S-SG-MK0826-IV-IM-102021

PRODUCT CIRCULAR

INVANZ®
(Ertapenem for Injection)

I. THERAPEUTIC CLASS

INVANZ (Ertapenem for Injection) is a sterile, synthetic, long-acting, parenteral, 1-β methyl-carbapenem that is structurally related to beta-lactam antibiotics, such as penicillins and cephalosporins, with activity against a wide range of gram-positive and gram-negative aerobic and anaerobic bacteria.

II. MICROBIOLOGY

Ertapenem has *in vitro* activity against a wide range of 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. Ertapenem has significant stability to hydrolysis by most classes of beta-lactamases, including penicillinases, and cephalosporinases and extended spectrum beta-lactamases, but not metallo-beta-lactamases.

INVANZ has been shown to be active against most strains of the following microorganisms *in vitro* and in clinical infections (see INDICATIONS):

AEROBIC AND FACULTATIVE GRAM-POSITIVE MICROORGANISMS:
Staphylococcus aureus (including penicillinase-producing strains)
Streptococcus agalactiae
Streptococcus pneumoniae (penicillin susceptible isolates only)
Streptococcus pyogenes
Note: Methicillin-resistant staphylococci and *Enterococcus spp* are resistant to INVANZ.

AEROBIC AND FACULTATIVE GRAM-NEGATIVE MICROORGANISMS:
Escherichia coli

Haemophilus influenzae (Beta-lactamase negative isolates only)
Klebsiella pneumoniae
Moraxella catarrhalis

ANAEROBIC MICROORGANISMS:
Bacteroides fragilis and other species in the *B. fragilis* Group
Clostridium species (excluding *C. difficile*)
Eubacterium species
Peptostreptococcus species
Porphyromonas asaccharolytica
Prevotella species.

The following *in vitro* data are available, **but their clinical significance is unknown**.
INVANZ exhibits *in vitro* minimum inhibitory concentrations (MICs) of ≤ 1 mcg/mL against most (≥ 90%) strains of *Streptococcus* species including *Streptococcus pneumoniae*, ≤ 0.5 mcg/mL against most (≥ 90%) strains of *Haemophilus* species, ≤ 2 mcg/mL against most (≥ 90%) strains of the other aerobic and facultative anaerobic microorganisms and ≤ 4 mcg/mL against most (≥ 90%) strains of the strict anaerobic microorganisms in the following list; however, the safety and effectiveness of INVANZ in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical studies:

AEROBIC AND FACULTATIVE GRAM-POSITIVE MICROORGANISMS:
Staphylococcus species, coagulase negative, methicillin susceptible
Streptococcus pneumoniae (penicillin-intermediate isolates only)

AEROBIC AND FACULTATIVE GRAM-NEGATIVE MICROORGANISMS:
Citrobacter freundii
Citrobacter koseri
Enterobacter aerogenes
Enterobacter cloacae
Haemophilus influenzae (beta-lactamase positive isolates)
Haemophilus parainfluenzae
Klebsiella oxytoca (excluding ESBL producing isolates)
Morganella morganii
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri

Providencia stuartii
Serratia marcescens

ANAEROBIC MICROORGANISMS:
Bacteroides vulgatus
Clostridium perfringens
Fusobacterium species

III. INDICATIONS

Treatment

INVANZ is indicated for the treatment of patients with moderate to severe infections caused by susceptible strains of microorganisms, as well as initial empiric therapy prior to the identification of causative organisms in the infections listed below:

- *Complicated Intra-Abdominal Infections*
- *Complicated Skin and Skin Structure Infections including diabetic lower extremity infections*
- *Community Acquired Pneumonia*
- *Complicated Urinary Tract Infections including pyelonephritis*
- *Acute Pelvic Infections including postpartum endomyometritis, septic abortion and post surgical gynecologic infections*

To reduce the development of drug-resistant bacteria and maintain effectiveness of INVANZ and other antibacterial drugs, INVANZ should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Prevention

INVANZ is indicated in adults for the prophylaxis of surgical site infection following elective colorectal surgery.

IV. DOSAGE AND ADMINISTRATION

The usual dose of INVANZ in patients 13 years of age and older is 1 gram (g) given once a day. The usual dose of INVANZ in patients 3 months to 12 years of age is 15 mg/kg twice daily (not to exceed 1 g/day). INVANZ is not recommended in children under 3 months of age, as no data are available.

INVANZ may be administered by intravenous (IV) infusion or intramuscular (IM) injection. When administered intravenously, INVANZ should be infused over a period of 30 minutes.

Intramuscular administration of INVANZ may be used as an alternative to intravenous administration in the treatment of those infections for which intramuscular therapy is appropriate.

The usual duration of therapy with INVANZ is 3 to 14 days but varies by the type of infection and causative pathogen(s). (See INDICATIONS.) When clinically indicated, a switch to an appropriate oral antimicrobial may be implemented if clinical improvement has been observed.

In controlled clinical studies, patients were treated from 3 to 14 days. Total treatment duration was determined by the treating physician based on site and severity of the infection, and on the patient's clinical response. In some studies, treatment was converted to oral therapy at the discretion of the treating physician after clinical improvement had been demonstrated.

Prophylaxis of surgical site infection following elective colorectal surgery: To prevent surgical site infections following elective colorectal surgery in adults, the recommended dosage is 1 g IV administered as a single intravenous dose given 1 hour prior to the surgical incision.

Patients with renal insufficiency: INVANZ may be used for the treatment of infections in adult patients with renal insufficiency. In patients whose creatinine clearance is >30 mL/min/1.73 m^2, no dosage adjustment is necessary. Adult patients with advanced renal insufficiency (creatinine clearance ≤ 30 mL/min/1.73 m^2), including those on hemodialysis, should receive 500 mg daily. There are no data in pediatric patients with renal insufficiency.

Patients on Hemodialysis: In a clinical study, following a single 1 g IV dose of ertapenem given immediately prior to a hemodialysis session, approximately 30% of the dose was recovered in the dialysate. When adult patients on hemodialysis are given the recommended daily dose of 500 mg of INVANZ within 6 hours prior to hemodialysis, a supplementary dose of 150 mg is recommended following the hemodialysis session. If INVANZ is given at least 6 hours prior to hemodialysis, no supplementary dose is needed. There are no data in patients undergoing peritoneal dialysis or hemofiltration. There are no data in pediatric patients on hemodialysis.

When only the serum creatinine is available, the following formula** may be used to estimate creatinine clearance. The serum creatinine should represent a steady state of renal function.

Males: $\frac{\text{(weight in kg) x (140-age in years)}}{\text{(72) x serum creatinine (mg/100 mL)}}$

Females: (0.85) x (value calculated for males)

No dosage adjustment is recommended in patients with impaired hepatic function (see CLINICAL PHARMACOLOGY, Characteristics in Patients, Hepatic Insufficiency).

INSTRUCTIONS FOR USE

Patients 13 years of age and older

Preparation for intravenous administration:

DO NOT MIX OR CO-INFUSE INVANZ WITH OTHER MEDICATIONS.

DO NOT USE DILUENTS CONTAINING DEXTROSE (α -D-GLUCOSE).

INVANZ MUST BE RECONSTITUTED AND THEN DILUTED PRIOR TO ADMINISTRATION.

1. Reconstitute the contents of a 1 g vial of INVANZ with 10 mL of one of the following: Water for Injection, 0.9% Sodium Chloride Injection or Bacteriostatic Water for Injection.
2. Shake well to dissolve and immediately transfer contents of the reconstituted vial to 50 mL of 0.9% Sodium Chloride Injection.
3. Complete the infusion within 6 hours of reconstitution.

Preparation for intramuscular administration:

INVANZ MUST BE RECONSTITUTED PRIOR TO ADMINISTRATION.

1. Reconstitute the contents of a 1 g vial of INVANZ with 3.2 mL of 1.0% or 2.0% lidocaine HCl injection*** (**without epinephrine**). Shake vial thoroughly to form solution.
2. Immediately withdraw the contents of the vial and administer by deep intramuscular injection into a large muscle mass (such as the gluteal muscles or lateral part of the thigh).
3. The reconstituted IM solution should be used within 1 hour after preparation. **Note: The reconstituted solution should not be administered intravenously**.

** Cockcroft and Gault equation: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976.

*** Refer to the prescribing information for lidocaine HCl.

Pediatric patients 3 months to 12 years of age

Preparation for intravenous administration:

DO NOT MIX OR CO-INFUSE INVANZ WITH OTHER MEDICATIONS.

DO NOT USE DILUENTS CONTAINING DEXTROSE (α -D-GLUCOSE).

INVANZ MUST BE RECONSTITUTED AND THEN DILUTED PRIOR TO ADMINISTRATION.

1. Reconstitute the contents of a 1 g vial of INVANZ with 10 mL of one of the following: Water for Injection, 0.9% Sodium Chloride Injection or Bacteriostatic Water for Injection.
2. Shake well to dissolve and immediately withdraw a volume equal to 15 mg/kg of body weight (not to exceed 1 g/day) and dilute in 0.9% Sodium Chloride Injection to a final concentration of 20 mg/mL or less.
3. Complete the infusion within 6 hours of reconstitution.

Preparation for intramuscular administration:

INVANZ MUST BE RECONSTITUTED PRIOR TO ADMINISTRATION.

1. Reconstitute the contents of a 1 g vial of INVANZ with 3.2 mL of 1.0% or 2.0% lidocaine HCl injection*** (**without epinephrine**). Shake vial thoroughly to form solution.
2. Immediately withdraw a volume equal to 15 mg/kg of body weight (not to exceed 1 g/day) and administer by deep intramuscular injection into a large muscle mass (such as the gluteal muscles or lateral part of the thigh).
3. The reconstituted IM solution should be used within 1 hour after preparation. **Note: The reconstituted solution should not be administered intravenously**.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to use, whenever solution and container permit. Solutions of INVANZ range from colorless to pale yellow. Variations of color within this range do not affect the potency of the product.

V. CLINICAL PHARMACOLOGY

Va. Mechanism of Action

Ertapenem has *in vitro* activity against a wide range of 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. Ertapenem has

*** Refer to the prescribing information for lidocaine HCl.

significant stability to hydrolysis by most classes of beta-lactamases, including penicillinases, and cephalosporinases and extended spectrum beta-lactamases, but not metallo-beta-lactamases.

Vb. Pharmacokinetics

Vb-1. Absorption

Ertapenem, reconstituted with 1% lidocaine HCl injection, USP (in saline without epinephrine), is well absorbed following IM administration at the recommended dose of 1 g. The mean bioavailability is approximately 92%. Following 1 g daily IM administration, mean peak plasma concentrations (C_{max}) are reached in approximately 2 hours (T_{max}).

Vb-2. Distribution

Ertapenem is highly bound to human plasma proteins. 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 mcg/mL to approximately 85% bound at an approximate plasma concentration of 300 mcg/mL.

Average plasma concentrations (mcg/mL) of ertapenem following a single 30 minute IV infusion of a 1 or 2 g dose and IM administration of a single 1 g dose in healthy young adults are presented in Table 1.

Table 1
Plasma Concentrations of Ertapenem After Single Dose Administration

Dose/Route	Average Plasma Concentrations (mcg/mL)								
	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	18 hr	24 hr
1 g IV*	155	115	83	48	31	20	9	3	1
1 g IM	33	53	67	57	40	27	13	4	2
2 g IV*	283	202	145	86	58	36	16	5	2
*IV doses were infused at a constant rate over 30 minutes.									

Area under the plasma concentration curve (AUC) of ertapenem in adults increases nearly dose-proportionally over the 0.5 to 2 g dose range.

There is no accumulation of ertapenem in adults following multiple IV doses ranging from 0.5 to 2 g daily or IM doses of 1 g daily.

Average plasma concentrations (mcg/mL) of ertapenem in pediatric patients are presented in Table 2.

Table 2
Plasma Concentrations of Ertapenem in Pediatric Patients After Single IV* Dose Administration

Age Group (Dose)	Average Plasma Concentrations (mcg/mL)							
	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	24 hr
3 to 23 months								
(15 mg/kg)†	103.8	57.3	43.6	23.7	13.5	8.2	2.5	-
(20 mg/kg)†	126.8	87.6	58.7	28.4	-	12.0	3.4	0.4
(40 mg/kg)‡	199.1	144.1	95.7	58.0	-	20.2	7.7	0.6
2 to 12 years								
(15 mg/kg)†	113.2	63.9	42.1	21.9	12.8	7.6	3.0	-
(20 mg/kg)†	147.6	97.6	63.2	34.5	-	12.3	4.9	0.5
(40 mg/kg)‡	241.7	152.7	96.3	55.6	-	18.8	7.2	0.6
13 to 17 years								
(20 mg/kg)†	170.4	98.3	67.8	40.4	-	16.0	7.0	1.1
(1 g)§	155.9	110.9	74.8	-	24.0	-	6.2	-
(40 mg/kg)‡	255.0	188.7	127.9	76.2	-	31.0	15.3	2.1

* IV doses were infused at a constant rate over 30 minutes.

† up to a maximum dose of 1 g/day

‡ up to a maximum dose of 2 g/day

§ Based on three patients receiving 1 g ertapenem who volunteered for pharmacokinetic assessment in one of the two safety and efficacy studies

The volume of distribution (V_{dss}) of ertapenem in adults is approximately 8 liters (0.11 liter/kg) and 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.

Ertapenem penetrates into suction-induced skin blisters. Concentrations of ertapenem achieved in skin blister fluid at each sampling point on the third day of 1 g once daily IV doses are presented in Table 3. The ratio of AUC in skin blister fluid to AUC in plasma is 0.61.

Table 3 Concentrations (mcg/mL) of Ertapenem in Adult Skin Blister Fluid at Each Sampling Point on the Third Day of 1-g Once Daily IV Doses						
0.5 hr	1 hr	2 hr	4 hr	8 hr	12 hr	24 hr
7	12	17	24	24	21	8

The level of ertapenem in breast milk of 5 lactating women was measured at random time points daily for 5 consecutive days following the last 1 g dose of intravenous therapy. The measured concentration of ertapenem in breast milk on the last day of therapy (5 to 14 days postpartum) in all 5 women was < 0.38 mcg/mL; peak concentrations were not assessed. By day 5 after discontinuation of therapy, the level of ertapenem was undetectable in the breast milk of 4 women and was detected at trace levels (< 0.13 mcg/mL) in 1 woman.

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 (see DRUG INTERACTIONS).

Vb-3. Metabolism

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

In vitro studies in human liver microsomes indicate that ertapenem does not inhibit metabolism mediated by any of the six major cytochrome p450 (CYP) isoforms: 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (see DRUG INTERACTIONS).

Vb-4. Elimination

Ertapenem is eliminated primarily by the kidneys. The mean plasma half-life in healthy young adults and 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 administration of a 1 g radiolabeled IV dose of 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, average concentrations of ertapenem in urine exceed 984 mcg/mL during the period 0 to 2 hours postdose and exceed 52 mcg/mL during the period 12 to 24 hours postdose.

Vb-5. Characteristics in Patients

Gender

The plasma concentrations of ertapenem are comparable in men and women.

Elderly

Plasma concentrations following a 1 g and 2 g IV dose of ertapenem are slightly higher (approximately 39% and 22%, respectively) in elderly adults (≥ 65 years) relative to young adults (<65 years). No dosage adjustment is necessary in elderly patients.

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 were generally comparable to those in healthy young adults. Three out of six patients 13 to 17 years of age received less than a 1 g dose. To provide an estimate of the pharmacokinetic data if all patients in this age group were to receive a 1 g dose, the pharmacokinetic data were calculated adjusting for a 1 g dose, assuming linearity. A comparison of results show that a 1 g once daily dose of ertapenem achieves a pharmacokinetic profile in patients 13 to 17 years of age comparable to that of adults. The ratios (13 to 17 years/adults) for AUC, the end of infusion concentration and the concentration at the midpoint of the dosing interval were 0.99, 1.20, and 0.84, respectively.

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, Distribution). 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 young healthy adults receiving a 1 g IV dose of ertapenem.

Hepatic Insufficiency

Since the pharmacokinetics of ertapenem sodium in hepatic insufficiency has not been established, it is to be used with caution in patients with hepatic impairment.

Renal Insufficiency

Following a single 1 g IV dose of ertapenem in adults, AUC is similar in patients with mild renal insufficiency (Cl_{cr} 60-90 mL/min/1.73 m^2) compared with healthy subjects (ages 25 to 82 years). AUC is increased in patients with moderate renal insufficiency (Cl_{cr} 31-59 mL/min/1.73 m^2) approximately 1.5-fold compared with healthy subjects. AUC is increased in patients with advanced renal insufficiency (Cl_{cr} 5-30 mL/min/1.73 m^2) approximately 2.6-fold compared with healthy subjects. AUC is increased in patients with end-stage renal insufficiency (Cl_{cr} <10 mL/min/1.73 m^2) approximately 2.9-fold compared with healthy subjects. Following a single 1 g IV dose given immediately prior to a hemodialysis session, approximately 30% of the dose is recovered in the dialysate. There are no data in pediatric patients with renal insufficiency.

A dosage adjustment is recommended for patients with advanced or end-stage renal insufficiency (see DOSAGE AND ADMINISTRATION).

Vc. Pharmacodynamics

SUSCEPTIBILITY TESTS

When available, the results of *in vitro* susceptibility tests should be provided to the physician as periodic reports which describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

The following are the MIC ranges for some organisms:

Microorganism	MIC Range (mcg/mL)
Enterococcus faecalis	4.0-16.0
Escherichia coli	0.004-0.016

Haemophilus influenzae	0.016-0.06
Pseudomonas aeruginosa	2.0-8.0
Staphylococcus aureus	0.06-0.25
Streptococcus pneumoniae	0.03-0.25

Dilution Techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method† (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ertapenem powder. The MIC values should be interpreted according to criteria provided in Table 3.

Diffusion Techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure† † requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10 mcg ertapenem to test the susceptibility of microorganisms to ertapenem. The disk diffusion interpretive criteria are provided in Table 4.

Anaerobic Techniques:

For anaerobic bacteria, susceptibility to ertapenem as MICs can be determined by a standardized test method† † †,*. The MIC values obtained should be interpreted according to the criteria provided in Table 4.

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† Clinical and Laboratory Standards Institute (CLSI) (Formerly NCCLS). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically. Seventh Edition. Approved Standard, CLSI Document M7-A7. CLSI, Wayne, PA, January 2006.

† † Clinical and Laboratory Standards Institute (CLSI) (Formerly NCCLS). Performance Standards for Antimicrobial Disk Susceptibility Tests. Ninth Edition. Approved Standard, CLSI Document M2-A9. CLSI, Wayne, PA, January 2006.

† † † Clinical and Laboratory Standards Institute (CLSI) (Formerly NCCLS). *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria* – Sixth Edition. Approved Standard, CLSI Document M11-A6. CLSI, Wayne, PA, January 2004.

* Clinical and Laboratory Standards Institute (CLSI) (Formerly NCCLS). Performance Standards for Antimicrobial Susceptibility Testing of Anaerobic bacteria: Informational Supplement. Approved Standard, CLSI Document M100-S16. CLSI, Wayne, PA, January 2006.

Table 4 NCCLS Interpretive Susceptibility Criteria for Ertapenem						
	Dilution Test (MICs in mcg/mL)			Disk Diffusion Test (zone diameters in mm)		
Pathogen	S	I	R	S	I	R
Aerobes and facultative anaerobes other than *Streptococcus* spp. and *Haemophilus* spp.	≤ 2	4	≥ 8	≥ 19	16-18	≤ 15
Streptococcus pneumoniae (penicillin-susceptible non-meningitis strains only)[b]	≤ 1[c]	2	≥ 4	—	—	—
Streptococcus spp. (beta-hemolytic only)[a d]	≤ 1[c]	—	—	—	—	—
Haemophilus spp.[a]	≤ 0.5[e]	—	—	≥ 19[f]	—	—
Anaerobes	≤ 4[g]	8	≥ 16	—	—	—

[a] The current absence of data on resistant strains precludes defining any category other than "susceptible". If strains yield MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.

[b] *Streptococcus pneumoniae* that are susceptible to penicillin (1 mcg oxacillin disk zone diameter ≥ 20 mm), can be considered susceptible to ertapenem. Isolates with 1-mcg oxacillin zone diameter ≤ 19 mm should be tested against ertapenem using an MIC method.

[c] *Streptococcus pneumoniae* that are susceptible to penicillin (MIC ≤ 0.06 mcg/mL) and *Streptococcus* spp. other than *S. pneumoniae* that are susceptible to penicillin (MIC ≤ 0.12 mcg/mL), can be considered susceptible to ertapenem. Testing of ertapenem against penicillin-intermediate or penicillin-resistant isolates is not recommended since reliable interpretive criteria for ertapenem are not available.

[d] Beta-hemolytic *Streptococcus* spp. that are susceptible to penicillin (10 units penicillin disk zone diameter ≥ 24 mm), can be considered susceptible to ertapenem. Isolates with 10-units penicillin disk zone diameter <24 mm should be tested against ertapenem using an MIC method. Penicillin disk diffusion interpretive criteria are not available for viridans group streptococci, which should not be tested against ertapenem.

[e] These interpretive standards are applicable to the broth microdilution procedure using *Haemophilus* Test Medium (HTM) inoculated with a direct colony suspension and incubated in ambient air at 35°C for 20-24 hrs.

[f] These zone diameters are applicable to tests performed by disk diffusion using *Haemophilus* Test Medium (HTM) agar inoculated with a direct colony suspension and incubated in 5% CO_2 at 35°C for 16-18 hrs.

[g] These interpretative standards are applicable only to agar dilution using *Brucella* agar supplemented with hemin, vitamin K1 and 5% defibrinated or laked sheep blood inoculated with a direct colony suspension or a 6 to 24 hour fresh culture in enriched thioglycollate medium and incubated in an anaerobic jar or chamber at 35-37°C for 42-48 hrs.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control:

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Standard ertapenem powder should provide the following range of values noted in Table 5. Quality control microorganisms are specific strains of organisms with intrinsic biological properties. QC strains are very stable strains which will give a standard and repeatable susceptibility pattern. The specific strains used for microbiological quality control are not clinically significant.

Table 5 Acceptable Quality Control Ranges for Ertapenem

QC Strain	ATCC®	Dilution Test (MICs in mcg/mL)	Disk Diffusion Test (zone diameters in mm)
Enterococcus faecalis	29212	4-16	Not Applicable
Staphylococcus aureus	29213	0.06-0.25	Not Applicable
Staphylococcus aureus	25923	Not Applicable	24-31
Streptococcus pneumoniae[h]	49619	0.03-0.25[i]	28-35
Escherichia coli	25922	0.004-0.016	29-36
Haemophilus influenzae	49766	0.016-0.06[j]	27-33[k]

Pseudomonas aeruginosa	27853	2-8	13-21
Bacteroides fragilis	25285	0.06-0.25[l] (0.06-0.5)[m]	Not Applicable
Bacteroides thetaiotaomicron	29741	0.25-1.0[l] (0.5-2.0)[m]	Not Applicable
Eubacterium lentum	43055	0.5-2.0[l] (0.5-4.0)[m]	Not Applicable

[h] This organism is used for quality control of susceptibility testing of *Streptococcus pneumoniae* and *Streptococcus* spp.

[i] These quality control ranges are applicable to *Streptococcus pneumoniae* ATCC 49619 tested by broth microdilution using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood inoculated with a direct colony suspension and incubated in ambient air at 35°C for 20-24 hrs.

[j] These quality control ranges are applicable to *Haemophilus influenzae* ATCC 49766 tested by the broth microdilution procedure using *Haemophilus* Test Medium (HTM) inoculated with a direct colony suspension and incubated in ambient air at 35°C for 20-24 hrs.

[k] These quality control ranges are applicable to *Haemophilus influenzae* ATCC 49766 tested by disk diffusion using *Haemophilus* Test Medium (HTM) agar inoculated with a direct colony suspension and incubated in 5% CO_2 at 35°C for 16-18 hrs.

[l] These quality control ranges are applicable only to agar dilution using *Brucella* agar supplemented with hemin, vitamin K1 and 5% defibrinated or laked sheep blood inoculated with a direct colony suspension or a 6 to 24 hour fresh culture in enriched thioglycollate medium and incubated in an anaerobic jar or chamber at 35-37°C for 42-48 hrs.

[m] Quality control ranges applicable for broth microdilution method.

VI. CONTRAINDICATIONS

INVANZ is contraindicated in patients with known hypersensitivity to any component of this product or to other drugs in the same class or in patients who have demonstrated anaphylactic reactions to beta-lactams.

Due to the use of lidocaine HCl as a diluent, INVANZ administered intramuscularly is contraindicated in patients with a known hypersensitivity to local anesthetics of the amide type and in patients with severe shock or heart block. (Refer to the prescribing information for lidocaine HCl.)

VII. PRECAUTIONS

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with beta-lactams. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe hypersensitivity reactions when treated with another beta-lactam. Before initiating therapy with INVANZ, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, other beta-lactams and other allergens. If an allergic reaction to INVANZ occurs, discontinue the drug immediately. **Serious anaphylactic reactions require immediate emergency treatment.**

Case reports in the literature have shown that co-administration of carbapenems, including ertapenem, to patients receiving valproic acid or divalproex sodium results in a reduction in valproic acid concentrations. The valproic acid concentrations may drop below the therapeutic range as a result of this interaction, therefore increasing the risk of breakthrough seizures. Increasing the dose of valproic acid or divalproex sodium may not be sufficient to overcome this interaction. The concomitant use of ertapenem and valproic acid/divalproex sodium is generally not recommended. Anti-bacterials other than carbapenems should be considered to treat infections in patients whose seizures are well controlled on valproic acid or divalproex sodium. If administration of INVANZ is necessary, supplemental anti-convulsant therapy should be considered (See DRUG INTERACTIONS.).

Seizures and other central nervous system (CNS) adverse experiences have been reported during treatment with INVANZ (see ADVERSE REACTIONS). During clinical investigations in adult patients treated with INVANZ (1 g once a day), seizures, irrespective of drug relationship, occurred in 0.5% of patients during study therapy plus 14 day follow-up period. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function. Close adherence to the recommended dosage regimen is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically and the dosage of INVANZ re-examined to determine whether it should be decreased or discontinued.

As with other antibiotics, prolonged use of INVANZ may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ertapenem, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of “antibiotic-associated colitis”.

Caution should be taken when administering INVANZ intramuscularly, to avoid inadvertent injection into a blood vessel (see DOSAGE AND ADMINISTRATION).

Lidocaine HCl is the diluent for intramuscular administration of INVANZ. Refer to the prescribing information for lidocaine HCl.

Based on the data available, it cannot be excluded that in the few cases of surgical interventions exceeding 4 hours, patients could be exposed to sub optimal ertapenem concentrations and consequently to a risk of potential treatment failure. Therefore, caution should be exercised in such unusual cases.

VIII. PREGNANCY

There are no adequate and well-controlled studies in pregnant women. INVANZ should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

IX. NURSING MOTHERS

Ertapenem is excreted in human milk (see CLINICAL PHARMACOLOGY, Distribution). Caution should be exercised when INVANZ is administered to a nursing woman.

X. PEDIATRIC USE

Safety and effectiveness of INVANZ in pediatric patients 3 months to 17 years of age are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in pediatric patients, and additional data from comparator-controlled studies in pediatric patients 3 months to 17 years of age in complicated skin and skin structure infections, complicated urinary tract infections, community acquired pneumonia and 2 to 17 years of age in complicated intra-abdominal infection and acute pelvic infection.

INVANZ is not recommended in infants under 3 months of age as no data are available.
INVANZ is not recommended in the treatment of meningitis in the pediatric population due to lack of sufficient CSF penetration.

There is no data in pediatric patients with renal insufficiency.

XI. USE IN THE ELDERLY

In clinical studies, the efficacy and safety of INVANZ in the elderly (≥ 65 years) was comparable to that seen in younger patients (<65 years).

XII. DRUG INTERACTIONS

When ertapenem is administered with probenecid, probenecid competes for active tubular secretion and thus inhibits the renal excretion of ertapenem. This leads to small but statistically significant increases in the elimination half-life (19%) and in the extent of systemic exposure (25%). No dosage adjustment is necessary when ertapenem is given with probenecid. Because of the small effect on half-life, the co-administration with probenecid to extend the half-life of ertapenem is not recommended.

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. *In vitro* studies in human liver microsomes indicate ertapenem does not inhibit metabolism mediated by any of the six major cytochrome p450 (CYP) isoforms: 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4. Drug interactions caused by inhibition of P-glycoprotein-mediated drug clearance or CYP-mediated drug clearance are unlikely. (See CLINICAL PHARMACOLOGY, Distribution and Metabolism.)

Other than with probenecid, no specific clinical drug interaction studies have been conducted.

Case reports in the literature have shown that co-administration of carbapenems, including ertapenem, to patients receiving valproic acid or divalproex sodium results in a reduction of valproic acid concentrations. The valproic acid concentrations may drop below the therapeutic range as a result of this interaction, therefore increasing the risk of breakthrough seizures. Although the mechanism of this interaction is unknown, data from *in vitro* and animal studies suggest that carbapenems may inhibit the hydrolysis of valproic acid's glucuronide metabolite (VPA-g) back to valproic acid, thus decreasing the serum concentrations of valproic acid. (See PRECAUTIONS.)

XIII. SIDE EFFECTS

Adult Patients

The total number of patients treated with ertapenem in clinical studies was over 1900 of which over 1850 received a 1 g dose of INVANZ. Most adverse experiences reported in these clinical studies were described as mild to moderate in severity. Drug-related adverse experiences were reported in approximately 20% of patients treated with ertapenem. Ertapenem was discontinued due to adverse experiences thought to be drug-related in 1.3% of patients.

The most common drug-related adverse experiences reported during parenteral therapy in patients treated with ertapenem were diarrhea (4.3%), infused vein complication (3.9%), nausea (2.9%) and headache (2.1%).

The following drug-related adverse experiences were reported during parenteral therapy in adult patients treated with ertapenem:

Common (≥ 1/100, <1/10)	Nervous system disorders	Headache
	Vascular disorders	Infused vein complication, phlebitis/thrombophlebitis
	Gastrointestinal disorders	Diarrhea, nausea, vomiting
Uncommon (>1/1000, <1/100)	Nervous system disorders	Dizziness, somnolence, insomnia, seizure, confusion
	Cardiac and vascular disorders	Extravasation, hypotension
	Respiratory, thoracic and mediastinal disorders	Dyspnea
	Gastrointestinal disorders	Oral candidiasis, constipation, acid regurgitation, *C. difficile*-associated diarrhea, dry mouth, dyspepsia, anorexia
	Skin and subcutaneous tissue disorders	Erythema, pruritus
	General disorders and administration	Abdominal pain, taste perversion,

	site conditions	asthenia/fatigue, candidiasis, edema/swelling, fever, pain, chest pain
	Reproductive system and breast disorders	Vaginal pruritus

In clinical studies, seizure was reported during parenteral therapy in 0.2% of patients treated with ertapenem, 0.3% of patients treated with piperacillin/tazobactam and 0% of patients treated with ceftriaxone.

In the majority of clinical studies, parenteral therapy was followed by a switch to an appropriate oral antimicrobial. During the entire treatment period and a 14 day posttreatment follow-up period, drug-related adverse experiences in patients treated with INVANZ included those listed in the table above as well as rash and vaginitis at an incidence of ≥ 1.0% (common) and allergic reactions, malaise and fungal infections at an incidence of >0.1% but <1.0% (uncommon).

In a clinical study for the prophylaxis of surgical site infections following elective colorectal surgery in which 476 adult patients received a 1 g dose of ertapenem prior to surgery, the only drug-related adverse experience during parenteral therapy that was not seen in previous clinical trials was sinus bradycardia reported at an incidence of >0.1% but <1.0% (uncommon).

Pediatric Patients

The total number of pediatric patients treated with ertapenem in clinical studies was 384. The overall safety profile is comparable to that in adult patients. In clinical trials, the most common drug-related clinical adverse experiences reported during parenteral therapy were diarrhea (5.5%), infusion site pain (5.5%) and infusion site erythema (2.6%).

The following drug-related adverse experiences were reported during parenteral therapy in pediatric patients treated with ertapenem:

Common (≥ 1/100, <1/10)	Gastrointestinal disorders	Diarrhoea, vomiting
	General disorders and administration site conditions	Infusion site erythema, infusion site pain, infusion site phlebitis, infusion site swelling

Skin and subcutaneous tissue disorders	Rash

Additional drug-related adverse experiences that were reported during parenteral therapy in >0.5% but <1.0% of patients treated with INVANZ in clinical studies include: infusion site induration, infusion site pruritus, infusion site warmth and phlebitis.

In the pediatric clinical studies, the majority of the patients had parenteral therapy followed by a switch to an appropriate oral antimicrobial. During the entire treatment period and a 14 day posttreatment follow-up period, drug-related adverse experiences in patients treated with INVANZ were no different than those listed above.

Post-Marketing Experience

The following post-marketing adverse experiences have been reported:

Immune System: anaphylaxis including anaphylactoid reactions

Psychiatric Disorders: altered mental status (including agitation, aggression, delirium, disorientation, mental status changes)

Nervous System Disorders: depressed level of consciousness, dyskinesia, gait disturbance, hallucinations, myoclonus, tremor, encephalopathy (recovery may be prolonged in patients with renal impairment)

Gastrointestinal Disorders: teeth staining

Skin and Subcutaneous Tissue Disorders: Acute Generalized Exanthematous Pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome), urticaria, hypersensitivity vasculitis

Musculoskeletal and Connective Tissue Disorders: muscular weakness

XIIIa. Laboratory Test Findings

Adult Patients

The most frequently observed drug-related laboratory abnormalities during parenteral therapy in patients receiving INVANZ were elevations in ALT, AST, alkaline phosphatase and platelet count.

In the majority of clinical studies, parenteral therapy was followed by a switch to an appropriate oral antimicrobial. During the entire treatment period and a 14 day posttreatment follow-up period, drug-related laboratory abnormalities in patients treated with INVANZ were no different than those listed above.

Other drug-related laboratory abnormalities included the following: increases in direct serum bilirubin, total serum bilirubin, eosinophils, indirect serum bilirubin, PTT, urine bacteria, BUN, serum creatinine, serum glucose, monocytes, urine epithelial cells, urine red blood cells; decreases in segmented neutrophils, white blood cells, hematocrit, hemoglobin and platelet count.

In a clinical study for the prophylaxis of surgical site infections following elective colorectal surgery in which 476 adult patients received a 1 g dose of ertapenem prior to surgery, there were no additional drug-related laboratory adverse experiences reported during parenteral therapy.

Pediatric Patients

Drug-related laboratory adverse experiences that were reported during therapy in ≥ 2.0% of pediatric patients treated with INVANZ, including those who were switched to therapy with an oral antimicrobial, in clinical studies were neutrophil count decreased (3.0%), ALT increased (2.2%), and AST increased (2.1%).

Other drug-related laboratory abnormalities during the entire treatment period plus 14 day follow-up included the following: decreases in white blood cells, increases in eosinophils.

XIV. OVERDOSAGE

No specific information is available on the treatment of overdosage with INVANZ. Intentional overdosing of INVANZ is unlikely. Intravenous administration of INVANZ at a 3 g daily dose for 8 days to healthy adult volunteers did not result in significant toxicity. In clinical studies in adults, inadvertent administration of up to 3 g in a day did not result in clinically important adverse experiences. In pediatric clinical studies, a single IV dose of 40 mg/kg up to a maximum of 2 g did not result in toxicity.

In the event of an overdose, INVANZ should be discontinued and general supportive treatment given until renal elimination takes place.

INVANZ can be removed by hemodialysis; however, no information is available on the use of hemodialysis to treat overdosage.

XV. STORAGE

Before reconstitution

Do not store lyophilized powder above 25°C.

Reconstituted and infusion solutions

The reconstituted solution, immediately diluted in 0.9% Sodium Chloride Injection (see DOSAGE AND ADMINISTRATION, INSTRUCTIONS FOR USE), 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 INVANZ should not be frozen.

XVI. AVAILABILITY

INVANZ is supplied as a sterile lyophilized powder for intravenous infusion or intramuscular injection containing 1 g ertapenem as free acid.

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Merck Sharp & Dohme LLC
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Packed by:

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