibiotic therapy; a careful medical history should be taken.

Infants

Ertapenem has not been studied for safety and efficacy in infants less than 3 months of age; the manufacturer does not recommend use of this product in patients < 3 months old.

Pregnancy

Available data from a small number of postmarketing cases with ertapenem use in pregnancy are insufficient to inform any drug-associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal studies evaluating doses 1.2 and 3 times the recommended human dose of 1 g, there was no evidence of fetal developmental toxicity; however, slight decreases in fetal weights and numbers of ossified sacrocaudal vertebrae were observed.

Breast-feeding

Ertapenem is excreted in human breast milk. The concentration in breast milk 24 hours after a 1 g dose ranged from less than 0.13 mcg/mL (lower limit of quantitation) to 0.38 mcg/mL in 5 lactating women. By day 5 after discontinuation, the concentration in breast milk was undetectable. There are no data on the effects of ertapenem on the breast-fed infant or on milk production. In general, unless the infant is allergic to ertapenem, breast-feeding is likely safe during maternal carbapenem therapy; observe the infant for potential effects. Consider the benefits of breast-feeding along with the mother's clinical need for ertapenem and any potential adverse effects on the breast-fed infant from ertapenem or the underlying maternal condition.

Geriatric

Clinical trial data and other reported clinical experience has not identified differences in responses between the elderly and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out. Ertapenem is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. The federal Omnibus Budget Reconciliation Act (OBRA) regulates medication use in residents (e.g., geriatric adults) of long-term care facilities (LTCFs). According to OBRA, use of antibiotics should be limited to confirmed or suspected bacterial infections. Antibiotics are non-selective and may result in the eradication of beneficial microorganisms while promoting the emergence of undesired ones, causing secondary infections such as oral thrush, colitis, or vaginitis. Any antibiotic may cause diarrhea, nausea, vomiting, anorexia, and hypersensitivity reactions.

ADVERSE REACTIONS

Severe

GI obstruction / Delayed / 2.1-2.1
seizures / Delayed / 0.5-0.5
ileus / Delayed / 0.1
GI bleeding / Delayed / 0.1
pyloric stenosis / Delayed / 0.1
pancreatitis / Delayed / 0.1
atrial fibrillation / Early / 0.1
cardiac arrest / Early / 0.1
asystole / Rapid / 0.1
bradycardia / Rapid / 0.1
heart failure / Delayed / 0.1
ventricular tachycardia / Early / 0.1
stroke / Early / 0.5
pleural effusion / Delayed / 0.1
pulmonary embolism / Delayed / 0.5
oliguria / Early / 0.1
azotemia / Delayed / 0.1
anuria / Delayed / 0.1
angioedema / Rapid / 0.1
wound dehiscence / Delayed / 0.5
hyperkalemia / Delayed / 0.1
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) / Delayed / Incidence not known
acute generalized exanthematous pustulosis (AGEP) / Delayed / Incidence not known
anaphylactoid reactions / Rapid / Incidence not known

Moderate

elevated hepatic enzymes / Delayed / 0.6-8.8
anemia / Delayed / 5.7-5.7
confusion / Early / 3.3-5.1
constipation / Delayed / 2.3-4.0
edema / Delayed / 2.9-3.4
vaginitis / Delayed / 1.4-3.3
dyspnea / Early / 1.0-2.6
hypotension / Rapid / 1.0-2.0
erythema / Early / 0.1
phlebitis / Rapid / 0.1
jaundice / Delayed / 0.1
hyperbilirubinemia / Delayed / 0.1
cholelithiasis / Delayed / 0.1
esophagitis / Delayed / 0.1
dysphagia / Delayed / 0.1
hemorrhoids / Delayed / 0.1
stomatitis / Delayed / 0.1
gastritis / Delayed / 0.1
oral ulceration / Delayed / 0.1
hypertension / Early / 0.1
sinus tachycardia / Rapid / 0.1
hematoma / Early / 0.1
chest pain (unspecified) / Early / 0.1
depression / Delayed / 0.1
hemoptysis / Delayed / 0.1
wheezing / Rapid / 0.5
dysuria / Early / 0.5

urinary retention / Early / 0.1
hematuria / Delayed / 0.1
candidiasis / Delayed / 0.1
pseudomembranous colitis / Delayed / 0.1
bleeding / Early / 0.5
flank pain / Delayed / 0.1
gout / Delayed / 0.1
hyperglycemia / Delayed / 0.1
hypokalemia / Delayed / 0.1
hypernatremia / Delayed / 0.1
delirium / Early / Incidence not known
hallucinations / Early / Incidence not known
dyskinesia / Delayed / Incidence not known
myoclonia / Delayed / Incidence not known
superinfection / Delayed / Incidence not known

Mild

diarrhea / Early / 5.5-11.7
vomiting / Early / 2.1-10.2
nausea / Early / 0.6-8.5
injection site reaction / Rapid / 0.2-7.1
headache / Early / 2.2-6.8
infection / Delayed / 0.6-6.5
agitation / Early / 3.3-5.1
drowsiness / Early / 0.6-5.1
fever / Early / 2.3-5.0
abdominal pain / Early / 0.6-4.7
cough / Delayed / 0.2-4.4
insomnia / Early / 0.6-3.2
rash / Early / 2.3-2.9
dizziness / Early / 0.6-2.1
pruritus / Rapid / 0.6-2.0
hyperhidrosis / Delayed / 0.1
flushing / Rapid / 0.1
urticaria / Rapid / 0.1
anorexia / Delayed / 0.1
flatulence / Early / 0.1
weight loss / Delayed / 0.1
dyspepsia / Early / 0.1
dysgeusia / Early / 0.1
xerostomia / Early / 0.5
vertigo / Early / 0.1
asthenia / Delayed / 0.1
paresthesias / Delayed / 0.1
hypoesthesia / Delayed / 0.1
fatigue / Early / 0.1
tremor / Early / 0.1
syncope / Early / 0.1
anxiety / Delayed / 0.1
hiccups / Early / 0.1
rhinitis / Early / 0.5
pharyngitis / Delayed / 0.1
rhinorrhea / Early / 0.5
epistaxis / Delayed / 0.1
increased urinary frequency / Early / 0.5
malaise / Early / 0.1
hypothermia / Delayed / 0.5
chills / Rapid / 0.1
arthralgia / Delayed / 0.5
tooth discoloration / Delayed / Incidence not known

DRUG INTERACTIONS

Colchicine; Probenecid: (Minor) Probenecid inhibits the renal excretion of ertapenem by competing with them for active tubular secretion. In some instances, this effect is used therapeutically to increase availability of the antimicrobial agent. However, the elimination half-life of ertapenem is increased only from 4 to 4.8 hours. Concurrent administration of ertapenem with probenecid is not recommended.
Oral Contraceptives: (Moderate) It would be prudent to recommend alternative or additional contraception when oral contraceptives (OCs) are used in conjunction with antibiotics. It was previously thought that antibiotics may decrease the effectiveness of OCs containing estrogens due to stimulation of metabolism or a reduction in enterohepatic circulation via changes in GI flora. One retrospective study reviewed the literature to determine the effects of oral antibiotics on the pharmacokinetics of contraceptive estrogens and progestins, and also examined clinical studies in which the incidence of pregnancy with OCs and antibiotics was reported. It was concluded that the antibiotics ampicillin, ciprofloxacin, clarithromycin, doxycycline, metronidazole, ofloxacin, roxithromycin, temafloxacin, and tetracycline did not alter plasma concentrations of OCs. Antituberculous drugs (e.g., rifampin) were the only agents associated with OC failure and pregnancy. Based on the study results, these authors recommended that back-up contraception may not be necessary if OCs are used reliably during oral antibiotic use. Another review concurred with these data, but noted that individual patients have been identified who experienced significant decreases in plasma concentrations of combined OC components and who appeared to ovulate; the agents most often associated with these changes were rifampin, tetracyclines, and penicillin derivatives. These authors concluded that because females most at risk for OC failure or noncompliance may not be easily identified and the true incidence of such events may be under-reported, and given the serious consequence of unwanted pregnancy, that recommending an additional method of contraception during short-term antibiotic use may be justified. During long-term antibiotic administration, the risk for drug interaction with OCs is less clear, but alternative or additional contraception may be advisable in selected circumstances. Data regarding progestin-only contraceptives or for newer combined contraceptive deliveries (e.g., patches, rings) are not available.
Probenecid: (Minor) Probenecid inhibits the renal excretion of ertapenem by competing with them for active tubular secretion. In some instances, this effect is used therapeutically to increase availability of the antimicrobial agent. However, the elimination half-life of ertapenem is increased only from 4 to 4.8 hours. Concurrent administration of ertapenem with probenecid is not recommended.
Sodium picosulfate; Magnesium oxide; Anhydrous citric acid: (Major) Prior or concomitant use of antibiotics with sodium picosulfate; magnesium oxide; anhydrous citric acid may reduce efficacy of the bowel preparation as conversion of sodium picosulfate to its active metabolite bis-(p-hydroxy-phenyl)-pyridyl-2-methane (BHPM) is mediated by colonic bacteria. If possible, avoid coadministration. Certain antibiotics (i.e., tetracyclines and quinolones) may chelate with the magnesium in sodium picosulfate; magnesium oxide; anhydrous citric acid solution. Therefore, these antibiotics should be taken at least 2 hours before and not less than 6 hours after the administration of sodium picosulfate; magnesium oxide; anhydrous citric acid solution.
Valproic Acid, Divalproex Sodium: (Major) Avoid concomitant carbapenem and valproic acid use. Consider alternative antibacterial therapies other than carbapenems to treat infections in patients whose seizures are well controlled with valproic acid or divalproex sodium. If coadministered, monitor valproic acid concentrations. Coadministration of carbapenems with valproic acid or divalproex sodium may reduce the serum concentration of valproic acid potentially increasing the risk of breakthrough seizures. Carbapenems may inhibit the hydrolysis of valproic acid's glucuronide metabolite (VPA-g) back to valproic acid, thus decreasing valproic acid serum concentrations.

Warfarin: (Moderate) The concomitant use of warfarin with many classes of antibiotics, including carbapenems, may result in an increased INR thereby potentiating the risk for bleeding. Inhibition of vitamin K synthesis due to alterations in the intestinal flora may be a mechanism; however, concurrent infection is also a potential risk factor for elevated INR. Monitor patients for signs and symptoms of bleeding. Additionally, increased monitoring of the INR, especially during initiation and upon discontinuation of the antibiotic, may be necessary.

PREGNANCY AND LACTATION

Pregnancy

Available data from a small number of postmarketing cases with ertapenem use in pregnancy are insufficient to inform any drug-associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal studies evaluating doses 1.2 and 3 times the recommended human dose of 1 g, there was no evidence of fetal developmental toxicity; however, slight decreases in fetal weights and numbers of ossified sacrocaudal vertebrae were observed.

Ertapenem is excreted in human breast milk. The concentration in breast milk 24 hours after a 1 g dose ranged from less than 0.13 mcg/mL (lower limit of quantitation) to 0.38 mcg/mL in 5 lactating women. By day 5 after discontinuation, the concentration in breast milk was undetectable. There are no data on the effects of ertapenem on the breast-fed infant or on milk production. In general, unless the infant is allergic to ertapenem, breast-feeding is likely safe during maternal carbapenem therapy; observe the infant for potential effects. Consider the benefits of breast-feeding along with the mother's clinical need for ertapenem and any potential adverse effects on the breast-fed infant from ertapenem or the underlying maternal condition.

MECHANISM OF ACTION

Ertapenem exhibits bactericidal activity due inhibition of cell wall synthesis mediated via binding to penicillin binding proteins (PBPs). It inhibits the third and final stage of bacterial cell wall synthesis by preferentially binding to specific penicillin-binding proteins (PBPs) that are located inside the bacterial cell wall. PBPs are responsible for several steps in the synthesis of the cell wall and are found in quantities of several hundred to several thousand molecules per bacterial cell. PBPs vary among different bacterial species. In Escherichia coli ertapenem has shown strong affinity towards PBPs 1a, 1b, 2, 3, 4 and 5 with preference for PBPs 2 and 3. PBP-1 is responsible for formation of the cell wall; PBP-2 is responsible for maintaining the rod-like shape; and PBP-3 is responsible for bacterial septum formation. Ertapenem is stable against hydrolysis by a variety of beta-lactamases, including penicillinases, cephalosporinases and extended-spectrum beta-lactamases. Like meropenem, but unlike imipenem, it has a 1-beta-methyl substituent and does not require protection with an inhibitor of human renal dihydropeptidase I.[26787] [30920] [50330]

Beta-lactams, including ertapenem, exhibit concentration-independent or time-dependent killing. In vitro and in vivo animal studies have demonstrated that the major pharmacodynamic parameter that determines efficacy for beta-lactams is the amount of time free (non-protein bound) drug concentrations exceed the minimum inhibitory concentration (MIC) of the organism (free T above the MIC).[34145] [34143] [35436] [35437] [35438] [35439] This microbiological killing pattern is due to the mechanism of action, which is acylation of PBPs. There is a maximum proportion of PBPs that can be acylated; therefore, once maximum acylation has occurred, killing rates cannot increase.[35439] Free beta-lactam concentrations do not have to remain above the MIC for the entire dosing interval. The percentage of time required for both bacteriostatic and maximal bactericidal activity is different for the various classes of beta-lactams. Carbapenems require free drug concentrations to exceed the MIC for 20% of the dosing interval for bacteriostatic activity and 40% of the dosing interval for maximal bactericidal activity.[35436] [35437] [35438] Carbapenems also are reported to have a post-antibiotic effect (PAE). PAE is defined as the suppression of bacterial growth that continues after the antibiotic concentration falls below the bacterial MIC. Ertapenem has a short PAE of 1.4 to 2.6 hours against gram positive strains only.[26788] [35441]
The susceptibility interpretive criteria for ertapenem are delineated by pathogen. The MICs are defined for Enterobacteriaceae as susceptible at 0.5 mcg/mL or less, intermediate at 1 mcg/mL, and resistant at 2 mcg/mL or more. The MICs are defined for Streptococcus pneumoniae as susceptible at 1 mcg/mL or less, intermediate at 2 mcg/mL, and resistant at 4 mcg/mL or more. The MICs are defined for Staphylococcus sp. as susceptible at 2 mcg/mL or less, intermediate at 4 mcg/mL, and resistant at 8 mcg/mL or more. The MICs are defined for beta-hemolytic group Streptoccoccus sp. and Viridans group Streptococcus sp. as susceptible at 1 mcg/mL or less. The MICs are defined for Haemophilus influenzae and Haemophilus parainfluenzae as susceptible at 0.5 mcg/mL or less. The MICs are defined for anaerobes as susceptible at 4 mcg/mL or less, intermediate at 8 mcg/mL, and resistant at 16 mcg/mL or more.[63320] [63321]
There are 4 general mechanisms of carbapenem resistance including decreased permeability of the outer membrane of gram-negative organisms due to decreased porin channel production, decreased affinity for the target PBPs, over-expression of efflux pumps, and enzymatic degradation. [28347] Generally, carbapenems show stability to the majority of beta-lactamases, including AmpC beta-lactamases and extended-spectrum beta-lactamases (ESBLs). However, specific intrinsic or acquired beta-lactamases, generally called carbapenemases, can hydrolyze the carbapenems. These include some class A enzymes, several class D (OXA) enzymes, and the class B metallo-beta-lactamases.[28347] [35440] [35441] A deficiency in the outer membrane porin protein (Opr) D2 is associated with decreased carbapenem susceptibility in gram-negative bacteria. However, it is theorized that a combination of resistance mechanisms is required for significant carbapenem resistance. Theoretically, efflux activity plus loss of membrane permeability is less likely to happen in vivo than AmpC beta-lactamase expression and loss of membrane permeability. [35440] [35441]

PHARMACOKINETICS

Ertapenem is administered via intravenous (IV) or intramuscular (IM) routes. It exhibits non-linear pharmacokinetics due to a high level of concentration-dependent plasma protein binding to albumin. Protein binding averages 95%; however, protein binding is not deleterious to the in-vivo efficacy against organisms for which the MICs are low. Ertapenem distributes into human breast milk and crosses the rat placental barrier. Activity is maintained by the parent drug until the beta-lactam ring is hydrolyzed resulting in an inactive metabolite. Ertapenem is not a substrate for P-glycoprotein mediated transport. It is eliminated via the kidney with a prolonged half-life of roughly 4.5 hours due to extensive protein binding. Approximately 80% is recovered in the urine, roughly 38% as unchanged drug and 37% as the inactive metabolite; 10% is recovered in the feces.

Affected cytochrome P450 isoenzymes: none
In vitro studies have shown that ertapenem does not inhibit metabolism mediated by cytochrome P450 isoenzymes 1A2, 2C9, 2C19, 2D6, 2E1, and 3A4. In vitro studies have also shown that it does not inhibit p-glycoprotein-mediated transport of digoxin or vinblastine.

Intravenous Route

Accumulation of ertapenem does not occur following multiple IV doses in healthy adults.

Intramuscular Route

Absorption of ertapenem is almost complete following IM administration with mean bioavailability of 90%. Peak plasma concentrations following a 1 g dose are achieved in roughly 2.3 hours. Accumulation does not occur following multiple IM doses in healthy adults.