PRODUCT CIRCULAR

PAK-IVZ-IV-032010

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 ANAEROBIC GRAM-POSITIVE MICROORGANISMS:
Staphylococcus aureus (including penicillinase-producing strains)
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes
Note: Methicillin-resistant staphylococci are resistant to INVANZ. Many strains of *Enterococcus faecalis* and most strains of *Enterococcus faecium* are resistant.

AEROBIC AND FACULTATIVE ANAEROBIC GRAM-NEGATIVE MICROORGANISMS:
Escherichia coli
Haemophilus influenzae (including beta-lactamase producing strains)
Klebsiella pneumoniae
Moraxella catarrhalis
Proteus mirabilis

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

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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 ANAEROBIC GRAM-POSITIVE MICROORGANISMS:
Staphylococcus species, coagulase negative, methicillin susceptible
Streptococcus pneumoniae, penicillin resistant
Viridans streptococci
Note: Methicillin-resistant staphylococci are resistant to INVANZ. Many strains of *Enterococcus faecalis* and most strains of *Enterococcus faecium* are resistant.

AEROBIC AND FACULTATIVE ANAEROBIC GRAM-NEGATIVE MICROORGANISMS:
Citrobacter freundii
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli producing ESBLs
Haemophilus parainfluenzae
Klebsiella oxytoca
Klebsiella pneumoniae producing ESBLs
Morganella morganii
Proteus vulgaris
Serratia marcescens
Note: Many strains of the above organisms that are multiply resistant to other antibiotics, e.g., penicillins, cephalosporins (including third-generation) and aminoglycosides are susceptible to INVANZ.

ANAEROBIC MICROORGANISMS:
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 and diabetic foot infections*
- *Community Acquired Pneumonia*
- *Complicated Urinary Tract Infections including pyelonephritis*
- *Acute Pelvic Infections including postpartum endomyometritis, septic abortion and post surgical gynecologic infections*
- *Bacterial Septicemia*

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

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

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

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).

The recommended dose of INVANZ can be administered without regard to age (13 years and older) or gender.

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.

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.

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. 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.)

VI. 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.**

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”.

VII. 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.

VIII. NURSING MOTHERS

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

IX. 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 with the following infections (see INDICATIONS and CLINICAL STUDIES, Pediatric Patients).

- *Complicated Intra-Abdominal Infections*
- *Complicated Skin and Skin Structure Infections*
- *Community Acquired Pneumonia*
- *Complicated Urinary Tract Infections*
- *Acute Pelvic Infections*
- *Bacterial Septicemia*

INVANZ is not recommended in infants under 3 months of age as no data are available.

X. 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).

XI. 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 coadministration 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.

Decreased serum levels of valproic acid with co-administration of ertapenem have been reported as post-marketing experiences. Careful monitoring of serum levels of valproic acid should be considered if ertapenem is to be co-administered with valproic acid.

XII. 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	Nervous system disorders	Dizziness, somnolence, insomnia,

(>1/1000, <1/100)		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 site conditions	Abdominal pain, taste perversion, 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 (see CLINICAL PHARMACOLOGY, Clinical Studies). 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 treatment of diabetic foot infections in which 289 adult diabetic patients were treated with ertapenem, the drug-related adverse experience profile was generally similar to that seen in previous clinical trials.

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 (very rare)
Psychiatric Disorders: altered mental status (including agitation, aggression, delirium, disorientation, mental status changes)
Nervous System Disorders: dyskinesia, hallucinations (very rare), myoclonus, tremor
Skin and subcutaneous tissue disorders: urticaria, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome)

XIIa. 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 (see CLINICAL PHARMACOLOGY, Clinical Studies). 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 treatment of diabetic foot infections in which 289 adult diabetic patients were treated with ertapenem, the drug-related laboratory adverse experience profile was generally similar to that seen in previous clinical trials.

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
The most frequently observed drug-related laboratory abnormality during parenteral therapy in patients receiving INVANZ was decreases in neutrophil count.

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

XIII. 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.

XIV. AVAILABILITY

INVANZ 1g I.V is available in one vial pack.